

Biomedical and



Health Research

Differential Diagnosis in Neurology

Revised Second Edition

Robert J. Schwartzman

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The purpose of an exercise in differential diagnosis is to establish crosslinks between medical facts stored in different sections of our memory.

This book, *Differential Diagnosis in Neurology*, is the unified perspective of an eminent physician with decades of clinical experience and teaching; one of the most skilled clinical neurologists of modern times and a seasoned researcher who was the primary investigator for many clinical trials, and who published numerous clinical and basic research papers. The “real world” aspects of the book are based on morning reports with neurology residents and students conducted over 40 years. The differential diagnosis generated by subspecialty division chiefs supplemented those proposed in morning reports.

The book is conceived as a guide that will give the clinician a concise snapshot or skeleton with a general background of the disease at hand. Other disease aspects included in this book are molecular genetics, physiology, and biochemistry that will elucidate mechanisms and assist in discovering new entities. Each chapter includes an extensive list of suggestions for further reading.

It is the art of crosslinking between medical facts that distinguishes Dr. Schwartzman from other teachers of Neurology and that makes this book uniquely valuable.

“The essence of a differential diagnosis is ‘splitting’ rather than ‘lumping’: it requires bringing knowledge to the table and then adding experience.”
- R.J. Schwartzman



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DIFFERENTIAL DIAGNOSIS IN NEUROLOGY

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Revised Second Edition

By

Robert J. Schwartzman

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Foreword

Dr. Robert Schwartzman's book entitled *Differential Diagnosis in Neurology* is unique in many ways. It is written by one of the most skilled clinical neurologists of modern times; someone who devoted his entire career to teaching the art of Neurology to generations of residents and students; someone who shaped the field of Neurology to become an independent specialty but never stopped teaching it in the greater context of Internal Medicine.

Dr. Schwartzman's unique way of teaching Neurology is reflected in this book. Every day as a Neurology resident in his program started with Morning Report – an hour of case review, differential diagnosis, discussion of diagnostic studies and treatment combined with quizzing the residents on pertinent literature, new and historical alike. It is here where the foundation was laid to taking the best possible care of our patients throughout the rest of the day. One of the most valuable experiences in morning report was the exercise in differential diagnosis, an aspect of clinical medicine that in the times of ever-increasing sub-specialization and reliance on “handheld” knowledge is at great risk of becoming extinct.

Writing a book on differential diagnosis is probably one of the most difficult tasks in academic medicine. By nature, these writings ought to be monographs as they reflect an individual style. The purpose of an exercise in differential diagnosis is to establish crosslinks between medical facts stored in different sections of our memory – sections that unless accessed through the same channel we learned them are irretrievable. It is the art of crosslinking that distinguishes Dr. Schwartzman from other Neurology teachers and that makes this book uniquely valuable. It helps you see the forest in spite of all the trees, the bigger picture, the bird's eye view.

Admittedly, I'm biased. I can truly say that my career has been shaped by Dr. Schwartzman and his way of teaching Neurology. Without him, I would have become a different Neurologist or maybe not a Neurologist at all. *Differential Diagnosis in Neurology* makes accessible his way of thinking, analyzing, and teaching to a much broader audience.

The book is organized by neuroanatomical structures. A separate chapter is devoted to epilepsy. For each level within the hierarchy of the nervous system and the vascular tree, neurologic syndromes are listed and their differential diagnosis is outlined. The depth and breadth with which these syndromes and differential diagnoses are described is one of a kind. In addition, the reader is provided with an unprecedented plethora of clinical tricks and secrets. The mostly tabular form of the book is the only way to fit such an abundance of information in a single book. While the book does not contain citations, most of the facts can be easily tracked in the literature. By not providing citations, Dr. Schwartzman honors some of his core principles in neurologic education: teaching by stimulating and challenging, avoiding the “Nuernberger Trichter” (Nuremberg funnel) method, using the competitive interplay between teacher and student.

The student and junior resident have to study this book, not read it. It does not prepare you for the board exam in the most efficient way but for life as a Neurologist. More experienced neurologists will find it to be a valuable when confronted with a difficult patient. Take on the challenge! It will be a transforming experience.

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Preface

The concept for Differential Diagnosis in Neurology was formed from my training in internal medicine and neurology.

Dr. Eugene A. Stead, chairman of Medicine at Duke for many years, taught me the importance of the fine points of the history and the significant details of the examination that separate one disease from another. "Let's sharpen the data," he would say, as he would elicit a small pearl from the history that would lead to the diagnosis.

Dr. Milton Shy was a master diagnostician whose great depth of knowledge for neurological diseases allowed him to meld each disease with its scientific basis.

Dr. W.K. Engel demonstrated just how adept one could become in an area of neurology. He described many new neuromuscular disorders by uncovering a seminal feature of the history or the examination.

It was a great privilege rounding with these physicians, I hope a trace of their medical knowledge, and scholarship comes through in these pages.

The "real world" aspects of the book are derived from giving morning report with neurology residents and students for over 40 years. Difficult patients were presented and examined in grand rounds. The differential diagnosis generated by subspecialty division chiefs supplemented those proposed in morning report. The discussion was always lively and new components of the examination or history were added.

The essence of a differential diagnosis is "splitting" rather than "lumping": it requires bringing knowledge to the table and then adding experience.

This book is meant to be a guide that will give the clinician a concise snapshot or skeleton with a general background of the disease at hand. Other disease aspects included in this book are molecular genetics, physiology, and biochemistry that will elucidate mechanisms and assist in discovering new entities.

Each chapter includes an extensive list of suggestions for further reading.

It is hoped that the clinician will use the volume as a workbook in which new diseases are added or older classifications revised on a molecular basis.

A strength of this work is that this is the unified perspective of one physician with decades of clinical experience and teaching; a seasoned researcher who has been the primary investigator for many clinical trials as well as publishing numerous clinical and basic research papers. The limitation of a work such as this is that obviously, one person can't know everything for the depth of information needed to be comprehensive for each topic.

Robert J. Schwartzman

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Chapter 1

Vascular Disease

Ischemic Stroke

Introduction to General Features of the Differential Diagnosis of Ischemic Stroke, Embolus, and Intracranial Hemorrhage

Cerebral thrombosis occurs most frequently in the early morning hours during sleep. Patients frequently awaken and fall as they are unaware of their deficits. Transient ischemic episodes occur prior to thrombotic stroke in approximately 30% of patients. They are almost always atherosclerotic in origin. Transient ischemic attacks are usually emboli that arise either from the heart or intra-arterial vessels (carotid, arch of the aorta or vertebral arteries to distal smaller branches). They occasionally occur from distal field ischemia due to compromised vessels and decreased cerebral perfusion or vasospasm (migraine). Emboli may cause symptoms at each level of the brain as they progress through the cerebral circulation. They often occur in showers so that a number of vessels may be occluded simultaneously. The symptoms of intra-arterial vessel to vessel emboli are usually less than 2 minutes. Longer transient ischemic attacks suggest a cardiac origin. Transient ischemic attacks may occur only a few times or up to several times a day or on rare occasions in a rapid series (crescendo transient ischemic attacks). They often are stereotypical, but careful examination may reveal a new sign or symptom with each transient ischemic attack. If an infarction follows the first transient ischemic attack, it will be within one month in 20% of patients and within one year in 50%. Anterior transient ischemic attacks involve the cerebral hemisphere and the eye. Visual loss in the ipsilateral eye is usually characterized by transient monocular blindness. A shade may descend over the eye uniformly or more rarely there is a wedge of visual loss, sudden blurring or bright scotoma. (This finding is often noted with concomitant carotid stenosis). The visual deficit clears painlessly and uniformly. Often ocular attacks precede hemispheric attacks. Hollenhorst plaques (yellow, birefringent, cholesterol particles) are rarely noted and occur at branch points of the retinal arterioles. Rarely the pupil is paralyzed from ischemia of the ciliary body. Hemispheric attacks are most often characterized by face and arm weakness with concomitant sensory loss. The face and lips may be involved together or singly, a cheiro-oral presentation. The sensory loss involves the corner of the mouth and usually the C6 to C8 hand sensory root distribution: most hemispheric transient ischemic attacks cause aphasia, heaviness, weakness and numbness of the face and arm (brachiocephalic) or of the arm, face and leg (internal capsule distribution). Rarely dysarthria or leg weakness may predominate. A pseudo radial palsy of the arm suggests ischemia of

the motor “knuckle” of the motor cortex. Simultaneous eye and hand involvement from a carotid embolus is extremely rare. Anterior transient ischemic attacks may cause: dizziness, confusion, both anterior and/or posterior aphasia, higher cortical sensory and cognitive deficits, and neglect to contralateral space with non-dominant hemispheric involvement. Headaches are common and are usually ipsilateral. The usual manifestation of transient ischemic attacks in the posterior circulation (includes the vertebral, basilar and posterior cerebral arteries) are: bilateral visual field loss, dizziness, perioral numbness, ataxia, diplopia, dysphagia, dysarthria and bilateral motor or sensory symptoms. A crural hemisensory deficit (ipsilateral face and contralateral body below the clavicle) is pathognomic of brainstem involvement but is extremely rare. Dizziness alone is rare as a posterior transient ischemic attack symptom but has been described with posterior inferior cerebellar artery involvement.

Unusual signs and symptoms of posterior circulation transient ischemic attacks are: veering to one side (posterior inferior cerebellar artery at the level of the inferior olive); staggering posterior inferior cerebellar artery territory; lateral pulsion (posterior inferior cerebellar artery territory, medial branch); a feeling of crossed-eyedness, bilateral dark vision; noise or pounding in the head or ear; unusual cephalic sensations; and pain in the face or head. Drop attacks, sudden loss of tone with falling may occur and are unaccompanied by loss of consciousness. The patients are stunned or slightly confused. Impaired hearing (sounds are faint or distant); deafness, forced eye deviation, hemiballismus, and a feeling of moving of a part and choreoathetosis have rarely been described. Peduncular hallucinosis has recently been demonstrated to occur from hippocampal formation ischemia. Forced eye deviation is encountered from unilateral para pontine reticular formation ischemia. Basilar artery ischemia may cause alternate hemiparesis. The affected extremities may be simultaneously weak or there is spread of weakness over 10 to 60 seconds which is much longer than expected from seizure activity. A basilar transient ischemic attack may resolve suddenly or gradually. Posterior transient ischemic attacks have a higher incidence of headache than anterior transient ischemic attacks. In general, ipsilateral carotid disease causes face and parietal headache. Vertebral artery involvement refers pain to the retroauricular area whereas basilar artery disease produces occipital and C2 distribution (forehead) pain. Posterior cerebral artery ischemia refers to the lateral eyebrow.

The major risk factors for thrombotic stroke are an important diagnostic feature. Hypertension, diabetes mellitus, cigarette smoking, prior stroke, heart and peripheral vascular disease are most common in older patients. Stroke in the young is embolic from the heart or secondary to dissection, collagen vascular disease, hypercoagulable states, genetic diseases, or associated medical conditions.

Development of neurologic deficits in thrombotic strokes occur in several ways: 1. single attack with the full deficit evolving over hours; 2. stuttering or intermittent progression

that may continue over hours to 1 to 2 days; 3. a partial deficit that may improve and then progress to a completed stroke; 4. fleeting deficits may be followed by a longer episode and then a major stroke that occurs within days.

The deficits may be regional at onset or evolve in a step-like pattern. Intermittent progression is a characteristic of thrombotic stroke. Rarely there is an apparent gradual progression of the deficit over 1 to 2 weeks which is most common in pure motor strokes.

In general, thrombotic strokes of the large conducting vessels of the middle cerebral artery (M1 and M2 components) reach maximum disability in three days which is dependent on consequent edema. Carotid occlusion, particularly if there is a fetal origin of the posterior cerebral artery (from the carotid artery) results in maximum edema and disability within 24 hours. Death is usually from transtentorial herniation at midbrain levels. Posterior fossa strokes, particularly of the vertebral artery, (the most common site of origin of posterior inferior cerebellar artery), may have delayed cerebral edema (4 to 7 days) and produce tonsillar herniation at this time (tonsillar coning).

Particular arteries will thrombose with different diseases. Diabetic patients suffer infarction of posterior inferior cerebellar artery and the thalamogeniculate and thalamoperforate arteries from the posterior cerebral artery to a greater extent than expected. Young hypertensive women on birth control pills infarct posterior inferior cerebellar artery. Lipohyalinosis and focal atheromatous plaques at the origin of penetrating arteries (lacunar strokes) occur most frequently in diabetic hypertensive patients. Dissection of the vertebral or carotid arteries usually causes stroke by emboli from the site of dissection but less commonly by decreased flow. Dissection of the vertebral artery is common in the horizontal component of the artery at C2. This frequently causes neck pain and may be followed by chiropractic manipulation which extends the dissection.

Diabetes accelerates atherosclerosis by approximately 10 years. Radiation therapy in the neck induces a vasculopathy that accelerates atherosclerosis and causes proliferative endarteritis over long segments of the artery. If the brain is involved, small vessels occlude in the cortex with focal deficits and strokes. In the spinal cord, the perforating sulcal arteries are involved which produces a Brown-Séquard syndrome. Polycythemia most often affects the posterior circulation. The vasculopathy of sickle cell disease affects large and small vessels.

The usual sites of atherosclerotic disease are the carotid bifurcation, siphon and the intracavernous portion of the artery. Rarely there may be isolated stenosis of superficial branches as well as the M1 and M2 segments of the middle cerebral artery. In the posterior circulation, the origins of the vertebral arteries, mid and top of the basilar artery, as well as the junction of the vertebral and basilar arteries, are major sites of disease. Stenosis may be seen singly or in tandem.

Anomalies of arteries from their embryological origin may be important in determining the extent of thrombotic stroke. Poor development of the anterior and posterior communicating arteries may isolate one cerebral hemisphere. In general, the right vertebral artery is atretic or smaller than the left. Atherosclerosis of the left vertebral artery may induce severe basilar symptoms because of lack of circulatory support from the right vertebral artery. Occlusion of a vertebral artery may occur with prolonged abnormal head positions during surgical procedures as the artery on the side of the ipsilaterally turned head is occluded. If it is the predominant artery, there is no effective basilar flow. Similarly, a single thalamic peduncle (Percheron's artery) at the top of the basilar may cause bilateral thalamic infarction as it will be the origin of the paired interpeduncular arteries that usually arise separately from the top of the basilar artery. Failure of regression of the four major embryologic connections between the carotid and basilar artery (persistent trigeminal, otic, hypoglossal and proatlantal) may allow an embolus from the anterior circulation to infarct posterior circulation territory or vice versa. A fetal origin of the posterior cerebral artery arising from the carotid may be the cause of complete hemispheric infarction following carotid occlusion.

A lacune is an area of infarction within the territory of a single perforating artery. The basic clinical syndromes associated with these lesions are: pure motor stroke, pure sensory stroke, homolateral ataxia and crural paresis, dysarthria – clumsy hand syndrome, ataxic hemiparesis and sensorimotor stroke. Approximately 80% of lacunes may be clinically silent. The temporal profile of a lacunar infarct may evolve over hours or rarely days in contradistinction to a cortical infarct. Lacunar strokes do not present with loss or impairment of consciousness, headache, seizure or higher cognitive deficits. Approximately 20% have transient ischemic attacks at the time of incipient occlusion and may be embolic. Often several perforating arteries are occluded in the latter circumstance. The capsular warning syndrome describes a crescendo of lacunar transient ischemic attacks prior to completion of internal capsule infarction.

A cerebral embolus strikes suddenly during wakefulness and frequently has a suggestive underlying cause. It may involve superficial surface cortical vessels giving pure cortical symptoms such as aphasia or hemianopia, or it may occlude stem arteries such as the M1 segment of the middle cerebral artery. This location causes deep internal capsular as well as surface hemispheric symptoms. Seizures occur in at least 15% of patients, and a similar number appear stunned and mute (stem middle cerebral artery territory and rarely supplementary motor area). A small percentage of patients lose consciousness. Smaller emboli characteristically are cholesterol-platelet-fibrin in origin and give shorter symptoms (minutes). Larger red emboli from the heart clear more slowly (hours). The deficit following an embolus is most severe at onset and then clears over time. Most emboli occur in the middle cerebral artery territory as this vascular territory receives the most

blood flow. There may be evidence at presentation of prior embolic events in other vascular territories. Approximately 30% of cerebral emboli are associated with blood in the cerebrospinal fluid (100 red blood cells/mm³).

The setting for a cerebral embolus is a cardiac arrhythmia of which atrial fibrillation is by far the most common. A patient with atrial fibrillation that has the onset of an acute isolated Wernicke's aphasia has almost certain embolization to the temporo-occipital branch of the inferior division of the middle cerebral artery. Brady-tachy arrhythmia is the second most common arrhythmia causing cerebral embolus (usually during the tachy phase). A myocardial infarction, subacute bacterial endocarditis, artificial heart valve, perforated foramen ovale (20% of patients), aneurysm of the atrial septum, cardiomyopathy, lower extremity thrombophlebitis (paradoxical emboli) and cancer (non-bacterial thrombotic endocarditis) all suggest an embolus as the cause of stroke. Newer transthoracic echo-cardiographic techniques have demonstrated the importance of the aortic arch as a source of emboli (approximately 15 to 25%).

The brain is the first clinical herald of systemic emboli from the heart in the overwhelming majority of patients. Recent diffusion/perfusion magnetic resonance imaging studies confirm the diagnosis particularly if two circulations are involved.

Arteries to artery emboli are smaller than those from the heart and often involve several territories in the circulation. It is not unusual to have a vertebral artery embolus produce lower brainstem, pontine, midbrain, thalamic and cortical symptoms and signs as it move up the posterior circulation. Carotid artery emboli to ophthalmic and central retinal arteries frequently produce amaurosis fugax, a shade descending in the involved eye that lasts for 1–2 minutes. It is coincident with a Hollenhorst plaque at a retinal artery bifurcation. The embolic deficit from a carotid or vertebral artery dissection may be associated with sympathetic ocular paralysis in the former and lateral neck pain in the latter. The clinical deficits caused from these events are from emboli at the site of dissection rather than cerebral blood flow limitation. Embolic disease both from artery to artery and from the heart may occur as a shower with several circulations affected. Characteristically, emboli may affect the same territory with each event, which is thought to be due to laminar flow characteristics of that circulation. In the vertebrobasilar system, the top of the basilar artery is narrowest and is most often occluded from emboli. Rarely, emboli occur in a stepwise fashion that simulates distal field ischemia. The use of transesophageal echocardiography has demonstrated the root of the aorta as a rich source of emboli (15 to 25% of all emboli). Grade V (pedunculated) atherosclerosed material is most likely to cause a clinical problem. The recent application of transcranial Doppler techniques during carotid endarterectomy and other procedures has demonstrated that emboli may be asymptomatic. Those from high frequency "hits" are smaller platelet fibrin emboli while lower frequency

"hits" favor larger clots in the heart. Lacunar disease of the basal ganglia and subcortical white matter is most often due to lipohyalinosis or atheromatous plaques at the origin of the penetrating vessels. If a group of these small penetrating vessels is occluded simultaneously emboli are the most likely cause. Persistent embryological arteries (trigeminal, otic, and hypoglossal) may allow an anterior embolus to infarct the posterior circulation or vice-versa.

Hemorrhagic vascular disease can easily be divided by location, age of the patient, underlying medical disease, iatrogenic factors and clinical features.

In general, hemorrhagic vascular disease occurs when the patient is awake and active. The exceptions may be aneurysms and cavernous hemangiomas that may rupture while the patient is asleep. The usual pattern of cerebral hemorrhage is the apoplectic onset of severe neurologic deficits with gradual headaches. Occasionally, the headache is severe, the patient vomits once (pressure on the floor of the fourth ventricle followed by compensating mechanisms), and there are focal neurologic deficits and loss of consciousness. Specific clinical points allow differentiation of the location and the most likely pathogenesis of the hemorrhage. Hypertensive hemorrhages occur in the setting of sustained hypertension. The most common locations for hypertensive hemorrhages are the basal ganglia (40%), the thalamus (20%), the cerebellum 10%, lobar 10%, the pons 5%, and infrequently the medulla 1%. Hemorrhages in the white matter of the centrum semiovale suggest platelet and clotting disorders. Several areas of hemorrhage in different lobes that have mixed magnetic resonance imaging signals (old and new blood surrounded by a dark hemosiderin ring) are suggestive of cavernous hemangioma. Blood in the suprachiasmatic cistern is often noted with posterior communicating artery, carotid and anterior communicating artery aneurysms. Blood tracking anteriorly between the hemispheric fissures is most characteristic of anterior communicating artery aneurysms. Blood in the Sylvian fissure on one side suggests middle cerebral artery aneurysm. Perimesencephalic prepontine blood in a patient with little or no focal abnormality is probably venous although a small arteriovenous malformation or causative has been reported. Cavernous sinus aneurysms decompress into the sinus and are associated with cranial nerve abnormalities (IIIrd, IVth, VIth). Approximately 50% of aneurysms have a short episode of loss of consciousness at the ictus. A small percentage of patients have seizures. Almost all have electrocardiogram changes. The neck is stiff, and Brudzinski's and Kernig's signs are positive. Frequently hydrocephalus is noted on the initial computed tomography scan. Dural irritation from blood may be associated with tender eyes, a retinal hemorrhage on the side of the lesion (Torsten's syndrome) and sore neck and shoulder muscles (meningeal irritation). Rarely, pain in the lower back is the major manifestation. Irritation of lower back meninges without headache should always raise the suspicion of a spinal arteriovenous malformation. Each aneurysm has its own clinical profile.

Posterior communicating arteries are associated with a pupil involving IIIrd cranial nerve palsy. Anterior communicating artery aneurysms show little focal neurological deficit (weak leg) but prominent personality defects. Middle cerebral artery aneurysms may have a prominent hemiparesis. Carotid aneurysms may be associated with a contralateral hemiparesis and IIIrd cranial nerve palsy. Ophthalmic artery aneurysms cause unilateral visual loss.

Parenchymal vascular malformations most often present with seizures rather than overt bleeding. These emanate from abnormal glial and neuronal tissue within the malformation. Migraine-like headaches are also common. Hemorrhage clearly can present with focal neurologic signs depending on the affected lobe. Arteriovenous malformations are associated with phakomatoses such as Von Hippel-Lindau, Cobb's, Sturge-Weber, Wyburn-Mason, Klippel-Feil-Trenaunay syndromes. There are genetic chromosomal defects with arteriovenous malformations and cavernous hemangiomas (Krit1 gene).

Elderly patients presenting with single or multiple lobar hemorrhages suffer congophilic angiopathy. Gradient Echo magnetic resonance imaging sequences demonstrate prior bleeds because this technique is very sensitive to hemosiderin deposition. Traumatic hemorrhages may be associated with blood in the subarachnoid space, a coup contra coup location (frontal lobe coup and contra coup in occipital lobe) with contusion of the crown of the gyrus. They may be delayed for four to seven days after the injury. If severe, the hemorrhage may be associated with loss of autoregulation, severe cerebral edema and "commotio retinae" (an increased light streak from the retinal blood vessels).

Venous hemorrhages occur in association with sinus thrombosis (particularly the superior sagittal sinus). They present with seizures, headache and focal deficits. They are accompanied by bilateral basal ganglia or thalamic hemorrhages. If cortical, they also are frequently seen in the middle cerebral artery territory. In the setting of pre or post-partum, they frequently present with seizures in a lower extremity that generalizes, associated with bloody spinal fluid. Venous malformations are linear and often connect to a ventricle. They seldom bleed spontaneously but will cause infarction and hemorrhage into the drained territory if they are clipped.

The use of tissue plasminogen activator will cause approximately 6% of hemorrhage into the occluded territory. Hyperextension, the size of the infarcted area and age are risk factors. Transformed hemorrhage which occurs in a previously infarcted area often is petechial but may be massive. Hemorrhage from anticoagulants usually is nonhomogeneous on magnetic resonance imaging scan (swirling effect). Arteriograms following infarction may appear to be hemorrhages.

Twenty percent of patients that have suffered a cerebral hemorrhage from cocaine abuse have an underlying vascular malformation. Rarely, propane ethanolamine and Dexedrine (Dextroamphetamine) may cause cerebral hemorrhage from hypertensive mechanisms.

Hereditary congophilic superficial hemorrhages are noted in Dutch, Swedish and Icelandic patients. Cavernous hemangiomas may be most common in Mexican Americans. The history and physical examination should localize vascular disease. The medical setting and this localization generates the differential diagnosis. Imaging proves the diagnosis, uncovers unsuspected pathology and allows insight into the basic mechanisms that are involved. There is no substitute for the history, physical examination, interpretation of the imaging studies and clinical judgment. The rapid advance of interventional radiological techniques, thrombolytic and possibly neuroprotective agents has made stroke neurology very therapeutic.

The Neurovascular Unit: Outline of Some Mechanisms Common to Stroke

The concept of a neurovascular unit composed of endothelial cells, a basal lamina, pericytes, a cellular matrix and neurons acting in concert to maintain central nervous system's homeostasis in health and disease are now well established. Clinical differential diagnosis is buttressed by a mechanistic approach which is rapidly evolving to an understanding of genetic, immune and molecular causes of pathology within the neurovascular unit. Major aspects of these mechanisms will be referenced as the diseases and their differential diagnoses are discussed.

Neurovascular Unit

The neurovascular unit is classically composed of endothelial cells, astrocytes, pericytes, the basal lamina and the extracellular matrix that surrounds the cerebral microvasculature. It was originally thought to primarily couple local cerebral glucose metabolism (increased by neural activity) to local cerebral blood flow. More recently it has been studied in regard to its role in brain homeostasis and physiology by its regulation of the blood-brain barrier. Recent anatomical and experimental studies support the existence of an extended neurovascular unit that includes pericytes, microglia and a specialized cellular compartment, the endothelial glycocalyx.

The glycocalyx has the following features:

1. It is located on luminal surfaces of endothelial cells of cerebral arteries, veins and cerebral capillaries
2. It is composed of proteoglycans, glycoproteins and glycolipids in a negatively charged network (platelets are also negatively charged)
3. It is an irregularly shaped layer of 50–100 nm thick that coats the vascular lumen
4. It contains enzymes and proteins that are involved in plasma and vessel wall integrity and homeostasis

The enzymes and proteins contained are:

1. Growth factors
2. Chemokines

3. Apolipoproteins
4. Lipoprotein lipase
5. Extracellular superoxide dismutase
6. Angiotensin converting enzyme
7. Antithrombin III
8. Endothelial nitric oxide synthase

The major functions of the glycocalyx are:

1. Cell – cell recognition
2. Modulation of red cell volume in capillaries
3. A permeability barrier that:
 - a. Decreases leukocyte adhesion which is pivotal in blood-brain barrier penetration
 - b. Inhibits coagulation
4. Protects vascular walls from the direct effects of blood flow (shear stress) by regulating local nitric oxide release
5. Modulates the filtration of interstitial fluid from capillaries into the interstitial space

Disruption of the glycocalyx causes:

1. Atherosclerosis
2. Vascular wall inflammation
3. Increase in vascular permeability
4. Inability to protect against fluid shear stress

Blood-Brain Barrier

A major function of the neurovascular unit important in ischemic/hypoxic injury from stroke is its regulation of the passage of proteins and cellular elements from the intravascular space into the brain parenchyma through the blood-brain barrier. This function is dependent on the integrity of tight junction proteins between endothelial cells and the functional interaction between these endothelial cells, their basal lamina and perivascular astrocytes. Adherens junctions are primarily formed by vascular endothelial – cadherin proteins that couple with catenin proteins which effects cell – cell adhesion by their connection to the actin cytoskeleton. The transmembrane components of tight junctions contain junctional adhesion molecule (JAM-1), occludin and claudin proteins that are linked by the zonula occludin (ZO-1 and ZO-2) proteins to the cytoskeleton. The tight junctions primarily determine blood-brain barrier permeability and the high electrical resistance of the endothelium. The basement membrane separates endothelial cells from the end feet of astrocytes, pericytes and neurons. Pericytes are opposed to endothelial cells opposite to tight junctions where they secrete trophic substances (paracrine function) in conjunction with perivascular astrocytes that strengthen and help to maintain the blood-brain barrier. Pericyte processes cover a significant portion of the capillary wall. Their location allows them to phagocytize red blood cells that may extrude from disrupted tight junctions during pathological states.

The basement membrane is composed of extracellular matrix proteins that include laminar, collagen IV, fibronectin and perlecan. Approximately 95% of the basal lamina of cerebral capillaries is encased by astrocytic end-feet processes

that also contain the osmoreceptor aquaporin 4 and inwardly rectifying potassium channels (K_{IR}). Their proximal poles are in contact with dendritic synapses of neurons. There is accumulating evidence that boutons from neuronal axons containing vasoactive neuropeptides are also in close contact with astrocytic end-feet and the basal lamina.

The adhesion of endothelial cells and astrocytes to the basal lamina depends on integrins and their ligands on the matrix. Integrins also activate cellular signaling pathways under pathologic conditions and are a component of endothelial cell and perivascular astrocyte regulation. Astrocytic secreted factors are important for: 1. the attachment of end-feet to the basement membrane; 2. the distribution and maintenance of interendothelial tight junction proteins. The integrin subunit $\beta 1$ is located in both endothelial cells and astrocytes whereas the $\alpha 2 \beta 4$ subunits are on astrocytic end-feet processes and interact with lamin-1 and -5 of the basal lamina. The interaction of perivascular astrocytes and the basal lamina is also important in determining the permeability of the blood-brain barrier. Disruption of the astrocytic end-feet processes from the basal lamina decreases transendothelial electrical resistance of the neurovascular unit and increases the permeability of the blood-brain barrier.

Immune Components of the Neurovascular Unit

The importance of the immune system in the neuropathology of ischemic stroke is evident at many levels. It orchestrates the inflammatory response, permeability of the blood-brain barrier, blood flow in the microcirculation and aspects of recovery. Immune surveillance is accomplished by circulating T- and B-cells in the glycocalyx as well as perivascular macrophages and the microglia. The cytokine tumor necrosis factor-like weak inducer of apoptosis (TWEAK) and its receptor fibroblast growth factor-inducible 14 (Fn14) are pivotal in the regulation of the endothelial cell – basement membrane – astrocyte interface. This component of the neurovascular unit is a major component of physiologic response of the blood-brain barrier in the ischemic hypoxic injury of stroke. TWEAK binding to Fn14 receptor activates intracellular NF κ B (nuclear factor kappa-light-chain-enhancer of activated B-cells), extracellular signal-regulated kinases and c-JUN N-terminal kinases (JNKs) signal transduction pathways that directly affect the composition of the basal lamina and the function of astrocytic end-feet processes and the basement membrane.

The functional adaptations of the neurovascular unit are effected by 1. cell – cell communication; 2. cell – extracellular matrix interaction; and 3. paracrine cell – cell communication.

The principal functions of the neurovascular unit:

1. Couples local cerebral blood flow to neuronal metabolic rate of glucose utilization (neuronal activity)
2. Blood-brain barrier permeability
3. Transport processes
4. Neuroimmune functions

5. Astrocytic interface between endothelial cells and neurons
The microvascular changes and neuronal injury evolve simultaneously and that suggests there is a coordinated response to ischemia.

Neurovascular Unit Pathology During Hypoxia and Ischemia

1. Early changes after ischemia/hypoxic injury within the neurovascular unit:
 - a. Lack of glucose and oxygen to the affected territory leads to:
 - i. Failure of the sodium/potassium ATPase membrane pumps on cellular elements in the ischemic territory (reflected by bright images on diffusion-weighted magnetic resonance imaging sequences)
 - b. Within 2 hours of experimental middle cerebral artery ischemia, neurons that are most distant from a proximate microvessel (about 30 μm radius) are heterogeneously affected and demonstrate DNA damage
 - c. Down regulation and loss of $\beta 1$ -integrin subunits $\alpha 1$, $\alpha 3$, $\alpha 6$ from endothelial cells; $\alpha 6\beta 4$ subunits from astrocytes and $\alpha \beta$ -dystroglycan from astrocyte end-feet occur most intensely in the ischemic core
 - d. In hypoxic tissue, immediate early response genes are induced that encode:
 - i. Secreted proinflammatory cytokines/chemokines
 - ii. Cytoplasmic enzymes – the pivotal inducible cyclooxygenase-2
 - iii. Inducible transcription factors
 - iv. Hypoxia-inducible factor HIF-1 α
 1. A specific transcription factor specifically activated by hypoxia that upregulates genes important for cell survival under hypoxic conditions that includes:
 - a. Oxygen dependency
 - b. Erythropoietin
 - c. Transferrin
 - d. Heme oxygenase
 2. Glucose transport
 - a. Glucose transporter-1
 3. Glycolysis
 - a. Lactate dehydrogenase A
 4. Angiogenesis:
 - a. Vascular endothelial growth factor
 - b. Inducible nitric oxide synthase
 - c. Angiopoietin-2
 - d. Fibroblast growth factor
 - v. HIF-1 α induces four major families of proteases in ischemic tissue (experimental studies) that are expressed on microvessels and neurons:
 1. Latent matrix metalloproteinase (pro-MMP)-2 and MMP-9:
 - a. MMP-2 associated with neuronal injury
 - b. MMP-9 associated with hemorrhagic transformation
 2. Cathepsin L (a cysteine protease) involved with degradation of perlecan and laminin of the microvessel basement membrane
 3. Heparanase
 4. Urokinase plasminogen activator binds to its receptor. These proteases degrade laminin collagen IV, cellular fibronectin and perlecan that are a component of matrix-adhesion receptors and also have major effects on basement membrane integrity
 5. In reperfusion injury, the early opening of the blood-brain barrier is effected by HIF-1 α -induction of the furin gene which induces furin convertase. This converts the constitutive enzymes pro-MT-MM2 (metalloproteinase) to its active form, MMP-2, which increases the permeability of the blood-brain barrier. This occurs during the first 12 to 24 hours post injury. At 24 to 48 hours, the permeability of the blood brain barrier is irreversibly due to the induction of MMP-3 and MMP-9 during the inflammatory responses. The induction of COX-2 (cyclooxygenase-2) is also important in the late irreversible changes of the blood-brain barrier during late reperfusion injury
 - vi. HIF-1 α and inflammation:
 1. An initial trigger of inflammatory gene transcription that produces:
 - a. Proinflammatory cytokines
 - b. Chemokines
 - c. Eicosanoids from endothelial cells, pericytes, astrocytes and perivascular macrophages
 2. Recruitment of peripheral inflammatory cells
 3. Recruited activated leukocytes releases free radicals, metalloproteinases and eicosanoids which damage the endothelium and disrupt the blood-brain barrier
 4. Local cerebral blood flow adaptation to local metabolic rate of glucose utilization:
 - a. Early studies demonstrated that the production of protons from neurologic activity dilated capillaries and arterioles by ligand binding to acid sensing receptors
 - b. Recent studies suggest that projections from basal forebrain neurons to cortical microvessels and surrounding astrocytes are important. These projections release vasoactive neuropeptides onto microvascular endothelial cells, smooth muscles cells and astrocytes that correlate local cerebral blood flow to neuronal activity
 - c. Intracellular Ca^{2+} concentration in astrocytes, through Ca^{2+} sensitive phospholipase

A₂ activated receptors initiate vasoconstriction or dilatation by activation of arachidonic pathways regulated by nitric oxide. Smooth muscle cells in arterioles and pericytes in capillaries effect constriction or dilatation in response to vasoactive mediators

5. Cortical spreading depolarization

- a. Is a slowly propagation wave of neuronal and glial depolarization that occurs in tissue affected by ischemia. It can be produced by endothelin-1 (a vasoconstrictor) or potassium ion applied to the cortex. Its exact mechanism is not entirely clear but in ischemia there may be an imbalance between vasoconstriction and dilatation (greater vasoconstriction) that causes spreading depolarization. In stroke there is little spread beyond ischemic tissue which differs from migraine. Under normal circumstances the neurovascular unit responds to increased neuronal activity by reactive hyperemia while during ischemia there may be vasoconstriction (inverse neurovascular coupling) with consequent neuronal injury

6. Metabolic and electrical processes during ischemia:

- a. Generation of free radicals
- b. Spreading depolarization
- c. Calcium mediated cell death
- d. Impaired mitochondrial function
- e. Decreased protein phosphorylation, synthesis and increased proteolysis
- f. Activation of lipolytic pathways

Late Neurovascular Unit Processes in Ischemia

1. Occlusion of nutrient microvessels occurs heterogeneously in ischemic territories which is dependent upon fibrin formation, platelet activation and endothelial cell adhesion of polymorpholeukocytes
2. Hemorrhagic transformation develops following degradation of the microvasculature basal lamina matrix from induced proteases
3. Dysfunction of the blood-brain barrier causes:
 - a. Changes of the brain extracellular milieu which causes an increase in potassium concentration and decrease in calcium and magnesium concentrations that increase neural and network excitability
 - b. A parenchymal influx of large size molecules (serum proteins) that cause water influx and edema. Albumin may be selectively transported into astrocytes to trigger transcriptional changes that also increase neuronal hyperexcitability
 - c. Astrocytic signaling from serum protein exposure triggers transcriptional changes that cause down regulation of inward rectifying potassium channels (K_{ir}4),

aquaporin 4 water channels, gap junction proteins and glutamate transporters. Inability of astrocytes to buffer potassium and glutamate leads to N-methyl-D-aspartate activation and neuronal depolarization that leads to neuronal death from excitotoxicity. Entrance of thrombin into the brain from a dysfunctional blood-brain barrier also increases neuronal excitability

- d. Angiogenesis and remodeling orchestrated by vascular endothelial growth factor is initiated by loss of microvascular integrity and the degradation of the vessel lamina matrix. The dysfunctions of angiogenesis and remodeling of the neurovascular unit after ischemic stroke are:
 - i. Increased blood-brain barrier permeability
 - ii. Dysfunctional neurovascular coupling
 - iii. Immune dysfunction with leukocyte adhesion and parenchymal infiltration
 - iv. Thrombosis in the microvasculature
- e. Liquefaction and cavitation of infarcted tissue

Components of the physiology and neuropathology of the neurovascular unit are evident in all ischemic and oxygen derived brain tissues. As understanding of the molecular basis of these events accrues, there will be advances in stroke therapy.

Risk Factors for Ischemic Stroke

Introduction to Modifiable Risk Factors

The Framingham study illustrated the first epidemiological evidence that identified specific risk factors associated with cardiovascular disease. It found a correlation between hypertension, deficient glucose tolerance, obesity, cigarette smoking and atrial fibrillation. The Northern Manhattan Stroke Study and the Honolulu Heart study corroborated these findings and added alcohol and inflammation as added risk factors. The treatment of risk factors prevents the first and subsequent strokes and is responsible for the decline in incidence of strokes in Western countries.

Non-Modifiable Risk Factors for Stroke

The primary non-modifiable risk factors are male sex, age, low birth weight, ethnicity and family history.

General Characteristics

1. The combined risk of fatal and non-fatal stroke increases by:
 - a. Men: 9%/year
 - b. Women: 10%/year
2. Incidence of ICH increases with age from <45 to >85
3. The Framingham Heart Study
 - a. The lifetime risk for stroke is 1 out of 6 for middle aged adults

Low Birth Weight

1. Low birth weight is associated with stroke in later life:
 - a. Stroke mortality rates among adults in England and Wales have been shown to be higher in adults with low birth weights
 - b. An odd ratio of 2.16 ($p < .001$) for low birth weight babies for the risk of stroke, MI or heart disease by 50 years of age
2. The association of low birth weight has not been proven to be causal
 - a. There are geographical differences in this epidemiology
 - b. Mothers may have been socially and economically disadvantaged

Race/Ethnicity

1. There are epidemiologic studies that support racial and ethnic differences in the risk of stroke
 - a. Hispanic/Latin Americans (some) and Black patients have higher incidence of all stroke types than Caucasians
 - b. Younger and middle-aged Blacks have a higher risk of SAH and ICH than Caucasians of similar age
 - c. Blacks had an incidence of all stroke type 38% higher than Caucasians (ARIC study)
 - d. Black patients have a higher prevalence of prehypertension, obesity and diabetes mellitus
 - e. Stroke risk may also have contributions from:
 - i. Social determinants
 - ii. Geography
 - iii. Language
 - iv. Access to healthcare
 - v. Nativity
 - vi. Neighborhood characteristics

Genetic Determinants

1. A positive family history increases the risk of stroke approximately 30%
2. A stroke prior to 65 years of age is associated with a three times increase in risk of stroke in children (Framingham study)
3. Monozygotic twins have a 1.65 higher risk of stroke than dizygotic twins
4. Genome-wide common variant single nucleotide polymorphisms (SNP) data heritability:
 - a. Cardioembolic (32.6%)
 - b. Large vessel disease (40.3%)
 - c. Small vessel disease (16.1%)
5. Chromosomal variants:
 - a. Variant on 9p21:
 - i. Adjacent to tumor suppressor genes CDKN2A and CDKN2B are associated with large vessel stroke and MI
 - b. Variants on 4p25 and 16q22:

- i. Are adjacent to genes involved in cardiac development:
 1. PITX2
 2. ZFHX3
- ii. May be associated with atrial fibrillation and ischemic stroke (primarily cardioembolic)
- c. Patients with European ancestry:
 - i. Large vessel stroke association:
 1. Locus in 6p21.1 and 7q21
 2. Near HDAC9 gene that encodes a protein in histone deacetylation
- d. Small vessel stroke in Asians:
 - i. Associated with PRKCH gene:
 1. Encodes a protein kinase

Defined Genes and Stroke

1. CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy)
 - a. NOTCH 3 gene
2. CARASIL (Cerebral Autosomal Recessive Arteriopathy with Subcortical Infarction and Leukoencephalopathy)
 - a. Autosomal recessive
3. Retinal vasculopathy with cerebral leukodystrophy
 - a. TREX1 gene
4. Collagen type IV (COL4A1 and A2) gene
 - a. Ischemic or hemorrhagic stroke
 - b. HANAC (Hereditary Angiopathy with Nephropathy, Aneurysms, and muscle Cramps)
5. Fabry's disease
 - a. Lysosomal α -galactosidase A deficiency
6. Autosomal dominant coagulopathies:
 - a. Protein C deficiency
 - b. Protein S deficiency
 - c. Factor V Leiden mutation
 - d. Prothrombin mutations
7. Lupus anticoagulant and anticardiolipin antibody
 - a. Familial in approximately 10% of patients
8. Autosomal recessive mutations in
 - a. V,VII,X,XI and XIIIth cranial nerves
9. A familial component of approximately 10 to 20% is seen in:
 - a. Moyamoya syndrome
 - b. Fibromuscular dysplasia
10. Autosomal dominant polycystic kidney disease
 - a. Intracranial aneurysm occur in approximately 8% of patients
11. Ehlers-Danlos syndrome (type IV):
 - a. Dissection of extracranial arteries
 - b. Dolichoectasia
12. Marfan's syndrome:
 - a. Fibrillin gene mutations
 - b. Dissection of extracranial arteries
 - c. Dolichoectasia
13. Cerebral cavernous malformations:
 - a. KRIT (CCM1)

- b. Malscavernin (CCM2)
- c. PDCD10 (CCM3)
- 14. Inherited cerebral angiopathy
- 15. Amyloid precursor protein gene:
 - a. Cystatin C
 - b. Gelsolin
 - c. BR12
 - d. D

Risk Factors That Predict Stroke

Independent Factors for Stroke Risk Prediction

1. Age
2. Systolic blood pressure
3. Hypertension
4. Cardiovascular disease
5. Myocardial infarction
6. Angina or coronary insufficiency
7. Congestive heart failure
8. Intermittent claudication
9. Atrial fibrillation
10. Left ventricular hypertrophy on ECG

Atrial Fibrillation (AF)

AF causes substantial morbidity. After adjustment for age, hypertension, smoking, diabetes, congestive heart failure, valvular heart disease, stroke and TIA, the risk of death was 1.5 times greater in men and 1.8 times greater in women with AF. In patients without valvular heart disease and pre-existing heart disease AF confers twice the mortality in both sexes.

The thrombogenic effects of AF are: 1. stasis in the left atrium; 2. abnormalities of vessel walls; 3. changes in clotting factors. AF accounts for approximately 15% of strokes. Anticoagulation is recommended for all AF patients with moderate or high risk for ischemic stroke or TIA that have no contraindications. The CHADS₂ scoring system helps to determine moderate to high risk persons that would benefit from anticoagulation therapy. One point is assigned for "C" congestive heart failure, "H" for hypertension; "A" for age >75 years and "D" for diabetes. Two points are assigned for a history of stroke or TIA. Patients that have a score of > or equal to 2 are at a high risk of stroke (1.9–7.65) per year. Refinements were made in the scoring system (CHA₂DS₂ – VAS_C) to evaluate patients from 0–1. Invasive fibrillation ablation procedures, Cox maze and catheter based ablation reduce recurrence approximately 70%. Newer anticoagulants are being investigated. The Framingham Heart Study score to predict 5 year risk of stroke alone or stroke or death in patients with recent onset of AF scores advancing age, female gender, and systolic blood pressure prior to stroke/TIA, diabetes and smoking. Stroke rates in low risk groups were 1.1 (14% of low risk cohort) and 1.5 (30% of cohort) per 100 person years. Warfarin has demonstrated a 64% stroke risk reduction relative to 22% for antiplatelet therapy.

Secondary Factors for Stroke Risk Prediction

Hypertension

Lowering of systolic blood pressure (BP) by 10 mm Hg may decrease stroke risk by 30–40%. Recent studies have drawn attention to blood pressure variability as an additional risk factor beyond mean or usual BP. Blood pressure is circadian and decreases 10–20% during sleep. An abnormal BP decline during sleep ("extreme dipping") or a rise in nocturnal BP ("reverse dipping") have been correlated with silent infarctions and clinical ischemia. Orthostatic hypotension also causes stroke. It has also been suggested that reduction in blood pressure variability is important in hypertensive control to decrease stroke risk.

Diabetes Mellitus

Approximately one third of patients with ischemic stroke have diabetes and insulin resistance is seen in 50% of patients with TIA or ischemic stroke. The combination of diabetes and hypertension doubles stroke risk. There is no strong data that treatment of hyperglycemia or management to a specific glycosylated hemoglobin level reduces stroke risk.

Dyslipidemia

The correlation of total cholesterol or low-density lipoprotein cholesterol (LDL-C) to ischemic stroke is not entirely clear. High serum cholesterol appears to be correlated with ischemic stroke and inversely correlated with hemorrhagic stroke. Strong evidence in favor of the deleterious effects of high LDL-C is the effect of lipid lowering agents. Statin treatment decreases non-fatal first ischemic strokes, a 21% decrease per 1.0 mmol/dL (39 mg/dL) of LDL-C. The evidence is equivocal that statin use increases the incidence of hemorrhagic stroke.

Smoking

Cigarette smoking is a major modifiable risk factor. It is associated with progression of atherosclerosis, endothelial dysfunction, hypercoagulability and an inflammatory state. Smokers have a 2-fold risk of ischemic stroke and subarachnoid hemorrhage which is dose-responsive and declines with cessation. The process evolves over 20 years (decreased risk at least in women).

Alcohol

There is a dose-response relationship between intracerebral and subarachnoid hemorrhage to alcohol consumption. There is a "J" shaped association for ischemic stroke. The benefits of mild alcohol consumption are: 1. decrease of fasting insulin levels; 2. increased insulin sensitivity and improved lipid profile; and 3. increased adiponectin plasma levels.

Diet

Hypertension is reduced by weight loss, decreased sodium and increased potassium intake. The Dietary Approaches to

Stop Hypertension (DASH) which is low in saturated and total fats and rich in fruits, vegetables and low-fat dairy products decreases hypertension and reduces components of the metabolic syndrome. This diet also improves the lipid profile, lowers LDL-C and improves insulin sensitivity and may reduce stroke risk. There is evidence that a Mediterranean diet maybe beneficial in stroke is but it is less clear. Consumption of fish in older patients has been correlated with a lower prevalence of subclinical infarcts and MRI white matter hyperintense lesions.

Physical Activity

Physical activity may reduce the risk of both ischemic and hemorrhagic strokes. The beneficial effects of aerobic exercise are blood pressure reduction, weight loss and improvement of the metabolic syndrome.

Obesity

The body mass index (BMI) defines obesity. A BMI (body weight (kg) divided by the square of height (m²) between 18.5–24.9 (kg/m²) is normal. The risk of stroke-related mortality increases linearly when the BMI is greater than 25 kg/m². There is an obesity paradox where an increased BMI has been protective for both ischemic stroke and intracranial hemorrhage. Weight control has been associated with lowered blood pressure and increased insulin sensitivity which reduce the risk of stroke.

Probable Secondary Factors for Stroke Risk Prediction

The Metabolic Syndrome

The metabolic syndrome consists of abdominal obesity, insulin resistance, hypertriglyceridemia, low levels of HDL-C and hypertension. The criteria for the syndrome have been associated with an independent risk factor for ischemic stroke.

Sleep Disordered Breathing

Obstructive sleep apnea, which affects 5–15% of the general population, is the most common form of sleep disordered breathing seen in stroke patients. Cheyne-Stokes respiration and central sleep apnea are also frequently encountered. Sleep disordered breathing maybe associated with stroke because of associated obesity, hypertension and intermittent hypoxemia from obstructive sleep apnea. It also is associated with pulmonary vasoconstriction and consequent increased pulmonary artery pressure, diastolic cardiac dysfunction and atrial fibrillation. Obstructive sleep apnea patients have a higher recurrence rate of AF following cardioversion. CPAP therapy has been shown to decrease the incidence and mortality of stroke. Oxygen and mechanical ventilation have been utilized for central sleep apnea and central hypoventilation.

Lipoprotein (a)

Lipoprotein (a) is composed of a LDL-like particle and apolipoprotein (a). Its plasma concentration is primarily con-

trolled by the apolipoprotein gene on chromosome 6q26-27.

Apo(a) is synthesized by the liver. Its structure is similar to plasminogen and tissue plasminogen activator (tPA). It stimulates secretion of PA inhibitor-1 and competes with plasminogen for its binding site – both of which decrease fibrinolysis. It may also predict a risk of early atherosclerosis. There is an independent association of lipoprotein (a) with stroke and carotid atherosclerosis. It is not clear if lowering lipoprotein (a) levels independently lowers stroke risk.

Hyperhomocysteinemia

High homocysteine levels have been associated with myocardial infarction, atherosclerosis and stroke. Homocysteine levels are determined by genetic background, cystathionine β -synthase and methylenetetrahydrofolate reductase allelic variants, diet, folic acid, vitamin B level and renal function. Homocysteine increases thrombosis and is associated with venous thromboembolism. It is less clearly associated with atherosclerosis as demonstrated by studies of carotid intima-media thickness.

Clotting Disorder

Hereditary clotting defects such as prothrombin 20210 mutation, protein C and S dysfunction, factor V Leiden and antithrombin deficiency cause venous thrombosis rather than arterial stroke. There is evidence that they are relevant in young stroke patients. Immune-mediated clotting disorders include anticardiolipin antibodies, lupus anticoagulant and anti- β_2 glyco-protein-1 antibody. The antiphospholipid syndrome has multiple manifestations due to venous arterial and small vessel thrombosis. Antiphospholipid antibodies activate endothelial cells, monocytes and platelets with overproduction of tissue factor and thromboxane A₂. Lupus anticoagulant may be the strongest predictor of the ensuing APL syndrome. There is conflicting evidence in regard to anticardiolipin antibody elevation and ischemic stroke. Risk of subsequent stroke or a differential response to aspirin or warfarin has not been correlated with anticardiolipin antibodies. Lupus anticoagulant may be significant in young women.

Atherosclerosis

Atherosclerosis is the major mechanism underlying both thrombotic and embolic stroke. It is a pathologic process that affects arteries and is characterized by: the formation of plaques that consist of modified lipids, inflamed smooth muscle cells, endothelial cells, leukocytes and foam cells. An atherosclerotic plaque has a necrotic core and a fibrin cap. Regions of involved arteries calcify. Low-density lipoprotein (LDL) is a major kinetic and metabolic component of the process. Immune and inflammatory mechanisms have been shown to be increasingly important in both initiation and progression of atherosclerosis. Endothelial dysfunction, lipid

metabolism and lipid retention as well as reactivity to self-antigens are pivotal. Atherosclerosis is a chronic inflammatory condition.

Definition of Factors That Affect the Vascular Wall

Wall Shear Stress

1. Shear stress is the component of stress coplanar with a material cross section
2. Arises from the force vector component parallel to the cross section. Normal stress arises from the force vector perpendicular to the material cross section
3. Important for adaptation of endothelial cells, the initiation of atherosclerotic lesions and the induction and growth of aneurysms

Turbulent Flow

1. Turbulent flow is a flow regime characterized by chaotic property changes
2. Laminar flow loses kinetic injury due to the action of fluid molecular velocity
3. Import function for endothelial cell, adherences molecules and remodeling of arterial walls

Lipid Core

1. Core region of atherosclerotic plaques
2. Composed of lipid deposition with absence of cells and matrix proteins
3. Arises early in plaque formation after the induction of a fatty streak
4. A major detrimental development in ischemic vascular disease and emboli

Fibrous Cap

1. A layer of fibrous connective tissue which is thicker and less cellular than the normal intima
2. Surrounds the lipid core of atherosclerotic plaques
3. Composed of collagen and elastin, macrophages, smooth muscle cells, foam cells and lymphocytes
4. With expansion of the lipid core it ulcerates and ruptures causing at site thrombosis and distal embolization

Vascular Smooth Muscle Cells

1. Primary function is contraction and relaxation
2. They expresses contractile proteins, ion channels and signaling molecules that regulate contraction
3. Contraction:
 - a. Initiated by Ca^{2+} calmodulin phosphorylation of the light chain of myosin
 - b. Removal of Ca^{2+} from the cytosol and stimulation of myosin phosphatase initiates relaxation
4. α_1 receptors bind norepinephrine and cause vasoconstriction; α_2 receptor stimulation cause vasoconstriction. β_2 receptor agonism causes vaso-dilatation

Macrophage

1. Precursors are monocytes
2. Engulf apoptotic cells and pathogens as well as secreting effector molecules
3. They exhibit plasticity and adopt pro or anti-inflammatory phenotype dependent on environmental signals. Different subsets contribute to tissue homeostasis or disease pathogenesis

Glycoprotein

1. Proteins that contain oligosaccharide chains that are covalently attached to polypeptide side-chains
2. Glycosylation is the process that attaches the carbohydrate to the protein
3. Secreted extracellular proteins and their extracellular segments are often glycosylated
4. They are important integral membrane proteins which are important in cell-cell interactions
5. Functions include:
 - a. As transport molecules
 - b. Immunology
 - c. Cell attachment recognition sites
 - d. Receptor
 - e. Affect protein folding
 - f. Hemostasis and thrombosis

Oxidized Low Density Lipoprotein Cholesterol

1. Oxidative modification of low density lipoproteins are important for foam cell formation and possibly the initiation or acceleration of atherosclerosis
2. Increased plasma low-density lipoprotein levels cause an increased rate of entry of low density lipoprotein into the intima. Low density lipoprotein undergoes oxidative modification by endothelial, smooth muscle cells or macrophages
3. Oxidized low density lipoproteins are recognized by scavenger receptors and can give rise to foam cells
4. Effects of oxidized low density lipoprotein:
 - a. Cytotoxic to endothelial cells in culture
 - b. Inhibit vasodilation by nitric oxide
 - c. Mitrogenic for smooth muscle cells and macrophages
 - d. Immunogenic

Endothelial Cell Adhesion Molecules (CAMs)

1. Cell adhesion molecules are located on the cell surface and bind with other cells such as the extracellular matrix
2. They are trans-membrane proteins with three domains:
 - a. An intracellular domain that interacts with the cytoskeleton
 - b. Transmembrane domain
 - c. Extracellular domain that interacts with cell adhesion molecules of the same kind (homophilic binding or with other endothelial cell adhesion molecules, heterophilic binding) as with the extracellular matrix

d. The important endothelial cell adhesion molecules for vascular disease are calcium-dependent:

i. Integrins:

1. A major class of receptor within the extracellular matrix
2. Mediate cell-extracellular matrix interactions with collagen, fibrinogen, fibronectin and vitronectin
3. Essential links between the extracellular environment and intracellular signaling pathways

ii. Cadherins:

1. Homophilic Ca^{2+} dependent glycoproteins
2. Concentrated at intermediate cell junctions
3. Link to the actin filament network through linking proteins (catenins)
4. Their extracellular domains are important for cell adhesion

iii. Selectins:

1. Heterophilic endothelial cell adhesion molecules
2. Bindmycins
3. E-selectin (endothelial); L-selectin (leukocyte); P-selectin (platelet)
4. Pivotal in transmigration of inflammatory cells through cerebral blood vessels into brain parenchyma

Monocytes

1. Circulating blood leukocytes that are pivotal in the inflammatory response as part of the innate immune response
2. Functions include:
 - a. Replenishment of resident macrophages
 - b. Respond to chemokines from the site of inflammation and then differentiate/divide into macrophage and dendritic cells as part of the immune response
 - c. Produced in the bone marrow from hematopoietic stem cells
 - d. In tissue, mature into different type of macrophages. Approximately 50% are held in reserve in the spleen

Foam Cell (Lipid Laden Cells)

1. Lipoprotein aggregate within the intima of blood vessels
2. Macrophages and endothelial cells generate free radicals that oxidize lipoproteins
3. Macrophages engulf the oxidized low-density lipoproteins by endocytosis utilizing scavenger receptors
4. Oxidized low density lipoproteins in macrophages and other phagocytic cells become foam cells which form the fatty streaks of the atheroma in the tunica intima during the atherosclerotic process

Internal Elastic Lamina

1. Thicker in arteries than arterioles and very thin in veins
2. Separates the intima and media of an artery wall
3. A restrictive barrier to macromolecular permeability

4. Holes within the internal elastic lamina allow for permeability of diffusible vasoactive molecules and the interface of endothelial cell projections with the smooth muscle of the vascular wall

5. Smooth muscle cells secrete elastin that forms sheets or lamellae which increase with age and form the internal elastic lamina

External Elastic Lamina

1. Found in the tunica adventia
2. The lamina is composed of collagen fibers secreted by fibroblasts
3. The external elastic lamina in at the inner boundary of the tunica adventia

Cholesterol Crystallization (Transformation)

1. Cholesterol crystallizes as it accumulates in the vascular wall
2. Transforms from a liquid to a solid state and expands
3. Expansion of the crystals is a mechanism of vulnerable plaque disruption
4. Cholesterol crystals induce inflammation in the arterial wall

Cholesterol Crystals

1. Trigger for inflammation in blood vessel walls
2. Activate "inflammasome" complex within immune cells that release inflammatory mediators (chemokines and cytokines)
3. Activates the innate immune system

Cholesterol Crystal Embolization

1. Refers to embolization of the contents of a ruptured atherosclerotic plaque from a more proximal larger-caliber artery to distal small to medium-sized arteries
2. End organ damage is both by ischemia and the induced inflammatory response
3. Systemic vessel embolization (cholesterol embolization syndrome) is characterized by showers of microemboli over time
4. Arterio-arterial thromboembolism is usually characterized by an abrupt release of emboli
5. Cholesterol emboli in the central nervous system often manifest as amaurosis fugax (fleeting blindness from retinal arterial occlusion by a Hollenhorst plaque) or an ischemic lesion in the cerebral circulation
6. Usual size of emboli 100–200 μm

Arterial Spasm (Cerebral)

1. Diffuse or focal narrowing of cerebral blood vessels
2. The pathophysiology is complex and not fully understood but includes molecular mechanism that involve smooth muscle contraction, endothelial dysfunction, and inflammatory changes

Plaque Histology

1. Type I
 - a. An increase of macrophages with scattered foam cells
2. Type II
 - a. Layers of macrophage foam cells and lipid-laden smooth muscle cells that constitute fatty streaks on the artery luminal surface
3. Type III
 - a. Lipid laden cells with scattered extracellular lipid droplets
 - b. Disruption of smooth muscle cells
 - c. Extracellular lipid
 - d. Intermediate stage between type II and type IV lesions
4. Type V
 - a. Contains a lipid core and layers of fibrous connective tissue
 - b. Calcification of a type V lesion is classified as Type V
5. Type VI
 - a. Contains a lipid core with a fissure, hematoma and thrombosis with minimal lipid as calcium

Adaptive (Blood Vessel Wall)

1. In vitro studies demonstrate:
 - a. Stretch may affect cell proliferation
2. Smooth muscle cells and endothelial cells also demonstrate proliferation
3. There may be a phenotypic switch in smooth muscle cells from contractile cells to synthetic cells
4. Vascular remodeling is an adaptive response to variations in wall shear stress and hemodynamic factors
5. A redistribution of the structural components of the ECM has been shown experimentally that involves up-regulation of metalloproteinase-2 and its enzymatic activity

Type I and Type III Collagen

1. Type I collagen is the most abundant collagen:
 - a. Alpha-1 type, collagen is a protein encoded by the COL1A1 gene
 - b. Component of the tunica media of cerebral vessel walls and the internal and external elastic lamina
 - c. Mutations in the COL1A1 gene are associated with Ehlers-Danlos syndrome, osteogenesis imperfecta and osteoporosis
2. Collagen Type III:
 - a. Encoded by COL3A1 gene on chromosome 2
 - b. Distributed in extensible connective tissues, skin, lungs and the vascular system
 - c. It is a fibrous scleroprotein
 - d. Mutation are associated with Ehlers-Danlos type IV and aortic and arterial aneurysms

Caspase

1. Cysteine dependent aspartate-directed proteases are a family of cysteine proteases
2. Major functions:

- a. Programmed cell death (apoptotic caspases)
 - i. Initiate caspases that cleave inactive proforms of effector caspases (CASP2, CASP8, CASP9, CASP10)
 - ii. Effector caspases (CASP3, CASP6, CAS7) that cleave other protein substrate within the cell as a component of the apoptotic process
 - iii. Maturation of red blood cells and myoblasts
 - iv. Maturation of lymphocytes

NLRP3

1. A cyto cytosolic protein complex important for early inflammatory responses
2. Processes interleukin-1 β (IL-1 β) to its active form
3. Activates Caspase-1 pathway

Interleukin-1 β

1. A cytokine protein that is cleaved by Caspase-1 to activate the protein
2. Produced by activated macrophages
3. Functions:
 - a. Mediator of the inflammatory response
 - b. Apoptosis
 - c. Cell proliferation
 - d. Induces cyclooxygenase-2 in the CNS

Mechanism of Factors That Affect the Vascular Wall*Lipoprotein Accumulation in the Artery Wall*

1. LDL is rapidly transported across an intact endothelium and is trapped by fibers and fibrins secreted by artery wall cells. LDLs are associated with the extracellular matrix of the sub-endothelial space. Early lesions develop at specific sites possibly due to wall shear stress and hemodynamic factors
2. The cells of the arterial wall secrete oxidation products that initiate lipid oxidation of the LDL that are trapped in the sub-endothelial space. The first stage of oxidative modification occurs prior to the recruitment of monocytes with little modification of Apolipoprotein B monocytes that are recruited to the lesion site, convert to macrophages and further oxidize the lipids. During this process the LDL receptor is modified such that there is LDL uptake by scavenger receptors or oxidized LDL receptors. These receptors are not regulated by the cholesterol content of the cell, accumulate cholesterol in their cytoplasm and are known as foam cells. They are the basis of the fatty streak of the arterial wall
3. Oxidation of LDL and the induction of arterial wall inflammation. Mildly oxidized lipids induce monocytes to bind to the endothelial cell surface by the usual mechanisms of binding, tethering, attachment and activation. The chemokine for monocytes MCP-1 has been found in atherosclerotic lesions. Mildly oxidized LDLs induce endothelial cells to secrete MCP-1 and monocyte stimulating

factor. Mildly oxidized LDL induces gene transcription for monocyte adherence, but not for lymphocyte or neutrophil adherence. The mildly oxidized LDL induces cAMP by a G-protein-mediated process that decreases the expression of ELAM-1 (endothelial-leukocyte adhesion molecule-1), the receptor for neutrophils. There is some experimental evidence that HDL may protect against LDL oxidation.

4. Lesion Progression

Arterial endothelial cells interact with monocytes by a complicated process that involves gap junction protein connexin 43, increased production of matrix molecules, interleukin-1 and interleukin-6. Monocytes and macrophages which have been attracted to the lesion site secrete smooth muscle growth factor and plate-derived growth factor which is a mechanism for the migration of smooth muscles into the lesion. Oxidized lipids stimulate the release of interleukin one (IL-1) from macrophages which is also a growth factor for smooth muscles.

LDL oxidation produces lysophosphatidylcholine that has several important functions in the cause of atherogenesis that include: a. chemo attraction for monocytes and T-lymphocytes; b. induction of vascular adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1); c. increased levels of platelet derived growth factor 1 and heparin-binding epidermal growth factor in endothelial and smooth muscle cells. Highly oxidized LDL inhibits endothelial cell migration, impairs the repair of ulcerated plaques and is toxic to macrophages all of which amplify the inflammatory process. The atherosclerotic lesion expands toward the adventitia through the media until a critical point is reached which starts to narrow the lumen. The lesions grow by: a. the entrance of mononuclear cells; b. the proliferation of monocytes, macrophages and smooth muscle cells; c. the production of increased extracellular matrix and d. the accumulation of extracellular lipid in a necrotic core.

5. Calcification of the Arterial Wall

Experimental evidence suggests that a soft plaque with an area of weakness due to inflammation when superimposed on calcified arterial wall causes: a. a difference in physical properties of the tissue interface; b. rupture from the pulsatile forces of arterial blood pressure. Recent observations suggest that a cell with characteristics of a pericyte is found in large and medium-sized arteries and is responsible for vascular calcification. These calcifying vascular cells express similar genes to those that are expressed during bone formation. They are induced by transforming growth factor- β (TGF- β) and oxysterol which are present in the fatty streak and atherosclerotic lesions. The calcific changes in the arterial wall change its physical properties and are a factor in plaque ruptures. Rupture most often occurs in the shoulder region of the lesion.

6. Differential Biologic Effects from the Degree of Oxidation of LDLs

Mildly oxidized lipids from LDLs induce the expression of tissue factor from vascular endothelial cells. Highly oxidized LDLs are cytotoxic and mildly oxidized LDLs are not. Specific oxidized lipids (possibly oxidized phospholipids) activate the NF κ B like transcription factor (pivotal for inflammation) and the genes induced by mildly oxidized LDLs.

Immune Mechanisms in Atherosclerosis

1. There is a great expansion of dendritic cells (antigen presenting) and lymphocytes in the adventitia of atherosclerotic arteries. Inflammatory cells, macrophages, dendritic cells, foam cells and lymphocytes are found in the intima of atherosclerotic lesions. Underneath these lesions there are clusters of adventitial leukocytes that resemble tertiary lymphocytic tissue.
2. During the progression of the atherosclerotic lesion endothelial nitric oxide production is decreased and there is an increase of reactive oxygen species and advanced glycation end products (AGE). The latter are formed by non-enzymatic modification of proteins by reducing sugars. This alteration in glucose and lipid metabolism leads to the increased production of aldehydes and the formation of AGEs. AGEs are important in the cross-linking of proteins of the extracellular matrix. AGE receptors (RAGE), a member of the immunoglobulin superfamily are expressed on endothelial cells, smooth muscle cells, monocytes and lymphocytes. Activation of the RAGE receptor causes: a. oxidative stress; b. endothelial dysfunction; c. increases proinflammatory cytokines and tissue factor; d. up regulates expression of adhesion molecules all of which accelerate atherosclerosis.
3. Reactive Oxygen Species

Production of reactive oxygen species occurs throughout the course of atherogenesis. They induce activation of the vascular endothelium and components of the immune system. Reactive oxygen species from vascular endothelial cells are generated from: a. nicotinamides adenine dinucleotide phosphate (NADPH); b. mitochondrial respiratory chain dysfunction; c. xanthine oxidase; d. lipoxygenase; e. nitric oxide synthases. Pivotal is superoxide generation from monocytes/macrophages and vascular endothelial cells.

Superoxide activates smooth muscle mutagenic signaling pathways while NADPH-induced superoxide causes enhanced availability of released ADP and increased recruitment of platelets. Reactive oxygen species production may overwhelm antioxidant systems that include superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase. This produces oxidative stress that damages nucleic acids, lipids, proteins and membranes.

The role of the complement system, heat shock proteins and toll-like receptors in the generation of atherosclerosis is being actively pursued. The immune response in atherogenesis is predominantly Th1.

Summary of the Mechanisms in the Development of Atherosclerosis

1. Occurs in large arteries and is characterized by local lipid accumulation. It is partially determined by vessel geometry flow and oscillatory wall shear stress that induces a chronic inflammatory state
2. Low density lipoproteins are transported into the subendothelial arterial space and are differentially oxidized by vascular cells
3. Oxidized LDLs trigger overexpression of adhesion molecules, chemokines, cytokines and growth factors that induce chronic arterial wall inflammation, cell proliferation and apoptosis
4. Many of the biological effects of mildly oxidized LDLs are mediated by transcription factors (NF κ B-like) and subsequent proinflammatory gene expression
5. Oxidized LDLs exert a biphasic effect on the redox-sensitive transcription factor NF κ B. It's up regulation activates proinflammatory gene expression but at high concentration may have an immunosuppressive effect
6. Inflammatory mechanisms regulate all phases of atherosclerosis that include immune cell function, activation of the vascular epithelium and alteration of metabolic parameters

The Arterial Wall and Aneurysms

Overview

The arterial blood vessel wall is composed of the tunica intima that is lined by endothelium, the media and the adventitia. The tunica media consists of smooth muscle cells and the extracellular matrix proteins, collagen, elastin and glycosaminoglycans. The adventitia is made of connective tissue, nerve fibers and the vasa vasorum. The internal elastic membrane separates the tunica intima from the tunica media. There is no external elastic lamina in cerebral blood vessel walls.

Vessel wall inflammation may occur from several different mechanisms. The proinflammatory cytokine tumor necrosis factor- α (TNF- α) is pivotal in many pathologic conditions. It damages structural components of the vessel wall that include the endothelium, smooth muscle cells and the internal elastic membrane. It induces inflammatory processes in the vessel wall that include migration of monocytes as well as inhibiting cell proliferation that inhibits cell repair. It also activates matrix metalloproteinases that degrade elastin and collagen which are major structural components of the arterial wall.

Vessel wall inflammation may also be induced by carbon monoxide. Carbon monoxide has a higher affinity for hemoglobin than oxygen which decreases the oxygen carrying capacity of blood that in turn causes hypoxemia induced inflammation. The putative pivotal cause of inflammation of the vessel wall is hemodynamic stress (parameters of shear

vessel stress that lead to degradation of the extracellular matrix and apoptosis of smooth muscle cells (the primary origin of the proteins of the extracellular matrix). Tissue infiltration of monocytes and macrophages release proinflammatory cytokines and chemokines (MCP-1) that amplify and recruit inflammatory cells as well as release matrix metalloproteins. Macrophages are found in a high percentage of surgical aneurysms. M1 (proinflammatory macrophages) predominate in ruptured aneurysms.

In early stages of aneurysm formation, smooth muscle cells migrate into the intimal layer and proliferate which then forms myointimal hyperplasia. Over time they undergo phenotypic differentiation from contracting cells to proinflammatory cells. In the process they change morphologically from compact bands to spider-like cells. They secrete less collagen and are a cause of a thinned media. There is evidence that the phenotypic switch noted in aneurysmal smooth muscle cells (SMCs) is induced by TNF- α which induces genes for MCP-1, MMPs, vascular cell adhesion molecule 1 and IL-1 β . Mast cells are detected in aneurysm walls and contribute to arterial wall inflammation during aneurysm formation by the release of proinflammatory mediators.

Cytokine mechanisms in arterial wall inflammation are:

1. TNF- α :
 - a. SMC phenotype modulation
 - b. Activation of metalloproteinases (MMPs)
 - c. Decreased expression of tissue inhibitor metalloproteinase-1
 - d. Proapoptotic effects through FAS
2. IL-1 β :
 - a. Induced in early stages of aneurysm formation
 - b. Causes SMC apoptosis

Both chemokines (MCP-1 and others) as well as complement are involved in the inflammatory wall mechanisms of aneurysm formation. Reactive oxygen species are being studied in regard to their role in direct endothelial cell injury, SMC phenotype switch of SMC and the up-regulation of genes that control chemotactic cytokines, adhesion molecules and activation of metalloproteinases (MMPs).

Hemodynamic Stress

Hemodynamic stress is a major initiating factor for the arterial wall structural modulation that occurs with aneurysm formation. Hemodynamic stress is greater at arterial junctions, bifurcations or at areas of vascular angulation. Hypertension, loss of autoregulation and increased blood viscosity may also be synergistic with other factors that cause hemodynamic stress. It has been postulated that hypertension may compromise the vasa vasorum which supply the tunica media of the vascular wall. The effects of wall shear stress (WSS) are complicated and while there is evidence that high WSS may be important in the initiation of aneurysm formation, low WSS may be involved in aneurysm rupture by inducing apoptosis of endothelial cells and structural remodeling of the arterial wall. It has also been suggested that low WSS triggers

the growth and rupture of large atherosclerotic aneurysms by an inflammatory mechanism while high WSS induces MMP activation, smooth muscle cell apoptosis and medial thinning in small aneurysms. There is accumulating evidence that endothelial dysfunction and vessel wall remodeling and inflammation are induced by WSS.

The Effects of Wall Shear Stress

1. Occurs at bifurcation, junctions and areas of acute vessel angulation
2. Induction of inducible nitric oxygen synthase (iNOS) produces peroxynitrate that is cytotoxic
3. Stimulation of endothelial production of matrix metalloproteinase
4. Smooth muscle cell injury in the tunica media from increased transmural flow gradients
5. WSS induced injuries are a component of:
 - a. Endothelial cell damage
 - b. Degradation of the internal elastic membrane
 - c. Thinning and phenotypic change of SMC in the tunica media

Collateral Circulation

Overview

The collateral circulation is a major determinant of the functional outcome following a stroke. It is a major factor in preserving cerebral perfusion by recruiting blood flow to the ischemic territory. The anatomical features of the collateral circulation are also an important determinant if the stroke will be territorial or border-zone. Cerebral arterial autoregulation is the primary mechanism that maintains CBF at 50 ml/100 grams/minute. Approximately 90% of blood is in the gray matter. Autoregulation in general is maintained between 50 and 150 mm Hg. There is some autoregulatory control by means of the locus coeruleus and the adrenergic system. There appears to be less sympathetic innervation of the posterior cerebral arteries that perfuse the occipital lobe.

Cerebral blood flow is determined by vascular resistance, perfusion pressure and autoregulation. Cerebral perfusion pressure is the difference between the mean arterial pressure minus the sum of the CSF pressure (intracranial pressure) and jugular venous pressure. Blood pressure, metabolic activity and neurogenic factors may modify autoregulation. The effectiveness of the collateral circulation for compensation of ischemia of an arterial territory depends on: 1. anatomical variation; 2. systemic arterial pressure; 3. age; 4. rate of development of occlusive disease. During large artery occlusion the Circle of Willis is the main effector of the collateral circulation. Following occlusion of the carotid artery the drop of perfusion pressure distally generates a pressure gradient between neighboring arterial territories that change the rate and fraction of blood flow which may occur in a matter of seconds. Trans cranial doppler (TCD) monitoring during carotid

endarterectomy has demonstrated an increase in contralateral anterior cerebral artery blood flow velocity within a few heart beats. In small cortical arterioles of 50–250 microns, the rapid decrease in intraluminal pressure relaxes smooth muscle which causes vasodilation and a fall of vascular resistance. A component of the cerebral collateral arterial network is in the pial leptomeninges. The extent of this pial circulation varies among individuals and impacts upon the severity of stroke.

Cerebral Collateral Circulation

The importance of the collateral circulation is underscored by: 1. collateral cerebral blood flow may have a greater impact on ultimate infarct volume than time from ictus to thrombolytic treatment; 2. pretreatment collateral status is correlated with infarct growth; 3. collateral status may predict the extent and location of cerebral infarcts.

Internal Arterial Connections

1. Internal arterial connections are internal carotid artery to basilar and posterior communicating arteries
2. Circle of Willis anterior cerebral arteries connected by the anterior communicating artery
3. Anastomosis between the internal carotid artery and the vertebral and basilar artery from embryonic vessels include:
 - a. Persistent trigeminal (.1–1%)
 - b. Persistent otic (rare occurrence)
 - c. Persistent hypoglossal (.1–.25%)
 - d. Proatlantal artery (rare occurrence)
4. Posterior cerebral and superior cerebellar artery anastomosis with the tectal rami (tectal plexus)
 - a. Connect supra and infratentorial arteries
5. Anastomosis between the terminal branches within and between the arterial territories of the ACA/MCA and the MCA/PCA
6. Leptomeningeal anastomosis:
 - a. Pia plexus-adjacent arterioles from same or adjacent arteries (branches of major cerebral arteries)
 - b. Cerebral and meningeal arteries
7. Extranial Anastomoses
 - a. Orbital plexus – connections of the ophthalmic and middle meningeal, maxillary and ethmoidal arteries
8. Rete mirabile caroticum – anastomosis between the internal and external carotid arteries

Anatomical Variants of the Circle of Willis

1. Absent posterior communicating arteries bilaterally
2. Absent A1 segment of anterior cerebral artery
3. Bilateral fetal origin of the posterior cerebral arteries (carotid artery to PCA)
4. Absent anterior or posterior communicating arteries

*Anatomic Variants of the Major Intracranial Arteries***Anterior Cerebral Artery (ACA)**

1. Azygos ACA (unpaired ACA: 0–5%)
2. Medial ACA (3–22%)
3. Bihemispheric ACA (2–7%)
4. Persistent POA (rare occurrence)

Middle Cerebral Artery

1. Duplicated (.7–2.9%)

Posterior Cerebral Artery (PCA)

1. Fetal PCA (20–30%)

Evolving Evaluation of Biomarkers in Acute Cerebrovascular Disease

At present there is no single or panel of biomarkers that is sensitive or specific enough for the diagnosis, stratification or usefulness in management of acute ischemic stroke. They reflect different components of the ischemic cascade. They do hold promise for 1. identifying patients at high risk for vertebral ischemic vascular disease; 2. stratifying the risk of reperfusion hemorrhage; 3. predicting the volume of penumbra tissue (salvageable); 4. prognosis of the ictus; 5. serve as a quantifiable surrogate measurement in clinical trials.

Markers of the Ischemic Cascade

The measurement of protein blood biomarkers released from neurons and glia following ischemic stroke is due to the breakdown of the blood-brain barrier. The early processes underlying the ischemic cascade are: failure of ion pumps; cortical spreading depression; glial activation; excitotoxicity of glutamate; neuronal injury and death; oxidative stress and release of inflammatory mediators.

1. Neuronal markers of cell death include:
 - a. Neuron specific enolase
 - b. Heart fatty acid binding protein
 - c. NMDA receptor antibodies
 - d. Virus-like protein
2. Specific glial activation markers include:
 - a. S100B:
 - i. Calcium-binding protein expressed by astrocytes and oligodendrocytes
 - ii. Predicts risk for hemorrhagic transformation after tissue plasminogen activator (tPa), successful clot lysis, infarct volume and prognosis
 - iii. Delayed time course and lack of specificity decrease its utility
 - b. Glial fibrillary acidic protein:
 - i. Intermediate filament
 - ii. Primarily expressed by astrocytes
 - iii. Differentiates ICH versus ischemic stroke
 - c. Myelin basic protein:

- i. Myelin sheath protein
 - ii. Diagnosis of early stroke
3. Lipid Peroxidation Markers:
 - a. Oxidized low density lipoprotein
 - b. Malondialdehyde
4. Markers of Hemostasis and Endothelial Dysfunction:
 - a. Thrombomodulin
 - b. D-dimer
 - c. Fibrinogen
 - d. Fibronectin
 - e. Von Willebrand factor
 - f. Asymmetric dimethylarginine
5. Markers of Inflammation:
 - a. C-reactive protein
 - b. Matrix metalloproteinase
 - c. IL-6
 - d. TNF-alpha
 - e. Cell adhesion molecules
 - f. PARK-7
6. Astrocytic Markers:
 - a. S-100B
 - b. Glial fibrillary acidic protein

Non-Specific Markers of Inflammation

1. C-reactive protein:
 - a. An acute phase protein
 - b. Prognosis of ischemic stroke
 - c. Risk of recurrent stroke
2. Matrix metalloproteinase 9:
 - a. A zinc-binding proteolytic enzyme
 - b. Affects BBB integrity and possible risk of HT
3. IL-6 and TNF- α :
 - a. Released from invading leukocytes, activated microglia and monocytes
 - b. Inflammatory cytokine
 - c. May initiate apoptosis
4. Adhesion molecules (VCAM, sICAM):
 - a. Immunoglobulin super family
 - b. Diagnosis, stratification, prognosis
 - c. Poor specificity
5. Oxidative Stress Markers:
 - a. PARK-7:
 - i. Redox-sensitive molecular chaperone
 - ii. Diagnosis of ischemic stroke
 - b. Oxidized low density lipoprotein:
 - i. Lipid peroxidation product
 1. Stroke prognosis
 - c. Malondialdehyde:
 - i. Lipid peroxidation product
 - ii. Diagnosis and prognosis of stroke
 - d. F₄-neuroprostane:
 - i. Derived from free radical-induced oxidation of docosahexaenoic acid (fatty acid highly concentrated in brain)

Markers of Neuronal Injury and Death

1. Neuron specific enolase (NSE):
 - a. An intracytoplasmic dimer glycolytic enzyme
 - b. Reflects infarct volume and prognosis
2. Heart fatty acid binding protein:
 - a. Cytosolic protein component of intracellular fatty acid transport
 - i. Early diagnosis of ischemic stroke
 - b. Released following neuronal injury
3. N-methyl-D-aspartate (NMDA) receptor antibodies:
 - a. Relatively neuron specific
 - b. Is an excitotoxic glutamate receptor
 - c. Decreased utility due to time course of the ischemic cascade

Endothelial and Hemostatic Markers

1. Components of the ischemic cascade:
 - a. Hypoxic endothelial cells up-regulate cell adhesion molecules
 - b. Subendothelial matrix proteins are exposed to the blood stream
 - c. Platelet surface receptor bind to endothelial von Willebrand factor
 - d. Platelets adhere to collagen which causes decreased blood flow and are a component of delayed ischemia
2. Following ischemia there is an increase of soluble glycoprotein VI which facilitates platelet adhesion and thrombus formation
3. D-dimer:
 - a. Fibrin degradation product
 - b. Predicts early recurrent ischemic lesions and prognosis
4. Plasminogen activator inhibitor-1:
 - a. Encoded by the SERPINE 1 gene on chromosome 7q21.3-q22
 - b. A serine protease inhibitor (serpin)
 - c. Produced by endothelial cells and also by adipose tissue
 - d. Inhibits matrix metalloproteinases
 - e. The principal inhibitor of tissue plasminogen activator (tPA) and urokinase (uPA), the activators of plasminogen and fibrinolysis
 - f. Predicts HT after tPA
5. Thrombomodulin:
 - a. CD141; endothelial glycoprotein
 - b. An integral membrane protein expressed on the surface of endothelial cells
 - c. Cofactor for thrombin's activation of Protein C
 - d. May be a procoagulant by inhibiting fibrinolysis by cleaving thrombin-activatable fibrinolysis inhibitor
 - e. Predicts ischemia prognosis
6. Fibronectin:
 - a. A glycoprotein of the extracellular matrix
 - b. Binds membrane spanning proteins similar to integrins
 - c. Binds collagen, fibrin and heparin sulfate (proteoglycans)

- d. Major role in cell adhesion
- e. Deposited at the site of injury; component of the blood clot
- f. Predicts HT after tPA
7. Fibrinogen:
 - a. Plasma glycoprotein that the serine protease thrombin cleaves to insoluble fibrin strands:
 - i. Factor XIII crosslinks fibrin strands
 - ii. Factor XIIIa stabilizes the fibrin further by incorporating into the clot:
 1. Thrombin activator fibrinolysis inhibitor
 2. α -2-antiplasmin
 - b. Leukocyte – endothelium interaction
 - c. Platelet aggregation
 - d. Predicts ischemia prognosis
8. von Willebrand Factor:
 - a. Glycoprotein
 - b. Synthesized in vascular endothelium, megakaryocyte, subendothelial connective tissue
 - c. Domains that bind to factor VIII and the GP16 platelet receptor and A3 domain of collagen
 - d. Thrombin cleaves vWB from factor VIII stress (fast flowing blood)
 - e. Increased in atrial fibrillation
9. Thrombin activatable fibrinolysis inhibitor (TAFI):
 - a. A carboxypeptidase that hydrolyzes C-terminal peptide bonds
 - b. Decreases clot lysis
 - c. Predicts HT after tPA

Biomarkers Predictive of Hemorrhage

1. After tPA:
 - a. Plasminogen activator inhibitor-1 (PAI-1)
 - b. D-dimer
 - c. Thrombin-activatable fibrinolysis inhibitor
 - d. Combination of admission PAI-1 <21.4 ng/mL and TAFI >180% had a sensibility of 75% and a specificity of 98%
 - e. Biomarkers predictive of hemorrhagic transformation following tPA treatment
 - i. Elevated baseline vascular adhesion protein-1

Possible Future Markers of Ischemia and Hemorrhage

1. Asymmetrical dimethyl arginine (ADMA):
 - a. A metabolic by-product of protein modification and related to L-arginine
 - b. Interferes with L-arginine in the production of nitric oxide
 - c. Its concentration is increased by oxidized LDL-C
 - d. Increased ADMA levels cause decreased nitric oxide production and decreased vasodilation
 - e. A marker of endothelial dysfunction
 - f. Possible marker of subclinical ischemic injury

2. Atrial Natriuretic Peptides (ANP) and brain natriuretic peptides (BNP):
 - a. Vasoactive polypeptide hormones primarily secreted by cardiomyocytes
 - b. Primary function is homeostatic control of water sodium and potassium
 - c. Released in response to atrial stretch and stimulation of β -adrenoreceptors
 - d. ANP released after stroke: source could be heart or brain; elevated after stroke; may predict stroke mortality
 - e. BNP is elevated after ischemic stroke and SAH
3. Lipoprotein associated phospholipase-A₂ (platelet-activating factor acetyl hydrolase PAF-AH):
 - a. PLA2G7 gene
 - b. Travels with LDL-C
 - c. Produced by inflammatory cells
 - d. Hydrolyzes oxidized phospholipids in LDL-C
 - i. Catalyzes the degradation of PAF
 - e. Both brought to plaque by LDL-C and synthesized de novo in the plaque by T-cells, mast cells and macrophages
 - f. Associated with coronary heart disease and stroke
 - g. Predicts first and recurrent stroke following TIA
4. Free hemoglobin:
 - a. Serum free hemoglobin which contain peaks of α and β chains
 - b. Associated with stroke but not its severity
5. Calcium levels:
 - a. Are elevated between 3 and 4 days following stroke
 - b. Failure of calcium antagonists to alter functional recovery
 - c. Predictive of outcome of ischemic stroke at 3 months
6. Nucleoside diphosphate kinase A:
 - a. Protein kinase
 - b. Catalyzes the exchange of phosphate groups between different nucleoside diphosphates
 - c. Increases in the CSF following ischemic stroke
7. Adiponectin:
 - a. Fat derived protein
 - b. Low levels noted in obese patients
 - c. Anti-inflammatory and antiatherogenic
 - d. Predicts ischemic stroke mortality but not stroke
8. Copeptin:
 - a. A component of pro-vasopressin which consists of neurophysin II and copeptin
 - b. Arginine vasopressin (AVP) release:
 - i. An early physiological response to cerebral ischemia
 - ii. May correlate with stroke severity
 - c. Copeptin released in an equimolar ratio to AVP and is easier to measure and more stable
 - d. An independent predictor of functional outcome and mortality. Improves the prognostic accuracy of the NIHSS
 - e. Copeptin mirrors stress better than cortisol

Differential Diagnosis of Ischemic Stroke Subtypes with Plasma Biomarkers

1. Embolic or thrombotic occlusion of large arteries is the major cause of stroke. Less usual causes include:
 - a. Obstruction of small perforating vessels (diabetes, hypertension, dyslipidemia)
 - b. Arterial dissection
 - c. Arteritis (immune)
 - d. Infection
 - e. Venous disease
 - f. Hyperviscosity
 - g. Anemia
2. Approximately 35% remain cryptogenic after extensive evaluation

The Combined Biomarkers Brain Natriuretic Peptide (BNP) and D-Dimer (DD) Are Predictors of Cardiac Embolic Stroke

1. BNP concentrations are increased with systolic and diastolic dysfunction. The left atrium is the main source of BNP in atrial fibrillation
2. Patients with atrial fibrillation and clinical evidence of stroke have higher levels of BNP than AF alone
3. High levels of DD are an independent predictor of cardioembolic stroke
4. The combination of biomarkers and clinical findings had a sensitivity of 66.5% and a specificity of 91.3% for cardioembolism

Biomarker Panels for Ischemic Stroke

1. Astroglial protein S100
2. β -type neurotrophic growth factor
3. von Willebrand factor (vWB)
4. Matrix metalloproteinase-9 (MMP-9)
5. Monocyte chemotactic protein-1:
 - a. Test sensitivity of 91% and specificity of 97% in:
 - i. 223 stroke patients (ischemic stroke, subarachnoid hemorrhage and ICH)
 - ii. Sample taken within 12 hours
6. Panel consisting of BNP, S100b, C-reactive protein and D-dimer:
 - a. Sample taken from 30 patients with acute deficits within 6 hours
 - i. Sensitivity of 81% and a specificity of 70% for the diagnosis of ischemic stroke
7. Prospective multicenter trial utilizing: D-dimer, BNP, MMP-9 and S100B:
 - a. 1100 patients enrolled for probable stroke within a 3 year period
 - b. Only moderate ability to differentiate between ischemic stroke, ICH and mimics
 - i. Sensitivity of 86% and specificity of 37% in separating stroke patients from mimics

Biomarkers for the Differentiation of ICH from Ischemic Stroke

1. 6 hours after onset:
 - a. GFAP was detectable in 81% of ICH patients and 5% with IS
 - b. 2.9 ng/L of GFAP provided a sensitivity of 79% and a specificity of 98% for ICH
2. A study of 776 patients with IS and 139 with ICH studies at 6 hours post ictus:
 - a. S100B and RAGE (receptor for advanced glycation end products)
 - i. Differentiated ICH from IS acutely
3. ICH had significantly lower ApoC-I and ApoC-III lipoproteins than IS (n of 15 and 16 respectively)
 - a. ApoC-III had a sensitivity of 94% and a specificity of 87% in differentiating ICH from IS

Markers for Hemorrhagic Transformation After Thrombolysis

Disruption of the blood-brain barrier (BBB) is a major determinant of hemorrhagic transformation (HT) after thrombolysis. Molecular components of the blood-brain barrier (MMP-9 and fibronectin) in addition to astroglial and coagulation proteins are pivotal. MMP-9 plasma levels prior to thrombolytic therapy predict hemorrhagic transformation in a graded manner. Fibronectins form cell to cell to matrix adhesive interactions. It is synthesized by endothelial cells and high circulation levels suggest endothelial damage and consequent hemorrhagic transformation: a cut-off value of pretreatment levels of c-Fn of 3.6 $\mu\text{g/ml}$ and MMP-9 at 140 ng/ml was predictive of hemorrhagic transformation.

Foerch demonstrated S100B to be elevated early after stroke onset (within 6 hours) which was found to be an independent predictor of hemorrhagic transformation. The combination of admission PAI-1 at <21.4 ng/ml and TAFI >180% conferred a sensitivity of 75% and a specificity of 98% for the prediction of parenchymal hemorrhagic transformation.

Malignant Infarction

Malignant infarction causes severe cerebral edema with consequent increased intracranial pressure and herniation. In general it occurs from occlusion of a major artery in the anterior circulation (usually the MCA) or the posterior inferior cerebellar artery in the posterior fossa. Biomarkers that correlate infarct volume (S100b) or degradation of the blood-brain barrier (c-Fn, MMP-9) have been evaluated to predict this complication. At 12 hours, an S100B value of >.35 $\mu\text{g/L}$ predicted a malignant infarction with 75% sensitivity and 80% specificity. A c-Fn (fibronectin) concentration of >16.6 $\mu\text{g/mL}$ had a sensitivity of 90% and a specificity of 100% for the prediction of malignant infarction.

Potential Biomarkers of Cell Death That Activate the Immune Response

1. Alarmins:

- a. Endogenous molecules released from necrotic cells injured by infection, trauma and ischemia
- b. They are not released by apoptotic cell death
- c. Produced by several cell types including immune cells and are released by the ER-Golgi secretory pathway
- d. Activate innate immune cells and recruit and activate antigen-presenting cells
- e. Activated by pattern recognition receptors (Toll-like receptors). The high-mobility group protein B1 (HMGB1), is a well characterized alarmin, that initiates components of the inflammatory cascade during ischemic brain injury. It also upregulates MMP-9 in astrocytes and neurons in all phases of ischemic injury. In one study, elevated HMGB/elevation in ICH correlated with severity scores and elevation of inflammatory cytokines. Circulating DNA may correlate with stroke severity and possible morbidity and mortality in hemorrhagic stroke

Microparticles

Microparticles are small vesicles released from dead cells. They are composed of a plasma membrane that surrounds a small amount of cytoplasm. Membranes of endothelial cell microparticles contain receptors and cell surface molecules that identify their endothelial origin. Arrays of cell surface molecules may reflect the state of endothelial dysfunction prior to their release into the circulation. They are being evaluated to determine stroke etiology and lesion volume. They may be of value in differentiating intra versus extracranial stenosis but not between stroke and mimics.

Summary of Biomarker Utility

1. Hemorrhagic transformation after thrombolysis
 - a. MMP-9 elevation (measured 3–24 hours)
 - b. Prior PAI-TAFI decreased levels
 - c. Elevated fibronectin
2. Malignant edema
 - a. Elevated S100B
3. In hospital deterioration
 - a. D-Dimer elevation
4. Elevated levels of BNP and D-Dimer predict cardioembolic stroke
5. Elevated levels of inflammatory cytokines IL-6, IL- β and TNF- α correlate with cardioembolic stroke
6. NMDAR antibodies signify possible stroke etiology
7. Heart fatty acid-binding protein; possible correlation with severity of stroke deficit and infarct volume
8. D-dimer elevation: possible correlation with poor functional outcome, recurrent ischemia, progressive ischemic stroke
9. Elevated fibrinogen after stroke: possible correlation with mortality
10. Elevated CRP levels have been correlated with an increased risk of ischemic stroke and poor prognosis

11. Decreased adiponectin correlates with neurological outcome
12. Infarct size severity and functional outcome correlate with serum levels of vWF, MDA and IL-6
13. Copeptin levels correlate with functional outcome, mortality are recurrent TIA

The Natural History of Extracranial and Intracranial Atherosclerosis

Extracranial Arterial Atherosclerosis

A discussion of plaque induction and evaluation is found in the section on atherosclerosis (see Plaque Histology). This process occurs on the luminal surface as well as between the internal and external elastic membranes. There is concomitant remodeling of extracranial and intracranial vessels during the process of atherosclerosis. A recent evaluation of participants from the Atherosclerosis Risk Communities (ARIC) study cohort involved a prospective biracial observational study with a cohort of 15,702 subjects between 45–64 years of age. Subjects were selected from four disparate communities. Arteries were evaluated over 9 years. Intima-media thickness was measured with B-mode ultrasound and MRI. The sample evaluation consisted of 3348 common carotid arteries and 1064 internal carotid arteries. The mean age of the population evaluated was 70.3 years. Only 1.3% of the subjects had carotid stenosis of at least 50%. The internal carotid artery (ICA) lumen was constant for wall thickness less than 1.5 mm but decreased when wall thickness increased above this level. Common carotid lumen size was smaller than that of the ICA at every wall thickness. Above a maximum wall thickness was associated with a smaller luminal area. Each 1 mm increase of wall thickness corresponded to an approximate 20% reduction of luminal area. At the 1.38 mm thickness of threshold, 62% of the total vessel area was composed of the vessel wall. There is less accommodation in the ICA versus the CCA as regards preservation of the lumen. Studies of remodeling of the common carotid artery are conflicting. Some studies have demonstrated paradoxically that lumen size increases with increased intima-media thickness. The relevance of extracranial atherosclerosis is multiple: 1. association with silent infarcts and white matter disease; 2. plaque rupture and 3. hypoperfusion of deep subcortical watershed circulation. Outward remodeling of the CCA may be associated with circumferential wall tension which has been associated with large artery stroke.

Intracranial Arterial Atherosclerosis (ICAD)

Overview

The epidemiology of intracranial arterial atherosclerosis reveals that it causes 30–50% of strokes in Asians and 8–10% of strokes in North American Caucasians. Intracranial arterial atherosclerosis, that preferentially affects Asians, Hispanic and blacks, is more prevalent than that which affects

the carotid bifurcation. There is some evidence that race and genetic background are responsible for differences in sites of cranial atherosclerosis possibly working through stroke suppressor genes. The risk factors associated with ICAD are: 1. ethnicity; 2. females greater than males; 3. hypertension; 4. smoking; and 5. lipid disorders. Compared to extracranial vascular disease some studies have demonstrated no association between male sex and hypercholesterolemia that is usually seen with coronary artery and peripheral vascular disease. The metabolic syndrome is an independent risk factor for intracranial versus extracranial atherosclerosis. More recent analysis suggests that the severity of intracranial stenosis may depend on diabetes and the metabolic syndrome.

Heritability for all ischemic strokes is approximately 38% and varies by subtype: 1. 40% for large vessel disease; 2. 33% for cardiac embolism; and 3. 16% for small vessel disease. Three loci from related gene wide association studies are significant for stroke: 1. PHACTRI for large vessel disease; 2. PTX2 and ZFHX3 for cardioembolic stroke. No candidate gene was significant for stroke.

General Characteristics

1. Prevalence of 20–40/100,000 persons worldwide; higher in African Americans and Hispanic than Caucasian patients
2. Intracranial atherosclerotic disease cause 33–37% of ischemic strokes in the Chinese population
3. Severe ICA affects 43% of subjects 65 years and older, 65% in those 60–69 years old and 80% of those 70–79 years old

Intracranial Arterial Disease Risk Factors

1. Non-modifiable:
 - a. Age
 - b. Men (younger age and in the basilar artery)
 - c. Hispanic subjects
 - d. Chinese subjects
 - e. Angiotensin converting enzyme polymorphisms
 - f. African American subjects
 - g. Plasma endostatin vascular endothelial growth factor ratio
 - h. Glutamine S-transferase. Omega-1 gene polymorphism
 - i. Plasma homocysteine levels
2. Modifiable Risk Factors:
 - a. Hypertension
 - b. Serum beta lipoprotein
 - c. Total serum cholesterol
 - d. Serum LDL-cholesterol
 - e. Serum Apolipoprotein
 - f. Serum HDL-cholesterol
 - g. Sickle cell disease
 - h. Meningitis
 - i. Extracranial carotid stenosis
3. Possibly Modifiable Risk Factors:
 - a. Diabetes mellitus

- b. Metabolic syndrome
- c. Alzheimer's disease
- d. Aortic Plaques
- e. X-RT (radiotherapy)
- f. Tuberculosis and cryptococcal meningitis
- g. Family history of stroke
- 4. Asymptomatic stenosis (50–99%) of other arteries in a proportion of patients
- 5. Patients with symptomatic intracranial arterial disease
 - a. Ischemic stroke, ICH or vascular death (not caused by ischemic stroke) occurred in 22% (WASD trial)
 - b. Ischemic stroke occurred in the territory of the symptomatic artery (14%); other vascular territories (19%)
 - c. One year risk of stroke in the territory of a symptomatic stenosis artery (greater than 70%) was 19%

Clinical Manifestations

- 1. TIA
- 2. Stroke
- 3. Recurrent stroke: highest risk within two weeks
- 4. Rate of recurrence of ischemic events is high regardless of antiplatelet or anticoagulation therapy

Neuropathology

- 1. Increased deposition of fibrinogen and LDL-cholesterol in the sub endothelial space
- 2. Inflammation in the walls of affected arteries

Neuroimaging

- 1. Spin-echo MRI with contrast demonstrates arterial wall enhancement
- 2. Intravascular ultrasonography
 - a. Provides real-time dynamic measurements and histology maps of the plaques

Localization of Ischemic Lesions

Motor Signs and Symptoms of Ischemic Lesions

Overview

The topographical pattern of motor deficits is extremely helpful in determining both the size and distribution of the arterial territory involved as well as the etiology of the stroke. Approximately 75% of patients with ischemic lesions demonstrate uniform weakness of the hand, foot and hip. In general, extensor musculature is more affected than flexor. A faciobrachial motor pattern is characteristic of conducting vessel deficits of the frontal branch of the superior division of the MCA (often embolic). This territory is adjacent to the frontal eye fields (FEF), supplied by the frontal branch of the superior division and Broca's area (BA44). Smaller cortical branches may give weakness of the distal arm and hand (the motor knuckle) which is frequently caused by embolic material from the carotid artery. Rarely individual fingers may

be involved. Often immediately following the ictus, reflexes may be increased which is never the case with internal capsule lesions. Large MCA artery disease does not involve the leg nearly as much as the arm (unless MI is involved which affects the internal capsule) as the homunculus for the leg on the cortical surface is supplied by the ACA. The leg may be more involved in cortical MCA infarction as edema progresses. Monoparesis may occur as noted from small lesions of the homunculus, the corona radiata and the centrum semiovale. Anterior lesions may affect the arm and face while posterior lesions affect the leg. Medial lesions of the pons may differentially affect the legs (pontine sludge on MRI-penetrating basilar artery arterioles) while more lateral lesions the arms. The anatomy of the internal capsule is complex and will be discussed in more detail with brainstem stroke. In general, corticospinal fibers in the capsule are somatotopically organized with arm fibers ventromedially and leg fibers dorso-laterally. More proximal extremity weakness suggests pontine involvement (weak shoulder but intact fractionated individual finger movement). Fractionated finger movement and particularly loss of thumb dexterity is almost invariant with MCA cortical involvement. MCA M1 involvement affects leg fibers in the internal capsule such that arm, face and leg may be equally involved (associated with depressed reflexes). Proximal limb paresis is most often infratentorial while distal involvement is supratentorial. Rarely faciobrachial predominant motor weakness is caused by anterior cerebral artery, basal ganglia and brainstem involvement.

Pure motor hemiparesis occurs in approximately 9 to 24% of patients with stroke. It most commonly occurs from lesions in the internal capsule and basis pontis (basilar artery). Extremely rarely it can occur from medullary pyramid involvement. In this instance, the face should be spared but it has been suggested that there are aberrant descending facial fibers that may be lesioned and give a slight central facial involvement. Rarely the P1 and P2 components of the posterior cerebral artery can be infarcted which affect the arm and leg solely (involved in the cerebral peduncle). Severe shoulder and upper arm weakness may be seen with watershed infarction between the MCA and ACA territories ("man in the barrel" syndrome). Isolated toe paralysis has been described from cortical homunculus infarction. The face may be singularly involved with corona radiata and genu capsular (usually dysarthria is present) lesions. Severe isolated facial palsy that may mimic a peripheral rather than central cause (upper face involvement) occurs with pontine lesions.

If pure motor signs are associated with corresponding sensory loss in an awake patient then the lesion is in the internal capsule (associated with decreased or absent reflexes). A lethargic patient with arm, face and leg involvement and hyperactive reflexes suggests subdural hematoma. The ipsilesional pupil may be slightly dilated, slower to react to light and assumes an oval or "tadpole" appearance. The patient will have a headache and the ipsilesional scalp is often sensitive

to mechanical stimulation. Patients with ataxia out of proportion to weakness (ataxic hemiparesis) usually have a lesion of pontine crossing fibers that comprise the middle cerebellar peduncle. It has been described with both cortical and corona radiata lesions (usually frontal lobe infarction). Infarctions of the ACA may cause severe distal leg weakness in approximately 25% of patients. Depending on the blood supply from the Circle of Willis (a single peduncle from which A2 arises, the medial frontal lobe can be infarcted with consequent upper extremity weakness and incoordination). There are multiple movement disorders that occur with stroke that include:

1. Lower body Parkinsonism – basal ganglia involvement; lacunar states
2. Hemichorea – thalamoperforate artery infarction; often seen in diabetic and hypertensive patients
3. Dystonia – thalamic stroke; thalamoperforate artery
4. Hemiballism – at least two-thirds involvement of the STN (corpus Luysii); interpeduncular or thalamoperforate artery infarction
5. Asterixis – reported from cortical and reticular formation lesions
6. Ataxic Syndromes:
 - a. Posterior inferior cerebellar artery PICA – leg ataxia more than arm; gait affected (inferior cerebellar peduncle affected)
 - b. Anterior inferior cerebellar artery AICA – arm is more affected than the leg; infarction of the middle cerebellar peduncle; unilateral hearing loss occurs if the internal auditory artery is affected
 - c. Superior cerebellar artery – upper and lower extremity ataxia; speech involvement; often from the top of the basilar embolic stroke
 - d. Interpeduncular artery infarction – total body ataxia; infarction of the decussation of the superior cerebellar peduncle (top of the basilar embolus; atherosclerosis; aneurysm)
 - e. Bruns' Ataxia – Involvement of frontopontine crossing fibers: the cerebellar proprioceptive zone (globose and emboliform nuclei); the thalamic cerebellar area (component of VL); Brodmann's area BA 3,1,2 which then projects back to BA4
 - i. Frontal component:
 1. Ataxia of the extremities out of proportion to weakness
 2. Pontine crossing fibers (origin is the pontine nuclei of the basis pontis) similar clinically to cortical involvement; basilar artery penetrating arteries are involved
 3. Cerebellar proprioceptive zone; extremely rare from stroke
 4. Thalamic involvement noted for ataxia of stance (thalamoperforate artery)
 - f. Anterior cerebellar infarction:
 - i. Gait ataxia; "Martinet gait"; an increase of extensor tone primarily of the legs and trunk

g. Hemispheric cerebellar infarction:

- i. Complete cerebellar syndrome of the affected extremities that includes dysmetria, hypotonia, hyporeflexia, dysdiadocho-kinesia

General Features of Sensory Signs Following Ischemic Lesions

Sensory signs may be apparent in 80% of stroke patients. Most stroke patients demonstrate several somatosensory deficits that include primary modalities of pain, temperature, vibration, proprioception and higher cortical function. A significant number of patients diagnosed with pure motor stroke have sensory dysfunction. The pattern and primary modality and higher cortical sensory deficits (stereognosis, graphesthesia; 2-point discrimination, posture copy, extinction to double simultaneous stimulation) are extremely helpful in topographical diagnosis in ischemic stroke. Studies reveal that between 53 and 64% of stroke patients have impairment of primary modalities after stroke. Impaired proprioception occurs at the same frequency and decreased stereognosis (tactual object recognition) is the most frequent sensory deficit after stroke. Pure somatosensory syndromes are frequent with lacunar stroke of the thalamus, internal capsule, brainstem, and parietal cortex.

Patterns of Brainstem Sensory Stroke

The usual brainstem sensory syndromes are the result of small infarcts or hemorrhages in the pons and medulla. The rostral mid pons (contain the nucleus and descending tract of V) and innervates the mid face. The lateral caudal pons (containing the N and descending tract of V) innervates the peripheral face. The more lateral pons contains sympathetic fibers that are frequently involved with lateral lesions. Trigeminal fifth cranial nerve dorsal root entry zone lesions are involved in syphilis and denervate the midface. In lateral medullary and pontine strokes, the ipsilateral face and contralateral body lose pain and temperature sensation. Circumoral bilateral sensory deficits suggest a pontine lesion while midface versus lateral face (concomitant central Horner's) is more characteristic of the pons. The spinothalamic tract fibers (pain and temperature) decussate at the segmental level of entry and therefore an ipsilateral lesion will give a contralateral deficit. These fibers are segregated such that the sacrum, leg and trunk representation is the most lateral. Hemianesthesia of the tongue suggests a medullary lesion and bilateral intraoral numbness most often occurs following a posterior ventromedial thalamic nuclear lesion.

The Stopford classification is helpful in organizing brainstem sensory loss:

1. Type I: ipsilateral face and contralateral leg (most lateral brainstem)
2. Type II: upper part of the body – a mediolateral infarction
3. Type III: larger infarction involving medial and lateral area and can cause a combination of crossed and unilateral deficits

Paramedian infarctions (penetrating arterioles from the basilar artery) affect vibration and proprioception (lemniscal afferents) and may show a cheiro-oral and leg weakness pattern (leg fibers are medial and arm fibers are supplied by short circumferential arteries). These infarctions causes gait ataxia (pontine crossing fibers that make up the middle cerebellar peduncle) and dizziness (vestibular fiber involvement).

Thalamic infarction (thalamogeniculate artery from P1) or more commonly lacunar infarction affects the VPL nucleus. Face, arm and leg are involved. The most common symptoms are numbness or paresthesia but some patients report “formication” (insects crawling on the skin), burning and pain. Pain may occur with the stroke, 2 to 15 days later or after months. This form of central pain is referred to as Dejerine’s syndrome. Characteristic of thalamic sensory loss is strict mid-line topology (occasionally bilateral sensory loss periumbilically), loss of vibration sensation (including the forehead) and bilateral intraoral numbness if VPM is involved.

Parietal sensory loss is characterized by deficits in higher cortical sensory function such as graphesthesia, 2-point discrimination, the ability to copy posture and identify textures. It often spares the trunk. Left parietal lesions may cause anomia, aphasia, deficits with reading, transcortical conduction aphasia with involvement of the supramarginal gyrus, Brodmann areas 41, 42 and the arcuate fasciculus. Right-sided lesions cause visuoconstructive and spatial deficits. Denial of individual body parts (asomatognosia), of illness (anosognosia) and neglect may be seen. The patient often will be lying asymmetrically in bed with both head and eyes turned to the side of the lesion. A parietal drift of the arm (updrift with polyminiomyoclonus) is common. If the patient has neglect but an extremity is in a peculiar position, the thalamus or parietal afferents may be involved. Higher cortical sensory loss with preserved vibration is characteristic of a parietal sensory lesion. The gait is hesitant and it appears that the patient explores space with the left foot. Motor function is frequently involved as there are dense projections from the superior parietal lobe through the superior longitudinal fasciculus to M1 for hand-eye coordination. The parietal cortical syndromes usually arise from infarction of the anterior and posterior parietal branches of the superior division of the MCA. Infarction of the central sulcal branch of the MCA causes M1 and S1 damage which affects primary modalities except vibration. Most patients report heaviness (S1 – 3a, 3b) or numbness of the affected areas. The posterior insular cortex encodes interoception, affect and intensity of pain. A lesion of the inferior anterior parietal cortex affecting the parietal operculum and the posterior insula is difficult to distinguish from a thalamo-sensory syndrome (pseudo-thalamic syndrome). Discriminative rather than affectual pain deficits are rare with cortical lesions although SI has recently been shown to encode pain and SII receives pain afferents. Recent electrophysiological studies, primarily trans-cortical magnetic stimulation, are furthering our understanding of the role of the cortex in pain. Somatosensory

deficits are more severe with right-sided lesions and there is a 17% incidence of ipsilateral sensory loss following unilateral stroke.

Transient Ischemic Attacks (TIA)

Overview/General Characteristics

The great majority of TIAs are atherothrombotic. They can involve any cerebral artery in either the anterior or posterior circulation. By definition, a TIA is a brief episode of ischemia that terminates within 24 hours without a clinical or imaging deficit. They present with focal neurologic deficits which may precede or rarely follow a stroke or they can occur without evolving into a stroke. The exact time limit for the neurologic deficit is controversial but most accept that it should be less than 24 hours. Longer TIAs suggest larger fibrin platelet emboli (red) while those lasting minutes are most often artery-to-artery cholesterol particles from atherosclerotic lesions.

TIAs may be separated into a single episode or recurrent stereotyped deficits. Prolonged fluctuating TIAs have a high proclivity for vascular occlusion. Approximately 20 to 30% of TIAs are followed by a stroke within one month and 50% by one year. A predictive tool to determine the likelihood of stroke within 1 week is the ABCD score and its variants. Unilateral weakness and deficits lasting longer than 1 hour are solid clinical signs of impending stroke. There is a strong correlation with carotid TIA and myocardial infarction. A significant number of TIAs may be diffusion weighted MRI sequence image negative.

Transient monocular blindness, also known as amaurosis fugax is a transient ischemic episode of the eye. Most of the episodes are short lived between 5 to 30 seconds.

Many patients describe the attack as if a shade comes down (or rarely rising) over the eye. The episode is painless but the eye may be completely blind. Vision returns slowly and uniformly. The variants of transient monocular blindness include a wedge or visual loss, generalized blurred vision or a bright scintillating light that obscures vision. The attacks of transient monocular blindness are more stereotyped than hemispheric TIAs and are markedly less correlated with stroke. Rarely a Hollenhorst cholesterol embolus may be seen as a “birefringence” yellow embolus occluding a retinal artery bifurcation. Progression of the embolus through the bifurcation coincides with visual clearing.

Lacunar transient ischemic attacks may be “stuttering” at onset but are difficult to distinguish from a large vessel TIA.

Clinical Manifestations

1. Transient monocular blindness (TMB)
2. Capsular warning syndrome
3. Aphasia
4. Hemiparesis
5. Hemisensory deficits (numbness or tingling)

6. Perioral numbness
7. Ataxia
8. Dysarthria
9. Diplopia
10. Dizziness
11. Visual field deficits
12. Alteration in consciousness

Neuropathology

The atherosclerotic plaque is pivotal in the mechanism of artery-to-artery embolism and flow limiting stenosis.

The arterial wall of the plaque is thickened and there is endothelial compromise with an accumulation of cholesterol. A chronic inflammatory response occurs in the walls of arteries in part caused by the accumulation of macrophages and leukocytes whose migration is induced by low-density lipoprotein oxidation and decreased removal of fat and cholesterol from macrophages by functional high-density lipoproteins (HDL). The site of plaque formation is due in part to the effects of wall shear stress and turbulent flow.

The core of atherosclerotic plaque is composed of lipid deposits with absence of cells and matrix proteins. Plaque formation starts after the induction of a fatty streak.

Oxidative modification of low-density lipoprotein (LDL) is important for foam cell formation and possibly the initiation or acceleration of atherosclerosis. Increased levels of plasma low-density lipoproteins cause an increased rate of low-density lipoprotein entry into the intima. Low-density lipoproteins undergo oxidative modification by endothelial smooth muscle cells or macrophages. The oxidized low density lipoproteins are recognized by scavenger receptors which give rise to foam cells. The effects of oxidized low-density lipoproteins are:

1. Cytotoxicity to endothelial cells (demonstrated in cell culture)
2. Inhibit vasodilation by nitric oxide
3. Stimulates mitogen-activated protein kinases in smooth muscle cells (SMC) and macrophages
4. Immunogenic

Foam cells are lipoprotein aggregates within the intima of blood vessels. Macrophages and endothelial cells generate free radicals that oxidize lipoprotein. The macrophages engulf the oxidized low-density lipoproteins by endocytosis utilizing scavenger receptors (SCAs). Oxidized low-density lipoproteins in macrophages and other phagocytic cells become foam cells which form the fatty streaks of the atheroma in the tunica intima during the atherosclerotic process.

The internal elastic lamina is thicker in arteries than arterioles and is very thin in veins. It separates the intima from the media of the arterial wall. It is a restrictive barrier to macromolecular permeability. Holes within the internal elastic lamina allow for permeability of diffusible vasoactive molecules and are the interface of endothelial cell projections with the

smooth muscle of the vascular wall. Smooth muscle cells secrete elastin that forms sheets or lamellae which increase with age and form the internal elastic lamina.

Cholesterol crystallizes as it accumulates in the vascular wall. It transforms from a liquid to a solid state and expands which is a mechanism of vulnerable plaque disruption. Cholesterol crystals induce inflammation in the arterial wall. Cholesterol crystals activate the "inflammasome" complex within immune cells that release inflammatory mediators (chemokines and cytokines). Cholesterol crystal embolization is the release of contents of a ruptured atherosclerotic plaque from a more proximal larger caliber artery to distally small to medium-sized arteries. Arterio-arterial thromboembolism is usually characterized by an abrupt release of emboli. The size of a cholesterol embolus is 100 to 200 μm and cause end organ damage both by ischemia and an induced inflammatory response.

Vascular remodeling is an adaptive response to variations in wall shear stress and hemodynamic factors. Experimental evidence supports the concept that wall stretch induces smooth muscle and endothelial cell proliferation as well as phenotypic switch in SMC from contractile to synthetic cells. Pericytes, vascular mural cells located within the albuminal vascular basal laminae regulate vascular development, stability, angiogenesis and remodeling. Extracellular membrane proteins (ECMs) drive angiogenesis by means of integrin receptors. The $\beta 1$ class unregulated fibronectin which is an important component of the vascular wall. Vascular remodeling is also promoted by several growth factors which include:

1. VEGF
2. bFGF
3. PDGF-BB
4. Cytokine TGF- β
5. Cytokine TNF- α

These growth factors and cytokines modulate ECM-integrin interactions. An important mechanism that effects change in the blood vessel wall during plaque formation is a TNF- α dependent switch from $\alpha 1$ to $\alpha 2$ that stimulate pericyte proliferation, migration and modulation of cerebral blood vessel collagen. The remodeling process can be summarized by the evolution of plaque formation.

Plaque Histology

1. Type I
 - a. An increase of macrophages with scattered foam cells
2. Type II
 - a. Layers of macrophage foam cells and lipid-laden smooth muscle cells that constitute fatty streaks on the artery luminal surface
3. Type III:
 - a. Lipid laden cells with scattered extracellular lipid droplets
 - b. Disruption of smooth muscle cells
 - c. Extracellular lipid
 - d. Intermediate stage between type II and type IV lesions

4. Type V:
 - a. Contains a lipid core and layers of fibrous connective tissue
 - b. Calcification of a type V lesion is classified as Type V
 5. Type VI:
 - a. Contains a lipid core with a fissure, hematoma and thrombosis with minimal lipid as calcium
- The identification of unstable plaques is of great clinical interest.

Neuroimaging

Ultrasound

1. A juxtaluminal black area of $>8 \text{ mm}^2$ in a plaque (which indicates a thrombus or a thin or absent fibrous cap)
2. Presence of discrete white areas in a hypoechoic plaque
3. TCD demonstration of reduced cerebral flow reserve

MRI

1. Intraplaque hemorrhage
2. Necrotic core size
3. Plaque volume
4. Silent embolic infarcts

Neuropathology

Mechanism of Plaque Growth and Rupture

Inflammation in a plaque is manifest by activated macrophages, mast cells and T-lymphocytes. The initiation of the process is the LDL-C particles into the arterial wall subintimal space. The particles are trapped by their high affinity for glycoprotein molecules at vulnerable sites (determined by wall shear stress and turbulent flow). If LDL-C is oxidized there is activation of endothelial surface adhesion molecules that attract monocytes to clear these oxidized lipid particles. The process initiates local inflammation and attracts smooth muscle cells. Monocytes differentiate into macrophages that engulf this lipid and transform into foam cells. When these macrophages die, lipid and free cholesterol is released into the extracellular space. Macrophages are attracted by chemokines secreted by inflammatory cells to form a necrotic core between the internal and external elastic membranes. The core is composed of cellular debris and free cholesterol which crystallizes; the sharp edges of the crystals disrupt fibrinous tissue. It appears that cholesterol expands during transformation from a liquid to a crystalline state and that this is what disrupts the overlying plaque's fibrinous cap. Statins decrease cholesterol crystallization and blunt sharp tipped crystal structures. The cholesterol crystals that pierce the arterial plaque and intima also trigger local and systemic inflammation.

The disruption of the fibrinous cap leads to thrombosis and distal embolization. Crystals in distal arteries can injure the endothelium leading to arterial spasm. Plaque instability persists after a TIA and then decreased with time after a stroke. Symptomatic carotid plaques remodel over time and become

more stabilized which has been associated with decreased expression of IL-6, caspase 3 and fewer macrophages. Plaques morphology as studies from carotid endarterectomy specimens revealed that younger patients had a greater inflammatory cell infiltrate while older patients had a larger lipid core and calcification. There was no linear progression of plaque instability with age. In asymptomatic patients with greater than 50% stenosis, plaques in men had:

1. Increased features that predict rupture
2. Thinner fibrous caps
3. Larger lipid cores (LRNC) for the same degree of stenosis than women

There is some evidence that larger LRNC causes plaque rupture while smaller LRNCs erode.

Alternative Mechanisms of TIA

1. Exercise and postural TIA
 - a. Suggestive of stenosis of aortic branch arteries
 - i. Takayasu's disease
 1. Amaurosis with walking or change of head position
2. TIA induced by hyperventilation
 - a. Moyamoya disease
3. Rheological causes of TIA include:
 - a. Polycythemia vera
 - b. Thrombocythemia
 - c. Hyperlipidemia
 - d. Macroglobulinemia
 - e. Sickle cell disease
 - f. Antiphospholipid antibodies
 - i. Emboli primarily from heart valves
4. Post thrombus TIA
 - a. Embolic material dislodged from the distal end of the thrombus (particularly in basilar artery stenosis)
 - b. Bypass the thrombus and enter vascular territory by collateral blood vessel
5. Hemodynamic alternations in brain circulation occur
 - a. Lumen in the carotid artery is decreased to 2.0 mm (normal is 5 to 10 mm)
 - b. A reduction of cross-sectional area of the vessel of $>95\%$
6. The clinical features most suggestive of cardioembolism are:
 - a. Sudden onset with maximum deficit at ictus
 - b. Decreased level of consciousness at onset
 - c. Sudden mutism (stunned appearance)
 - d. Sudden Wernicke's aphasia (temporo-parietal-occipital branch of the inferior division of MCA) in a setting of atrial fibrillation
 - e. Global aphasia without hemiparesis (top of the carotid; break-up of stem MCA embolus)
 - f. Valsalva maneuver at time of ictus (possible PFO)
 - g. Co-occurrence of cerebral and systemic emboli
 - h. The appropriate clinical setting

Lacunar presentations and especially multiple lacunar infarcts suggest small vessel disease. Bilateral cerebellar infarctions (territory of the posterior inferior cerebellar artery; dorsomedial thalamic lesion) suggest embolism to the top of the basilar artery often from a burst plaque in the vertebral artery.

Distal Field Ischemia

Another major cause of transient ischemic episodes is those from distal field ischemia that may lead to deep or superficial watershed hypoperfusion. The most frequent cause occurs in a setting of hypotension. A cerebral conducting vessel or a deep penetrating arteriole may be compromised from atherosclerosis and in the face of systemic hypotension cannot perfuse its usual territory after an embolus (poor washout). The M1 and P2 segments of the middle and posterior cerebral arteries as well as superficial branches of the cortical circulation are also often involved. Clinically, changing the position of a patient from the supine to the erect position may induce symptoms. Symptoms clear with position change and restoration of perfusion pressure. The major cortical areas of involvement are between the anterior cerebral/middle cerebral arteries and middle cerebral/posterior arteries. In the deep circulation of the carotid territory the watershed is between ascending lenticulostriate vessel from the MCA and descending cortical medullary arteries. MRI T2-weighted sequences demonstrate a rosary-like pattern of white matter hyper-intensities approximately 1 cm from the ventricle. Another possible mechanism is micro emboli dislodgement from a thrombus in a partially blocked arterial lumen.

Differential Diagnosis of Transient Ischemic Attacks

Overview

The differential diagnosis of transient ischemic attacks (TIA) is best thought of by mechanism. As noted above, most TIA's are embolic; either burst plaques (artery to artery) or fibrin/platelet clots from the heart. TIAs that are widely separated in time may arise from a large artery that is undergoing gradual occlusion. This process frequently occurs at the carotid bifurcation with shedding of cholesterol crystals and platelet/fibrin clots from the area of ulceration. The small cholesterol crystals may enter the ophthalmic and retinal arteries (Hollenhorst plaques) to cause amaurosis fugax. As an artery reaches a critical flow limiting state (usually greater than 70% occlusion) TIAs may occur sequentially from a combination of distal field ischemia or artery-to-artery emboli: They have been reported up to several hundred per day. They are known as crescendo TIAs and most often present as multiple episodes of amaurosis fugax. Tight stenosis of intracranial proximal conducting vessels occurs at characteristic locations (M1 of the MCA and A1 and P1 of the anterior and posterior circulations). This stenosis combined with lower systemic pressure and decreased cerebral pressure perfusion compromise cerebral blood flow in the distal field of the affected artery. MRI scans frequently demonstrate high

signal T2-weighted lesions periventricularly (rosary-lesions) that constitute the ischemic perivascular stripe (about 1/2 cm from the lateral ventricle). Tandem lesions of the carotid siphon and M1 segment cause neurological deficits that occur with fluctuations of blood pressure. Specific stenotic lesions cause stereotypical neurological symptoms as opposed to emboli that are slightly different from attack to attack, but often lodge in the same or adjacent vessels due to laminar flow characteristics.

Embolic TIAs, particularly from the heart cause specific neurologic deficits. Some are pathognomonic such as a pure receptive aphasia (in the setting of atrial fibrillation) which is characteristic of occlusion of the temporo-parietal-occipital branch of the inferior division of the MCA. Top of the basilar lodgment of emboli are also common and cause deficits depending on the course and lodgment of embolic material (midbrain, thalamus, parietal or occipital lobe). Patients suffering a dilated cardiomyopathy (ejection fraction less than 20–30%) invariably embolize over time.

Emboli overwhelmingly occur during wakefulness and during activities of daily living. Occasionally they occur when a patient gets up to urinate at night or during a valsalva maneuver (suggestive of a patent foramen ovale).

The characteristic clinical features of an embolus are: 1. a maximum deficit at ictus; 2. partial or complete recovery over hours to days; 3. pure Wernicke's aphasia (TPO branch of the inferior division of the MCA); 4. top of the basilar syndrome (signs dependent on cerebellar, midbrain, thalamic parietal or occipital vessel occlusion). Emboli may not cause catastrophic symptoms. A sudden headache or dizziness rather than hemiparesis, hemisensory loss or aphasia may be the only symptoms. Silent visual loss in superior quadrants suggests an embolus to the lower banks of the calcarine cortex in the setting of atrial fibrillation. Headache occurs if the dura is involved. There is often a small amount of blood in the CSF (about 100 RBCs/mm³). Seizures occur at onset in approximately 20–30% of patients.

Emboli are common with atrial fibrillation and the time required for EKG monitoring to rule out cryptogenic paroxysmal AF is being determined. The embolic material is often larger than that from artery to artery burst plaque material, the occlusion is more severe and the deficit longer lasting. Cardiomyopathies with ejection fractions of less than 20–30%, dyskinetic ventricular wall segments following myocardial infarction and rheumatically involved heart valves are common cardiac settings. Non-bacterial thrombotic emboli occur in 10% of cancer patients. Patent foramen ovale with atrial septal aneurysm as well as other congenital heart defects with right to left shunts have a significant risk of embolization. Sub-acute bacterial endocarditis is frequently announced by an embolus to the middle cerebral artery territory (mitral greater than aortic valve). Atrial myxomas are noted for small embolic strokes but the clinical picture may be clouded by fever or a remittent course from an immunological response to the myxomatous material. A peripheral cerebral vessel aneurysm suggests atrial myxoma or SBE.

Mobile plaques of the arch of the aorta and associated atherosclerotic detritus account for 30% of emboli to the posterior circulation and can now be evaluated with transesophageal echocardiography (TEE). Patent foramen ovale with or without atrial septal aneurysms or tunnel emboli account for a large number of formerly cryptogenic emboli in younger patients. Symptoms from extracranial arterial dissections are usually from emboli rather than limitation of flow.

Rarer causes of emboli are myxomatous degeneration of valves noted in mitral valve prolapse, verrucous endocarditis of SLE and air, fat, and calcium.

The only common condition that causes vasospasm and TIA is migraine. The differential points for migraine versus embolism or ischemia as a cause of neurological dysfunction are clear. Migraine is noted for positive visual symptoms of scintillating or fortification scotoma a gradual evolution over 20 minutes, one somatosensory complaint gradually merging with the next (visual symptoms merging with parietal sensory loss) and a headache after the neurological symptoms. Embolic or ischemic events are characterized by for the occurrence of all deficits simultaneously with primarily negative symptomatology (heaviness, visual loss and weakness). Family history and risk factors are different. However, CADASIL (cerebral AD arteriopathy with subcortical infarction and leukoencephalopathy) as well as mitochondrial disease are noted for concomitant migraine headaches. SLE and other connective tissues have a high incidence of associated migraine.

Emboli may occlude deep penetrating blood vessels that mimic lacunar disease (10–12 perforators from M1 or M2) that infarct the internal capsule or basal ganglia. Congophilic angiopathy patients may suffer repeated small bleeds that mimic emboli.

Imaging studies are extremely helpful. CT scan may demonstrate older lesions in two circulations or a dense MCA sign at the site of embolic occlusion. Diffusion weighted MRI demonstrates areas of acute ischemia and in tandem with perfusion studies, demonstrates the ischemic penumbra. Occasionally, one sees lesions not only in different circulation, but also with different intensities that suggest earlier events.

Transcranial Doppler studies, particularly during carotid surgery, have shown that most emboli are asymptomatic (similar to the lung). The frequency characteristics suggest size of the embolic material. Carotid Doppler characteristics suggest qualities and morphology of the ulcerated plaque or dissection. As Dr. Caplan has pointed out, it is most important to discover the type of bird that has left the nest (the nature of the embolic material).

Stroke Mimics

General Characteristics

Definitions

1. Stroke mimic:

- a. Acute neurologic symptoms that have other causes that simulate ischemic stroke
 - b. In many large series stroke mimics account for 10–20% of emergency room apparent strokes
2. Stroke chameleon:
 - a. Neurologic signs that present as other conditions that in fact are stroke
 - b. Thrombolytic therapy administered to stroke mimics has not resulted in symptomatic intracranial hemorrhage
 - i. Approximately less than 1% of symptomatic ICH after thrombolytic use for myocardial infarction

Neuroimaging

1. Neuroimaging negative cerebral ischemia:
 - a. The patient has had a stroke, but it is not documented on diffusion weighted MRI sequences (DWI):
 - i. The affected artery may have recanalized prior to loss of sodium/potassium membrane pump failure
 - ii. DWI resolution with 1.5 and 3 Tesla magnets may not detect microinfarcts (<2 mm)
 - iii. Transient ischemic attack or aborted stroke
2. Stroke mimics with neuroimaging negative cerebral ischemia (NNCI) have shorter hospital stays, a greatly improved NIHSS and good functional recovery

Differential Diagnosis of Stroke Mimics

1. Seizures with Todd's paralysis
2. Complicated migraine
3. Psychiatric conditions (somatization)
4. Tumors (with or without bleeding)
5. Metabolic dysfunction:
 - a. Hypoglycemia
 - b. Liver failure
6. Phenobarbital overdose
7. Mitochondrial disease (MELAS)
8. Methotrexate leukoencephalopathy
9. Demyelinating disease
10. Cervical epidural blood or infection

Differential Diagnosis of a Chameleon

1. Syncope
2. Altered mental status
3. Deterioration of a compensated stroke from sepsis or metabolic dysfunction
4. Acute coronary syndrome (PICA may cause chest pain)
5. Hypertensive emergency
6. Systemic infection

Differential Points Between Acute Ischemic Strokes Versus Stroke Mimics

1. Acute ischemic stroke patients are older than stroke mimics

2. Increased chance of having atrial fibrillation and dyslipidemia (stroke)
3. No pure sensory signs or symptoms (mimics)
4. Stroke mimics have a higher incidence in females than males; females have lower admission NIHSS
5. Stroke mimics tend to have loss of function that is not consistent with a vascular territory
6. The onset of symptoms in stroke mimics is often not apoplectic
7. A blood pressure of less than 55 mm Hg (diastolic) is against stroke

Differential Diagnosis of Restricted Diffusion

1. Acute ischemia
2. Bacterial abscess
3. Epidermoid tumors
4. Central portions of some primary and secondary brain tumors that have outgrown their blood supply
5. Demyelinating diseases and other inflammatory conditions

Differential Diagnosis of Cortically Restricted Diffusion

1. Ischemia
2. Venous infarction
3. Viral encephalitis
4. Meningitis
5. Creutzfeldt-Jakob disease
6. Mitochondrial cytopathies
7. Post-ictal stroke

Differential Diagnosis of Stroke Mimics

Seizure

Overview

A history of loss of consciousness, Jacksonian march and post-ictal state are most helpful. The pattern of seizure activity if involving the motor strip is determined by innervation density of the body part and depolarization threshold of the affected neurons. In general, if the motor strip is the elliptical zone, the corner of the mouth and thumb twitch first which is progressively followed by the arm and then the distal leg. The shoulder and hip are often spared. Most patients who have lost consciousness awaken confused, have a dull throbbing headache and are perspiring. They require minutes to hours to return to normal. They frequently complain of subscapular and quadriceps pain. If there is an underlying structural lesion they may suffer a Todd's paralysis. Todd's paralysis from a focal seizure usually lasts less than one hour but may persist for one week to 10 days, particularly if the seizures emanate from speech areas. Extremely rarely, a seizure emanating from the suppressor strip of the motor cortex (area 6) may cause contralateral paralysis of the face and arm. A shaking TIA from carotid stenosis and hemispheric ischemia (distal field ischemia) occurs from decreased cerebral blood flow.

The movements are brief, arrhythmic, flailing or jerking of the arm or leg. There is no loss of consciousness, aura, incontinence or Jacksonian march. The symptoms are initiated by maneuvers that may decrease hemispheric perfusion such as arising from a supine position or getting out of a chair. Rarely does it occur from hyperextension of the neck or hyperventilation (decreasing pCO₂ and consequent cerebral vasospasm). These features also differentiate a shaking unilateral TIA from hemiballism, dystonia and focal myoclonus which may occur on an ischemic basis. Bilateral shaking of the upper extremities and lower extremities may occur with internal capsule or cerebral peduncle ischemia (top of the basilar distal field ischemia).

Atrial Fibrillation

General Characteristics

1. The normal regular impulse generated by the atrial node is overwhelmed by rapid depolarization originating in the atria and adjacent parts of the pulmonary veins
2. The source of these depolarizations are autonomous foci (pulmonary veins) or a left atrial reentrant electrical spiral waves (rotors) or repetitive focal beats

Clinical Manifestations

1. AF may be asymptomatic as the atria account for about 15% of the cardiac ejection fraction
2. Frequent micturition
3. Awareness of the abnormal rhythm by the patient

Neurologic Manifestations

1. There is a 5X risk of cardioembolic stroke
2. Classic sudden onset of Wernicke's aphasia without hemiparesis
3. Emboli most often go to the MCA vascular territory
4. Usually long TIA as fibrin platelet clots (red) are large
5. A putative cause of cryptogenic stroke

Neuropathology

1. Progressive fibrosis of the atria due to atrial dilatation. There are genetic, endocrine (thyroid) and inflammatory pathologies (sarcoid). Inflammation occurs with sarcoid
2. Autoimmune disorders demonstrate antibodies against myosin heavy chains
3. Mutation of the Lamin A/C gene causes fibrosis of the atria with fibrillation
4. Molecular events leading to fibrosis:
 - a. Activation of the renin aldosterone angiotensin system that induce metalloproteinases and disintegrins. These process leads to remodeling and fibrosis if it extends to the sinus node and atrioventricular node, it correlates with sick sinus syndrome
5. Lower atrial wall motility
6. Large left atrium

Laboratory Evaluation

1. Fibrillary conduction occurs due to heterogeneous atrial recovery from excitations
2. Depolarization electrical waves generated by AF sources undergo repetitive, spatially distributed break-ups and fragmentation ("fibrillatory conduction")
3. Absent P waves
4. Rhythm is irregularly irregular and may be rapid or slow
5. No difference in plasma levels of hemostatic markers in patients with atrial flutter and those with normal sinus rhythm

Atrial Flutter*General Characteristics*

1. Caused by a reentrant rhythm from the right or left atrium. It is due to differences in the refractory periods of atrial tissue. This causes depolarization of atrial tissue that moves in a self-perpetuating loop
2. The AV node blocks atrial impulses at about 180 beats/minute due to its longer refractory period. The block is dependent on the patient's age

Clinical Manifestations

1. If the patient is cardiovascularly compromised the rapid heart rate may cause shortness of breath, chest pain, dizziness and occasionally feelings of impending doom (ischemia of the medial temporal lobes)
2. Rate related hypotension due to poor ventricular filling and a decreased ejection fraction
3. Type I atrial flutter has an atrial rate of 240–340 beats/minute. The reentrant loop traverses a fibrous band in the lower atrium between the inferior vena cavae and the tricuspid valve
4. Embolism
5. Sudden Death

Neuropathology

1. Thrombus formation in the atrial appendages
2. The reentrant electrical loop traverses a fibrous band in the lower atrium between the inferior vena cavae and the tricuspid valve

Laboratory Evaluation

1. Atrial flutter is an organized electrical conduction usually in the right atrium. EKG reveals:
 - a. Characteristic: saw-toothed P-waves of constant amplitude and frequency

Mechanism of Embolism in Atrial Fibrillation and Atrial Flutter

The traditional concept is that atrial thrombosis forms after greater than two days of AF or flutter and embolizes due to shear forces. In the setting of AF, the thrombus organizes

over 14 days. Left atrial thrombus may form before the onset of AF in the face of sinus arrhythmia. Conversion to sinus rhythm may increase the thrombogenic milieu of the left atrium. An atrial thrombus may form in the acute phase of AF. Atrial flutter, which is characterized by a rate of greater than 240 beats/minute in the absence of an isoelectric baseline between deflections, occurs secondary to atrial dilatation. It may occur in patients with a pre-existing accessory conduction pathway (bundle of Kent in Wolff-Parkinson-White syndrome). Extremely high ventricular rate may degenerate into ventricular fibrillation with hemodynamic collapse.

Hypoglycemia*Overview*

The usual neurological symptom of hypoglycemia include: 1. altered level of consciousness; 2. personality change; 3. seizure; 4. hemiplegia; 5. coma. The most common cause is inadvertent overdose of insulin or hypoglycemic agents. Systemic causes include renal or hepatic failure, Addison's disease, severe sepsis and rarely an insulin secreting tumor. Lesions can be seen on DWI MRI within 45 minutes after symptom onset and are present at 12 hours on T2-weighted imaging. Patients with good clinical recovery have clearing of lesions within 6 hours. Acute hypoglycemia may mimic acute stroke or brain imaging in 20% of patients. CT generally reveals unilateral cortical and adjacent subcortical hypodensities and swelling to a greater degree than cortical or lacunar stroke. Less severe episodes cause hemiparesis and smaller corticospinal tract lesions. Rapid response to glucose is diagnostic. A parasympathetic response (hyper salivation), slightly low temperature 97°F are helpful. The imaged lesions may not strictly conform to a vascular pattern.

Multiple Sclerosis (MS)*Overview*

Clinically isolated neurologic signs and symptoms are frequent in MS. The most usual of these are optic neuritis, paresthesia, and intranuclear ophthalmoplegia. The MRI findings of Dawson's fingers (callosal lesions), optic nerve involvement, and multiple white matter intensities on T2-weighted MRI secure the diagnosis. The short symptoms of MS, those that last for a few minutes are thought to occur from the Uhthoff phenomena (failure of partially demyelinated axons to conduct if their temperature is raised) or block from ion blocking antibodies. Focal motor and sensory deficits often occur with MS. However optic nerve involvement, cognitive dysfunction, ataxia and bilateral hyperreflexia that persist differentiate it from TIA. Spinal cord signs predominate.

Migraine*Overview*

Complex, familial and Bickerstaff's migraine may all be confused with transient cerebral ischemia. In general, various

forms of migraine can be differentiated from transient cerebral ischemia by triggering factors, age and hereditary patterns. Most migraine symptoms are positive and the progression is from one modality to the next serially. Thus, visual loss or scotoma slowly melds with parietal sensory loss and then weakness. The spreading cortical depression usually occurs over twenty minutes and is then followed by a unilateral or bifrontal throbbing headache. Though patients with ischemia suffer deficits in several modalities simultaneously, in general these are negative and include loss of vision, numbness and weakness. The headache is usually concomitant with the deficits occur most frequently from posterior rather than anterior circulation ischemia. Bickerstaff migraine affects the vertebrobasilar circulation and is associated with parenthesis of the hands, perioral numbness, bilateral visual disturbance (visual field deficits, scintillating scotoma, and teichopsia), dysarthria, ataxia and loss of consciousness. It may be confused with a brainstem stroke. Complicated migraine (that with neurological signs) and hemiplegic migraine may also be confused with TIA. Hemiplegic migraine usually affects the same side of affected family members and is less likely to cause permanent deficits than the sporadic form. The usual deficit (hemiplegia) lasts for 2–3 days.

Systemic Infection

Overview

1. Chest most common source
2. Acute illness exacerbates an old ischemic lesion (breakdown of prior compensatory mechanisms)
3. Activation of immune aspects of atherosclerotic lesions

Hypotension

Overview

1. Unusual in ischemic disease and TIA; blood pressure of less than 120/80 occurs at presentation in 7.1% of stroke patients
2. May occur if the stroke or ischemia impairs the vasomotor centers of the dorsolateral medulla or pons (severe vertebral or basilar atherosclerosis)

Dural Arteriovenous Fistula

Overview

1. Clinical history of a brief focal neurologic deficit
2. Imaging evidence of a perfusion deficit in the appropriate location
3. Increase of mean transit time (MTT) and regional cerebral blood volume (rCBV); a measure of venous congestion
4. In rare instances, transient neurological deficits may be due to venous congestion

Central Nervous System Vasculitis

Overview

1. Primary angiitis of the CNS (PACNS)

2. Systemic vasculitis (the CNS is involved in 20% of patients)
3. Usual presenting symptoms of PACNS are headache and cognitive impairment
4. Affects small and medium-sized vessels of the brain parenchyma, spinal cord and leptomeninges
5. PACNS is most common in males in the fourth and fifth decades and represents 1.2% of vasculitis involving the CNS
6. In PACNS, transient ischemic attacks occur later in the course of the illness and is seen in approximately 28% of patients

Cerebral Amyloid Angiopathy (CAA)

Overview

1. Usual presentation is cognitive decline or lobar symptomatic intracerebral hemorrhage
2. Some attacks similar to migraine with aura
3. Patients that experience prolonged stereotyped sensory symptoms: may predate ICH

Focal Subarachnoid Hemorrhage (FSH)

Overview

1. FSH presented in 4 patients with transient migraine auras
 - a. No prior migraine history in these elderly patients
 - b. FSH of contralateral cortical sulcus
 - c. Mechanism is possible cortical spreading depression; possible underlying CAA

Mitochondrial Disease (MELAS)

Overview

1. Migraine like headaches
2. Painful myoclonic jerks
3. Visual complaints
4. Rapid resolving stroke-like picture in parietal, temporal and occipital lobes
5. Non-vascular territory involvement
6. Usually presents in childhood or adolescence but may occur for the first time in the elderly
7. Headaches, muscle cramps, blurred vision, cardiac conduction deficits, hearing loss, psychiatric disorders, seizures and gastrointestinal symptoms may occur concomitantly
8. MRI predominantly reveals gray matter lesions not confined to vascular territories

Intracranial Tumors That Mimic Transient Cerebral Ischemia

Overview

1. Underlying features associated with tumor are:
 - a. Focal seizure-like activity
 - b. Pure sensory symptoms
 - c. Loss of consciousness
 - d. Isolated aphasia or speech arrest

Subdural Hematoma (SDH)

Overview

1. Direct bleeding into the subdural space from head trauma
2. Vessels in the leptomeninges rebleed that may produce intermittent symptoms
3. Usually spasticity of the afferent extremities
4. Third cranial nerve signs
5. Ruptured intracranial aneurysm
6. Ruptured cortical artery
7. Neoplasm
8. Hematological disorders
9. Anticoagulant/thrombolytic therapy
10. Cerebral Amyloid Angiopathy
11. Dural arteriovenous fistula
12. Acquired immune deficiency syndrome

Temperature Dependent Disease

Overview

1. Diseases that are exacerbated by heat may demonstrate the onset of focal symptoms:
 - a. Demyelinating disease (Uhthoff phenomena)
 - b. Myasthenia Gravis
 - c. Lambert-Eaton syndrome
 - d. Fabry's disease
2. The neuromuscular junction diseases have cranial nerve involvement; fluctuating weakness and maintained reflexes
3. Lambert-Eaton patients lose reflexes but gain strength with exercise
4. Myasthenic patients weaken with exercise but may have increased reflexes (spread of sarcolemma acetylcholine sensitivity)

Subclavian Steal

Overview

1. Rarely is clinically significant
2. In general, the process is exacerbated when the patient vigorously exercises the left arm overhead (which further lowers the pressure in the arm by dilating muscular vessels)
3. The subclavian artery is stenosed prior to the origin of the vertebral artery (decreases arm blood pressure)
4. Blood flows from the ipsilateral vertebral artery into the exercising arm
5. Patients demonstrate brainstem signs and symptoms which include vertigo, drop attacks, arm claudication (rare occurrence), ataxia presyncope, hearing loss
6. Linear correlation between increasing arm blood pressure difference and symptoms
7. Symptomatic patients may have concurrent cerebrovascular disease

Syncope (Discussed in Chapter on Convulsions)

Overview

1. Reflex (neurally – mediated):

- a. Emotional distress (a major trigger)
- b. Reflex causes: cough, gastrointestinal, micturition, post-exercise, post prandial and stretch
- c. Specific functions (weight lifting, laughing, wind instrument)
- d. Carotid sinus pressure
- e. Atypical (no specific triggers)
2. Orthostatic syncope:
 - a. Primary autonomic failure (genetic mutations)
 - b. Secondary autonomic failure (processes that destroy autonomic nerves or central nuclei and pathways)
 - c. Volume depletion
3. Cardiac syncope:
 - a. Arrhythmia
 - i. Bradyarrhythmia
 - ii. Tachyarrhythmia
 - iii. Drug-induced
 - iv. Brugada syndrome
 - v. Long QT syndrome
 - b. Structural cardiovascular disease
 - c. Miscellaneous:
 - i. Pulmonary embolus (spasm of blood vessels and cardiac arrhythmia)
 - ii. Aortic dissection (hypotension, cardiac tamponade, hemispheric or spinal lesions)
 - iii. Pulmonary hypertension (cerebra; hypoxia)

Cryptogenic Stroke

General Characteristics

1. The TOAST classification (Trial of ORG 10172 in Acute Stroke Treatment): a brain infarction that is not attributable to a source of definite cardioembolism (CE), large artery atherosclerosis (LAA) or small artery disease (SAD)
2. Risk factors include:
 - a. Left ventricular thrombi (often infarction)
 - b. Aortic plaques
 - c. Hypercoagulable states
 - d. Patent foramen ovale/atrial septal aneurysm and atrial septal defects
 - e. Inflammation and infection
 - f. DM, homocysteinemia, hypertension, family history, hyperlipidemia are possible causes
 - g. Prior TIA
 - h. Smoking
 - i. Race and ethnicity

Clinical Manifestations

1. Superficial hemispheric infarction in 75% of patients
2. Lacunar infarcts are rare: less than 5%
3. Severity at presentation: less than cardioembolic stroke but greater than lacunar stroke
4. A significant proportion of cryptogenic strokes respect embolic infarct topography

5. The same incidence of parenchymal hemorrhage as cardioembolic stroke
6. Large subcortical strokes greater than 15 mm suggest cardioembolism or are cryptogenic
7. Abnormalities detected by transthoracic echocardiography include:
 - a. Enlarged left atrium
 - b. Thrombus in an atrium
 - c. Spontaneous echo contrast ("smoke" poor quality of the stroke ejection fraction)
 - d. Patent foramen ovale
 - e. Atrial septal aneurysm
 - f. Aortic plaques
 - g. Mitral valve prolapse
8. Possibly a better prognosis with lower recurrence rate than identifies strokes

Arterial Localization – (Arterial Topology/Stroke Localization)

Clinical Symptoms and Signs of Major Vessel Stroke

Carotid Occlusion Overview

A patient that has suffered a complete carotid occlusion is not infrequently asymptomatic if the process has been insidious and has been accompanied by extensive collateralization. Patients have been described with slowly developing complete carotid and vertebral occlusion that are relatively asymptomatic. In the face of acute occlusion without sufficient collateralization patients suffer weakness or paralysis of the contralateral arm, face and leg, the head and eyes are deviated to the side of the lesion (may not be dolled across the midline to the opposite side for 12–24 hrs) and may have a contralateral hemisensory deficit to all modalities. Cerebral edema supervenes within the first 12–24 hours and is manifest by lethargy, Cheyne–Stokes respiration exacerbated (if cardiac or pulmonary disease is present) and slight downward deviation of the eyes (5° below the horizontal). The arm on the contralateral side is pronated and the leg externally rotated. If the infarction is in the dominant hemisphere (90% of dextral and sinistrals are dominant in the left hemisphere) expressive and receptive aphasia is evident. If the occluded carotid affects the non-dominant hemisphere (NDH) hemineglect may be associated with unnoticed weakness of the contralateral leg and consequent falling when walking or standing. Similarly contralateral coarse shaking or involuntary movements may be seen in the extremities opposite the stenotic carotid artery precipitated by standing, walking, or head hyperextension due to ischemia of the ipsilateral corticospinal pathways (shaking TIA).

Severe Preocclusive Carotid Disease

Severe preocclusive carotid disease may present with recurrent TIA's, a stepwise onset, or a pseudotumoral slowly progressive form. Ischemic orbital pain may awaken the patient

from sleep and is described as severe, deep and boring. Ischemic oculopathy with a swollen disc, and neovascularization may occur in conjunction with engorgement of conjunctival and episcleral vessels. The intraocular pressure may be extremely low. Optic atrophy on the ischemic side is rare. High-grade stenosis may be associated with a unilateral loss of vision in bright light which may persist for seconds to hours and is related to delayed regeneration of visual pigments in the retinal pigment epithelial layer. These phenomena may occur bilaterally if both carotids are severely stenotic. Monocular visual loss may also be described as dimming or blurring of vision or seeing through a fog. The attacks are short, from 1–2 minutes, but occasionally last for 20 to 30 minutes. They are not positionally related.

Bruits are frequently associated with severe stenosis but frequently disappear when the occlusion reaches approximately 90% of the arterial diameter. A diastolic component of the bruit is very significant. A bruit may be heard contralaterally in a minimally affected carotid due to augmented blood flow through the less diseased artery.

Acute Carotid Occlusion

Carotid occlusion at or below the bifurcation may cause a complete Horner's syndrome with ptosis meiosis, facial anhidrosis and apparent enophthalmos. If only the internal carotid is occluded past the branching of the external carotid there, will be no facial anhidrosis. The sympathetics surround the internal carotid artery to innervate the iris whereas the external carotid carries sympathetic innervation to the face. In a few patients, the pupil on the affected side will be dilated (less than 10%) and unresponsive to light due to iris ischemia. Pupillary cortical representation may lie in the motor sensory cortex or the prefrontal eye fields so that unilateral infarction may cause unilateral or bilateral ptosis (cortical innervation to the central caudal nucleus which innervates the levator palpebrae) and ipsilateral meiosis. This constellation is known as a cortical baby Horner's syndrome. If severe carotid stenosis has preceded acute occlusion, the arcus senilis may be less apparent on the affected side. A major motor seizure may occur in a small proportion of patients concomitant with the occlusion. Waxing and waning of consciousness occurs during the first few days and Cheyne–Stokes respiration is common. The anterior 2/3 of the hemisphere is most severely affected. Rarely the affected side demonstrates hyperhidrosis (involvement of the anterior hypothalamus supplied by the meningo-hypophyseal trunk of the cavernous carotid).

The hemisphere may be more severely involved if it is isolated due to hypoplasia of the anterior or posterior communicating arteries or if there is a fetal origin of the posterior cerebral artery from the carotid (concomitant hypoplastic ipsilateral posterior communicating artery). The stenotic or emboli lesions may extend to occlude the origin of the anterior cerebral artery with its consequent occlusion or in the case of a fetal origin of the posterior cerebral artery it may be occluded along with the middle cerebral artery.

The size of the ICA occlusion may be minimized by collateral circulation through the Circle of Willis, cortical leptomeningeal vessels and those from the external carotid (internal maxillary, superficial temporal artery to meningeal vessels, ophthalmic and external carotid vessels to middle cerebral artery branches).

Clinical Correlate of the Acute Carotid Occlusion

1. Lethargy, fluctuating level of consciousness, rare seizures
2. Horner's syndrome (ipsilateral)
3. 10% dilated unresponsive pupil (iris ischemia)
4. Periodic respiratory breathing pattern
5. Head and eyes deviated ipsilaterally (frontal eye fields are 8 and 10)
6. Hemisensory deficit to all modalities (contralaterally); vibration spared
7. Broca's aphasia > Wernicke's (DH)
8. Hemineglect contralateral side (NDH)
9. Pronated arm, externally rotated leg (contralaterally)
10. Depressed reflexes (contralaterally) acutely
11. Babinski sign (contralaterally)

Features of Intracranial Internal Carotid Occlusive Disease

Atherosclerosis of the Carotid Siphon

Calcification of the siphon is common and is coexistent with extracranial disease. There is a high death rate from coronary artery disease and disease in this location is more common in Afro-Americans than Caucasians. There are frequent concordant lesions in the origins of the internal carotid and vertebral arteries. Tandem ICA and siphon disease is common. There is a higher ratio of stroke to TIA in carotid siphon disease than cervical carotid disease. The major clinical differential points of siphon versus internal carotid diseases are:

1. Few episodes of amaurosis fugax
2. No ocular retinal pathology
3. Retrograde extension of the siphon clot may cause delayed optic ischemia
4. Leg is more affected than the arm
5. Associated scattered ACA and MCA infarcts are noted. These may involve the foot and face, sparing the arm
6. Slowly progressive symptoms
7. Worse prognosis than ICA origin disease
8. There are no collaterals through the external carotid artery

Occlusion of the Top of the Carotid (T Portion)

A block at the top of the carotid causes infarction of both the anterior cerebral and the internal carotid artery. It is most common with sickle cell disease and with circulating anticoagulants.

The Anterior Choroidal Artery (ACHA) Syndrome

The anterior choroidal artery is the second branch of the internal carotid artery. It partially supplies the caudal 2/3 of

the posterior limb of the internal capsule, the posterior optic tract, the uncus of the temporal lobe, medial GP₁, cerebral peduncle, lateral geniculate body and portions of the thalamus. AchA does not supply the corona radiata or the ventricular wall. Its most consistent branches are to the optic tract, cerebral peduncle and choroid plexus. There are variable anastomosis with branches of the MCA, PCA and posterior communicating artery. This artery supplies territories in both anterior and posterior circulations.

Most Consistent Clinical Presentation

1. Hemiparesis, hemisensory loss, hemianopsia
 - a. Pure motor hemiplegia (face, arm and leg affected)
 - b. Bilateral AchA infarcts:
 - i. Pseudo bulbar palsy
 - ii. Mutism
 - iii. Quadriparesis
 - c. Hemisensory symptoms: incomplete or temporary and comprise all modalities

Unusual Sensory Manifestations

1. Hemisensory deficit with spared proprioception
2. Painful thalamic-type syndrome
 - a. Formication (crawling paresthesias)
 - b. Feeling of limb swelling
 - c. Pain in the arms and legs
3. Hemiataxia with the sensory symptoms
4. Temporary sensory loss

Clinical Manifestations

1. Motor Deficits:
 - a. Face, arm and leg affected
 - b. Ataxic hemiparesis (thalamic)
 - c. Hypesthetic ataxic hemiparesis
2. Visual field deficits and eye movement abnormalities:
 - a. Congruent homonymous visual field deficit sparing the central sector
 - i. Lateral geniculate body infarcted
 - ii. Known as a quadruple sectoranopic defect
 - b. Homonymous congruent superior quadrantanopia
 - i. With or without macular sparing
 - c. Congruent homonymous hemianopia
 - d. Ipsilateral conjugate eye deviation

Higher Cortical Deficits with AchA Infarction (Unusual)

1. Non-dominant hemisphere
 - a. Visual neglect
 - b. Constructional apraxia
 - c. Short term visual memory loss
 - d. Anosognosia
 - e. Motor impersistence
2. Dominant hemisphere infarction
 - a. Decreased fluency
 - b. Semantic paraphasia

- c. Perseveration
- d. Deficits in language processing
- e. Poor understanding of word associations
- f. Poor comprehension
- g. Short term verbal memory loss

AchA Infarction of Lateral Thalamus and Posterior Limb of the Internal Capsule

1. Dysarthria
2. Language processing defects
3. Short term verbal memory loss

Bilateral AchA Infarction

1. Urinary incontinence without dementia
2. Dysarthria
3. Dysphagia
4. Dysphonia
5. Palatal paralysis – (may occur with unilateral stroke)
6. Pseudobulbar affect
7. Depression
8. Blunted affect
9. Mutism
10. Lethargy

Anatomic Variants of AchA

1. Anastomosis with:
 - a. MCA
 - b. Posterior communicating artery
2. Paraventricular areas
 - a. Watershed between the deep MCA perforators and lateral lenticulostriate arteries
 - b. Watershed between the posterior choroidal arteries (near the superior portion of the internal capsule)
3. May supply the temporo-occipital lobe (PCA territory)

Pathogenesis of AchA Occlusion

1. Surgical manipulation
 - a. Aneurysm (spasm)
 - b. Seizure surgery
2. Hyperviscosity states
3. Decreased perfusion
4. Embolism
 - a. Cardiac
 - b. Often with concomitant MCA embolism
5. Thrombosis
 - a. Intracranial atherosclerosis

Anterior Cerebral Artery

Overview

The anterior cerebral artery arises from the internal carotid artery at the level of the anterior clinoid process to supply the medial surfaces of the frontal and parietal lobes as well as the anterior 4/5 of the corpus callosum, the ventrobasilar frontal cortex (substantia innominata, septal nuclei, and

nuclei of the diagonal band) and the anterior thalamus. The A1 segment from the carotid joins the anterior communicating artery AcoA in the interhemispheric fissure. There are approximately 8 perforating branches from the A1 segment. Proximal A1 branches perfuse the genu, contiguous areas of the posterior limb of the internal capsule, the anterior hypothalamus, anteroventral putamen and pallidum. Distal A1 segment branches perfuse the optic nerve, chiasm and tract. The perforating branches of the AcoA perfuse the most anterior aspects of the hypothalamus, the basal forebrain, and the medial anterior commissure, fornix and lamina terminalis, corpus callosum and anterior cingulum. A2 branches, part of the ascending segment, perfuse the gyrus rectus, the inferior frontal cortex, the anterior thalamus and the rostrum of the corpus callosum. The recurrent artery of Heubner takes origin near the AcoA and travels backward along the A1 segment to penetrate the brain at the lateral anterior perforating substance, Sylvian fissure or orbitofrontal cortex to supply the head of the caudate and anterior limb of the internal capsule.

The distal A2–A5 segments comprise the pericallosal and callosomarginal arteries. If the callosomarginal artery is absent, all cortical branches originate from the pericallosal artery (18–60%) of patients. The ascending orbitofrontal and the frontopolar arteries arise from the A2 segment and supply the inferior, medial and lateral surfaces of the frontal pole. The superior frontal gyrus is supplied rostrocaudally by A2–A4 segments of the pericallosal artery. The paracentral artery, the superior parietal artery may arise from either the callosal marginal or the A4–A5 segment of the pericallosal artery to supply the superior precuneus while the posterior inferior cuneus is supplied by A5 branches of the inferior parietal artery from the pericallosal artery. There are a great number of normal variations of the anterior cerebral artery and anterior portion of the Circle of Willis.

The usual etiology of ACA-territory infarction is a cardioembolic stroke particularly if there is increased blood flow through the artery due to a contralateral ICA occlusion or a congenital defect of the anterior Circle of Willis. In situ thrombosis of the artery is more common in Asian patients. Extension of thrombus from the ipsilateral carotid is the usual atherosclerotic mechanism. Occlusion by transtentorial herniation, vasospasm from ruptured ACOA aneurysm or embolisms from these aneurysms are particular causes of infarction peculiar to this artery. Bilateral occlusion is rare but has been reported. Approximately 25% of these patients have had an azygous or unilateral supply of both ACAs from one carotid artery, the others having suffered probable emboli from atrial fibrillation or recent myocardial infarction. Bilateral infarction of the ACA causes akinetic mutism with poor recovery. The artery may be infarcted by the angitis of collagen vascular disease, prothrombotic states, lacunar infarction, rare emboli (fat, air, and atrial myxoma), dissection or fibromuscular dysplasia.

Anterior Cerebral Artery (ACA) Stroke: Clinical Signs and Symptoms

The clinical signs and symptoms of ACA are distinct. The artery is involved primarily following vasospasm secondary to anterior communicating aneurysm rupture, damage from neurosurgical procedures, propagation from ICA occlusion and artery-to-artery embolism from more proximal atherosclerotic occlusive disease.

Cortical branch occlusion causes severe weakness of the distal foot and leg, the proximal arm with sparing of the face and tongue. The patient can frequently perform fractional movement of the hand and thumb. Muscle tone is flaccid early and then becomes spastic. The paracentral lobule, upper motor cortex and subcortical fibers from these areas that project into the corona radiata are affected. A few patients may only suffer a crural monoplegia (contralateral weakness of the leg). The pattern of weakness may vary considerably with some patients suffering arm and leg weakness to the same degree, others with hemiparesis and brachial predominance. Distal occlusion of the ACA may also cause pure motor hemiparesis and homolateral ataxia and crural paresis.

Patterns of ACA Weakness

1. Paresis of foot and leg > arm; face and tongue spared
2. Crural monoplegia (contralateral paralysis of leg and foot)
3. Contralateral arm and leg involved equally
4. Contralateral hemiparesis with brachial facial predominance
5. Homolateral ataxia with crural paresis
6. Pure motor hemiparesis

Infarction of the recurrent artery of Heubner from the A1 segments affects the head of the caudate, the putamen and the anterior limb of the internal capsule. This lesion may cause faciobrachial predominance in the observed hemiparesis. The proximal perforators from A1 may also supply the genu and anterior internal capsule. Right-sided > left-sided medial frontal infarction that includes the SMA may cause contralateral motor neglect.

Sensory deficits are most severe in the foot and leg contralaterally. They are most often in discriminative touch but may be severe to all modalities.

Psychomotor Dysfunction

The anterior cerebral artery supplies regions of the limbic system and basal ganglia essential for integration of emotional aspects of movement and frontal lobe function. Transient loss of consciousness may occur with ACA infarction. Bilateral damage to the anterior cingulate gyrus or head of the caudate nucleus may cause akinetic mutism. These patients do not initiate speech or movement and have no emotional expression. They do not respond to sensory stimuli but may follow the examiner with their eyes. Transient abulia may be seen with a unilateral lesion of the caudate head and cingulate gyrus and is characterized by decreased spontaneous speech and delayed response to questions, minimal spontaneous activity

and impersistence. These patients may speak almost normally on the telephone.

Infarction of projections from the caudate nucleus to the orbital and dorsolateral prefrontal cortex causes agitation hyperactivity and delirium. If they occur on the dominant side and disrupt connections into the thalamus, aphasia may be noted. Medial frontal lobe infarction causes euphoria, lability of affect and pathological jocularity. Antegrade amnesia may occur from damage to the paramedian basal forebrain during aneurysm surgery that damages perforators from the ACOA. If concomitant mesial frontal damage occurs confabulation may occur with the amnesia.

Aphasia and Language Disorders

Damage to the left supplementary motor area (SMA) may cause decreased spontaneous speech, normal articulation, repetition and comprehension. Transcortical motor or mixed transcortical aphasia has been documented with SMA lesions. Mirror writing can develop with right SMA lesions. Acquired stuttering may occur with anterior callosal or bifrontal lesions. Occlusion of either the right or left anterior cerebral artery may cause muteness.

Anterior Cerebral Artery Speech Disorders

1. Muteness
2. Transcortical motor aphasia
3. Transcortical sensory aphasia
4. Acquired stuttering
5. Whispered speech
6. Reduced spontaneous speech
7. Normal comprehension
8. Normal articulation

Urinary and Fecal Incontinence

Unilateral or bilateral ACA infarction may cause urinary and fecal incontinence by damaging the midportion of the superolateral and medial superior frontal gyrus and the anterior cingulate gyrus. Damage to the paracentral lobule may induce precipitate micturition that cause patients to urinate uninhibitedly when their bladder is partially full.

The Grasp Reaction of ACA Infarction

The grasp reflex is caused by a contralateral basal ganglia or frontal lesion. This response is flexion and adduction of the hand when an object is gently moved from the palmar hypothenar eminence through the palmar index finger and thumb. This is an involuntary response. The instinctive grasp reaction is elicited by a stationary touch in the same areas of the hand and consists of: 1. several grasping movements directed toward the object; 2. a true grasp is one grasp in response to an object; 3. the traction response follows stretching of the patient's flexed fingers that he cannot release; 4. in a magnetic response in which the patient shadows the movements of the examiner's hand. A contralateral lesion of the mesial superior frontal and cingulate gyrus or rarely the basal ganglia causes a grasp reflex.

Callosal Disconnection Syndromes Following ACA Infarction

In right-handed patients, a left handed ideomotor apraxia may occur following ACA infarction. The patient is unable to perform a simple command with the left hand such as a military salute. This is due to disconnection of Wernicke's area and the premotor cortex from the premotor and primary motor cortex of the right hemisphere. It may also occur after infarction of the left premotor area (8), the anterior corpus callosum or the right premotor cortex. The patient may have impaired ability to imitate the examiner's movements with the left hand.

Left-hand agraphia may be seen with ACA infarction. Patients are unable to write readable letters, utilize correct words and often demonstrate substitutions or perseverations both to dictation and with spontaneous writing. No linguistic mistakes are made with the right hand. They are able to write or copy correctly but cannot type or use block letters. In general, ideomotor apraxia and agraphia occur concomitantly with callosal lesions but may be dissociated. The callosal fibers for praxis cross the midline in the rostral portion of the posterior body of the corpus callosum.

Unilateral tactile anomia occurs in the left hand. The patient can manipulate the objects correctly with either hand. He has an associated unilateral left agraphia that is caused by a lesion of the posterior part of the body of the corpus callosum. Right handed constructional dysfunction and crossed pseudoneglect to both visual and tactile stimuli. Line dissection tasks have been noted with callosal posterior body infarction. A crossed visuomotor apraxia results from damage to the dorsal aspect of the posterior callosum. A crossed avoiding reaction (patient unable to move the left hand when an object is placed in the right hemisphere) has been seen with a lesion of the genu and body of the corpus callosum.

The alien hand syndrome denotes a patient who has a feeling that the left hand does not belong to him and notes that one hand works at cross purposes with the other. In general, these patients have suffered a mesial frontal lobe and corpus callosum lesion. The patient cannot voluntarily suppress motor perseveration in which the he or she compulsively repeats stereotyped movements. These movements are usually associated with a grasp reflex and instinctive grasp reaction. Compulsive manipulation of tools placed in front of the patient is a release of praxis from damage of the left mesial frontal lobe, cingulate gyrus and genu of the corpus callosum. The syndrome occurs with a concomitant grasp reflex and instinctive grasp reaction but no disconnection syndrome. The utilization behavior of Lhermitte differs from compulsive manipulation of tools because it is bilateral and lacks the compulsive quality noted in the compulsive manipulation of tools. Diagnostic dyspraxia is a dissociative movement in which the left hand undoes the actions of the right. Usually the left hand works at cross-purposes to the right. Damage to the body of the corpus callosum is required for this behavior. Damage to the contralateral mesial frontal lobe and genu of the corpus callosum may cause purposeless movements of the contralateral hand such as an updrift, tucking the hand in the axilla or grasping the throat.

Alien Hand Phenomena and Variants

1. Le signe de la main étagée "strange hand"
2. Intermanual conflict
3. Motor perseveration
4. Compulsive manipulation of tools
5. Diagnostic dyspraxia
6. Updrift, hand in the axilla, grasping the throat

Callosal Disconnection Syndromes

1. Ideomotor apraxia – left hand
2. Agraphia – left hand
3. Tactile anomia – left hand

Pathologic Grasp Phenomena

1. Grasp reflexes
 - a. True grasp
 - b. Instinctive groping
 - c. Traction response
 - d. Magnetic response

The Middle Cerebral Artery

Overview

The middle cerebral artery is most commonly affected in ischemic cerebral vascular disease. African-American or Asian patients have a higher incidence of infarction of this artery than white patients.

The TIAs of MCA disease are less frequent than those stemming from carotid disease and occur over a shorter time period. White patients present with TIAs of the MCA more frequently than with stroke; cigarette smoking is a strong risk factor for all groups that suffer MCA infarction.

Major differential points of MCA occlusive disease from that of the ICA are: 1. deficits on awakening; 2. fluctuation or progression of symptoms; over the following 1–7 days; 3. probable low flow mechanism. Carotid disease is more suggestive of an embolic mechanism. There are no ocular symptoms with MCA disease.

Approximately 2/3 of all first brain infarcts are in the MCA territory. Approximately 1/3 affects the deep MCA territory and 10% occlude both deep and superficial territories. Approximately 50% of MCA infarctions are restricted to the superficial pial arteries.

Anatomy of the MCA and Its Patterns

1. Pial branches supply:
 - a. Almost the entire convex surface of the brain
 - b. Lateral frontal, parietal and temporal lobes
 - c. Insula, claustrum and extreme capsule
2. MCA emerges from the ICA for 1.8–2.6 cm as a single trunk
 - a. Proximal M1/M2 segments give rise to medial and lateral lenticulostriate arteries
3. The stem divides into three patterns:
 - a. Bifurcation pattern
 - i. Superior and inferior division – 79%

- b. Trifurcation pattern:
 - i. Superior, middle, inferior division – 12%
- c. Four or more trunks – 10%

Bifurcation Pattern (Superior/Inferior Division)

1. Superior division (pial branches):
 - a. Ascending orbitofrontal branch
 - b. Prefrontal branches
 - c. Precentral branches
 - d. Central or central sulcal branches
 - e. 2–3 anterior parietal branches
 - f. 1–3 angular branches
2. Inferior division (pial branches):
 - a. Ascending temporopolar branch
 - b. Anterior temporal branch
 - c. Middle temporal branch
 - d. Posterior temporal branch

Trifurcation Pattern

1. Superior division:
 - a. Ascending orbitofrontal branch
 - b. Prefrontal branches
 - c. Precentral branches
2. Middle division:
 - a. Central/central sulcal branches
 - b. Variable origin of:
 - i. Precentral/anterior and posterior parietal branches
 - ii. Angular/temporo-occipital branches
3. Inferior division (pial branches):
 - a. Ascending temporopolar
 - b. Anterior temporal branches
 - c. Middle temporal branches
 - d. Posterior temporal branches
 - e. Variable origin of (posterior parietal/angular/temporo-occipital arteries):
 - i. In both bifurcation and trifurcation patterns superficial branches may come from the stem of the MCA prior to its division:
 1. Ascending temporopolar branches
 2. Anterior and middle temporal branches

Anomalies of the Middle Cerebral Artery

1. Rare: occur in 3% of individuals
2. Duplication of the MCA:
 - a. A second vessel arises from the ICA which supplies the anterior and middle temporal territories
3. Variable patterns of ACA and PCA pial terminal anastomosis at hemispheric border zones
4. If the main MCA trunk is short the lenticulostriate arteries may arise from the superior division

General Features of Superficial Middle Cerebral Artery Territory Infarction

Patients frequently develop distal MCA trunk occlusions that spare the deep penetrators from the M1 and M2 segments of

the proximal MCA. The pathogenesis is most often thrombosis in situ rather than embolic. Complete infarction of the superficial MCA territory of the dominant hemisphere causes head and eye deviation to the side of the lesion, lethargy, global aphasia (often early mutism) and perseveration. The hemiparesis and hemisensory loss is brachiocephalic predominant with an invariant contralateral homonymous hemianopia. Non-dominant hemisphere infarction in addition to similar motor and eye signs demonstrate contralateral neglect, constructional apraxia, alloesthesia, anosognosia and multiple non-dominant (ND) parietal lobe symptomatology.

Superior division dominant (D) hemisphere infarction causes brachiofacial predominant motor and sensory symptoms, no visual field deficits, but gaze preference or eye deviation (Brodmann's 8 and 10) to the affected side. Broca's aphasia, ipsilateral ideomotor or limb kinetic apraxia and oral buccal lingual apraxia may be seen. Non-dominant infarcts have similar motor and sensory deficits with hemispatial neglect and emotional aprosody. Inferior division territory infarction causes minimal weakness but usually an up drift can be appreciated acutely. Astereognosis, difficulty with dynamic and static parietal copy and point localization is noted after the ictus. The most common visual field deficit is a contralateral superior quadrantanopsia if Meyer's loop is involved, although a contralateral non-congruent homonymous hemianopsia may also be seen (optic tract). Dominant hemisphere lesions cause a Wernicke's aphasia with an occasional patient demonstrating acute agitation. Characteristics of non-dominant lesions are a contralateral predominant sensory hemineglect, anosognosia, constructional apraxia and an agitated confusional state.

Superior Division of the Middle Cerebral Artery (Pial Branches)

Ascending Orbital Frontal Artery

This artery perfuses the orbital portion of the middle and inferior frontal gyrus and the inferior pars orbitalis. Its infarction (emboli or arteritis) causes behavioral disinhibition and a contralateral grasp sign.

Prefrontal Arteries

The territory perfused by these arteries is the middle frontal gyrus, pars triangularis, anterior pars opercularis and superior pars orbitalis. The clinical symptomatology includes apathy, abulia, poor ability to change motor sets, perseveration (DH), impersistence (NDH), poor judgment and abstraction, imitation and utilization behavior, and poor retrieval of short term semantic material. A transcortical motor aphasia may be noted with (DH) lesions and motor neglect with non-dominant hemisphere infarction.

Precentral Arteries

This group of arteries supplies the posterior middle frontal gyrus, the posterior pars opercularis and the anterior and mid-portion of the precentral gyrus. The clinical features of infarction of this branch or branches are proximal upper extremity

weakness or distal brachiofacial weakness. Dominant hemisphere lesions may have a concomitant transcortical motor aphasia. Due to infarction of area 8, patients may have bilateral upper extremity ideomotor apraxia. If the infarction involves the posterior left middle frontal gyrus (Exner's area) they may have agraphia out of proportion to hand weakness.

Central Sulcal Artery

The central artery group supplies the posterior bank of the precentral gyrus and the anterior half of the post central gyrus. A pathognomic clinical sign of infarction of this territory is monoparesis of the upper extremity (pseudoradial palsy) although brachiofacial weakness is the most common pattern. Infarction of the motor knuckle anteriorly causes selective weakness of muscles innervated by C5 and C6. Posterior infarction causes C8–T1 innervated muscle weakness. Sensory loss is noted in the same distribution. Rarely a pure motor stroke affecting arm, face, and leg occurs. Infarction of the parietal operculum may cause a cheiro-oral sensory loss (corner of the mouth and hand). Dominant hemisphere infarctions cause Broca's aphasia or dysarthria and dysprosody. Non-dominant hemisphere infarction usually causes less severe dysarthria.

Anterior Parietal Artery

This artery or group of arteries supplies the post central gyrus, parasagittal portion of the central sulcus, and the anterior inferior portions of both the inferior and superior parietal lobules.

Anterior parietal branch occlusions may cause a contralateral updrift of the arm with abnormal proprioceptive finger movements (mini myoclonus). Loss of touch and position sense is common in the arm and face distribution. Vibration is usually spared. The distal upper extremity may be most severely affected. Incoordination of the affected hand may be noted. Dominant hemisphere infarction may cause conduction aphasia while non-dominant lesions are associated with visual-spatial deficit.

Posterior Parietal Artery

Infarction of this territory involves the posterior portions of the superior and inferior parietal lobules and the supramarginal gyrus. Discriminative sensations such as two point localization, stereognosis and graphesthesia are predominantly involved. Patients may demonstrate an inferior quadrantanopsia or non-congruent homonymous hemianopsia. Dominant hemisphere lesions may cause anomia (aphasia (SMG), agraphia, and alexia (areas 39, 40, 41). Ideational and bilateral representational ideomotor apraxia as well as a posterior alien hand syndrome may occur. Left right confusion, finger agnosia, dyscalculia, inability to cross the midline and dysgraphia (Von Gerstmann's syndrome) may be seen singularly or concurrently. Non-dominant hemisphere infarction causes contralateral sensory spatial neglect, constructional apraxia and visuospatial deficits.

Differential Diagnosis of Parietal Sensory Loss

In general, parietal sensory symptoms from infarction have a regional pattern. Dramatic involvement of 1/2 of the body is characteristic of thalamic disease. Other thalamic signs are the upper extremity is more severely affected and often the trunk is spared. The deficit may be limited to the fingertips (ventral posterior inferior nucleus) and primarily involves the discriminative aspects of sensation. Vibration loss is a thalamic or dorsal column nuclear deficit. Motor dysfunction with these sensory symptoms occurs in a large majority of patients. This motor deficit first described by Foerster as an afferent paresis or tactile paresis (loathness to move). Partial pseudosegmental, pseudoradicular, cheiro-oral (posterior parietal operculum) pseudospinal patterns may be seen with parietal lesions. The usual pseudoradicular pattern is C6 or C8–T1. A pseudothalamic pattern (SI area) consists of deficits of elementary modalities of sensation with faciobrachial predominance (syndrome of Roussy and Foix). Spinothalamic type of sensory loss (Brodmann's area 43, part of SMG and the posterior insula) may be seen. Patients may demonstrate asymbolia for pain, if SII is infarcted (adjacent to the lower extent of SI). Portions of the cortical sensory syndrome with loss of discriminative touch, position sense, astereognosis, ability to copy posture, sensory hemineglect (NDH) with preserved vibration sense may be seen with both anterior and posterior parietal branch infarctions. Corona radiata and occasionally SI infarction may cause a feeling of heaviness in the contralateral extremities and are associated with difficulty initiating and sustaining movement (disconnection of deep SI, 3b and area 4) in the depths of the central fissure.

Angular Artery Branch

This artery supplies the posterior portion of the superior temporal gyrus, parts of the supramarginal and angular gyri and the superior lateral occipital gyri. The major features of infarction of this branch are the angular gyrus syndrome (Von Gerstmann). Frequently associated is anomia or transcortical aphasia, alexia without agraphia, an inability to cross the midline and constructional apraxia. Non-dominant lesions are associated with: 1. contralateral spatial neglect; 2. visuospatial and constructional deficit; 3. loss of opticokinetic nystagmus (eyes remain; toward the ipsilateral side); 4. hemianopia or inferior quadrantanopsia; 5. anosognosia (denial of illness); 6. asomatognosia (denial of a limb); and 7. alloesthesia (perception of sensation on the normal side when the affected side is stimulated are seen).

If there is a short mainstem MCA, the lenticulostriate arteries may originate from the superior trunk. Infarction in this circumstance would involve the basal ganglia and the internal capsule.

Inferior Division of Middle Cerebral Artery

The general characteristics of an inferior division MCA infarction are:

1. Wernicke's aphasia (DH)

2. Contralateral superior quadrantic VF deficit
3. Poor drawing and copying (NDH)
4. Agitation (NDH)

Ascending Temporopolar/Anterior Temporal/Middle Temporal Branch Occlusion

The anterior temporal artery supplies the anterior portion of the superior, middle, and inferior temporal gyri. The temporopolar artery complex supplies the anterior pole of the superior middle and inferior temporal gyri. The middle temporal group of arteries supplies the superior gyrus below the pars triangularis and pars opercularis as well as the middle portion of the middle temporal gyrus and posterior portion of the inferior temporal gyrus.

The clinical features of infarction of the anterior temporal branches are a contralateral homonymous superior quadrantanopsia. If on the dominant side, the visual field deficit may be associated with an anomic aphasia with category-predominant naming deficits. Non-dominant infarction may cause hemispatial neglect and an acute confusional syndrome.

Temporo-Occipital/Posterior Temporal Branch Occlusion

These arteries supply the posterior half of the superior temporal gyrus and the posterior portions of the middle and inferior temporal gyri and the inferior portion of the lateral occipital gyri. These occlusions cause a contralateral superior quadrantanopsia or hemianopsia. Dominant hemisphere infarction of the posterior superior temporal gyrus causes Wernicke's aphasia. This infarction is frequently embolic and if pure (no other neurologic symptoms) is often caused by atrial fibrillation or another cardiac source. Non-dominant hemisphere infarction produces an acute confusional state, contralateral hemispatial neglect and constructional apraxia.

Other Common MCA Occlusions of the Superficial Territory Insular Branch Occlusion

The insula is supplied by the MCA trunk or proximal portions of its division and is rarely infarcted in isolation. Bilateral infarctions from serial strokes cause the Foix-Marie-Chavany syndrome which consists of severe apraxia for all of the muscles of branchial origin. Patients have difficulty swallowing, moving the face and tongue, buccal movements and initiating and articulating speech. This is a cause of aphemia which is a dramatic dysarthria that renders speech unintelligible. It may occasionally occur from unilateral insular branch occlusion.

Long Penetrating Medullary Artery Occlusion

Infarction of a group of long-penetrating arteries causes large infarcts in the centrum semiovale. Their origin is in the MCA pial branches and they usually cause a contralateral motor and sensory deficit as well as a non-congruent hemianopsia. If in the dominant hemisphere, patients are dysphasic while

NDH lesions are associated with hemineglect and visuospatial deficits.

Infarcts of less than 1.5 cm in diameter cause pure motor or sensory strokes, ataxic hemiparesis without cognitive impairment or isolated involvement of face, arm or leg (fibers are widely separated). This fractionation is less common than with deep subcortical infarcts. Severe ipsilateral carotid disease produces the lesions by distal field ischemia or embolic disease.

Deep Territory MCA Infarction

The deep territory is composed of penetrating branches from the M1 and M2 proximal segments of the MCA which are known as the lenticulostriate arteries. If these arteries are infarcted, the process is usually embolic and occlusion of many perforators occurs simultaneously. This type of infarction is a striatocapsular infarction rather than a lacunar infarction in which only one lenticulostriate perforator is occluded. In general, striatocapsular infarction involves the head of the caudate, the putamen, and the lateral internal and external capsule and may extend into the corona radiata. The insular cortex and the thalamus is spared. Striatocapsular infarcts may involve the territory of Heubner's artery (recurrent branch from A1) or the anterior choroidal artery. In general, the area infarcted is in the range of 2–7 cm, is wedge or comma shaped, and is not ovoid as are the smaller lacunar infarctions. Cortical symptoms are rare and if present resolve quickly. The cortex is not infarcted due to leptomeningeal anastomoses. In situ thrombosis or cranial arteritis involving a segment of M1 that occludes multiple perforators is rare.

Acutely, patients present with predominantly motor or sensory motor hemiparesis with or without dysarthria. Hemiparesis results from damage to the posterior limb (mid 1/3) of the internal capsule (motor cortex corticospinal fibers) or if only the frontal part of the internal capsule is involved (the lateral premotor cortex corticospinal fibers or those from the SMA cortex in the genu) are involved.

The differential diagnosis of striatocapsular infarcts are: 1. lacunar syndromes; 2. pure sensory stroke; 3. strokes in the basis pontis; 4. ICH of the striatum. If the leptomeningeal anastomosis fails patients may suffer cortical deficits which add to the underlying deficit and rule out lacunar stroke.

In striatocapsular stroke, cortical deficits such as aphasia or neglect resolve in the face of persistent motor or sensory deficits. In a moderate or large territorial or MCA branch occlusion the cortical deficits are more severe and long lasting. Extended striatocapsular stroke is most often associated with Wernicke's aphasia (involvement of insular or superior temporal gyrus). Rarely focal dystonia, contralateral choreoathetosis, or hemiballismus has been noted. Bilateral striatocapsular infarction may cause tetraplegia and akinetic mutism.

Striatocapsular Stroke

1. Predominant motor or sensorimotor hemiparesis

2. Minimal cortical signs and symptoms that resolve
3. 2 to 7 cm in size
4. Wedge or comma shaped
5. Involves caudate, putamen, anterior or posterior limb of the internal capsule
6. Rare contralateral movement disorder
7. Rare tetraplegia with akinetic mutism (if bilateral)

Distal field infarction (or low flow state in the periventricular white matter) between the penetrating cortical branches and the ascending lenticulostriate branches that does not infarct the basal ganglia or internal capsule may mimic some of these findings.

If the head of the caudate nucleus, the putamen and the anterior portion of the internal capsule are infarcted the pattern represents that of occlusion of the recurrent artery of Heubner whose origin is the A1 segment of the ACA aberrant (medial lenticulostriate artery). The resultant hemiparesis has brachiocephalic predominance with tongue involvement. A similar infarction can occur from occlusion of the perforating branches of the most proximal portion of the A1 segment of the ACA artery. If the caudate head and the anterior limb of the internal capsule are involved, the eyes may be deviated ipsilaterally and the face and arm are more severely affected than the leg. Caudate infarction interrupts fibers that project to the frontal and dorsolateral prefrontal cortex and may be associated with an acute confusional, agitated or an abulic state. If the infarction extends anteriorly and destroys fibers that project to the medial dorsal and anteroventral thalamic nuclei, patients may have an expressive aphasia. Rarely with infarctions in this area patients demonstrate a hemisensory defect that affects the face and hand more severely than the leg. Dysarthria is more severe with left-sided than right-sided capsular lesions (corticobulbar projections to cranial nerves VII, X and XII). A non-congruent homonymous hemianopsias results from optic tract infarction. This may also be accompanied by a Behr's pupil (larger, poorly reactive pupil on the ipsilateral side).

The lateral lenticulostriate group of perforators takes origin from the M2 proximal middle cerebral artery segment and supplies the putamen, claustrum, external and extreme capsule and the insular cortex. Putaminal infarction causes brachiocephalic predominant weakness with increased tone and hyperreflexia but no sensory loss. Rarely putaminal infarction causes contralateral dystonia, choreoathetosis, and abnormal contralateral hand posture. Bilateral insular cortex infarction (insular branches of the MCA) produces the Foix–Chavany–Marie syndrome which causes apraxia of all branchial derived musculature and disrupts speech and swallowing. The dysarthria may be so severe that speech is unintelligible (usually requires bilateral infarction).

The Capsular Warning Syndrome

These are TIA's restricted to the face, arm and leg and are not often seen with severe carotid stenosis accompanied by a low flow state. The major clinical features are:

1. Simultaneous sensorimotor involvement of face, arm and leg
2. No neglect, dysphasia or dyspraxia
3. Three or more clinical events within 24 hours
4. Onset over seconds
5. Pure motor hemiparesis is most common
6. Sensory symptoms clear prior to motor signs
7. Capsular infarction follows in approximately 40% of patients

As noted above, the capsule may be predominately involved in specific areas.

Capsular Genu Syndrome

1. Contralateral facial, lingual and brachial weakness
2. With or without ipsilateral horizontal conjugate eye deviation
3. Rare thalamic aphasia

Midpoint Infarction of the Upper Capsule with Lower Corona Radiata Extension (Anterior 1/3 of the Posterior Limb)

Clinical Signs and Symptoms

1. Dysarthria
2. Contralateral clumsy hand
3. Faciolingual weakness
4. Blood supply is from the lenticulostriate arteries that concomitantly supply the upper ventricular wall (anastomosis with ependymal vessels)
5. Posterior 1/3 limb of internal capsule infarction:
 - a. Middle third
 - i. Face < arm < leg weakness
 - ii. Purely motor
 - b. Posterior 1/3:
 - i. Pure sensory
 - ii. Arm, face, and leg involved
 - c. Arterial supply (lenticulostriate)
6. Rare behavioral signs and symptoms of striatocapsular stroke are:
 - a. Fluctuating alertness
 - b. Inattention
 - c. Memory loss
 - d. Apathy
 - e. Frontal lobe deficits
7. These deficits are caused by infarction of:
 - a. Inferior and anterior thalamic peduncles
 - b. Anterior limb of internal capsule

The Differential Diagnosis of Striatocapsular Infarctions

1. Lacunar infarcts (1–2 perforating vessels)
 2. Pure sensory stroke (thalamic infarction)
 3. Infarction of the basis points (penetrating basilar branches)
 4. Small striatal or intracranial hemorrhage
- If leptomeningeal anastomoses fail, or there is a concomitant shower of emboli, patients may suffer cortical deficits. As noted earlier, lack of cortical dysfunction is characteristic of lacunar stroke.

Clinical Differential Diagnosis of Capsular Infarction

1. The first of frequent hemiplegic events is more likely capsular than pontine
2. Premonitory events are characteristics of anterior choroidal artery ischemia
3. Capsular ischemia: patients are aware of its onset; it resolves over seconds to minutes
4. Incipient occlusion of the ICA often is accompanied by repetitive events with cortical dysfunction
5. Hemodynamic events are posturally influenced and are shorter than embolic events
6. Artery-to-artery embolic events are more widely separated in time

Rare Patterns of Stroke in the MCA Territory

Central sulcal branch artery infarction may cause a right pseudothalamic sensory loss (primary sensory modality involvement), ideational apraxia and conduction aphasia. Wernicke's aphasia and hemianopsia often follows embolic occlusion of the temporooccipital branch of the inferior MCA division particularly in the setting of atrial fibrillation. Precentral branch occlusion may cause transcortical motor aphasia, proximal weakness of the arm and ideomotor apraxia.

The anatomical variants of the middle cerebral artery, specifically the origin of the angular artery may determine unusual stroke symptoms following infarction in the MCA territory. Stenosis of the M1 segment of the MCA in conjunction with hypertension may cause periventricular longitudinal infarction.

Double infarcts are those that involve two components of one arterial territory. Aphasia without hemiparesis occurs when Broca's and Wernicke's area are infarcted leaving the motor strip intact. Hemiplegia with visual field deficits occur when the superior division (central sulcal branches) are occluded concomitantly with temporo/occipital branches (inferior division) thus sparing the primary sensory cortex. Conduction aphasia with hemiparesis has been noted with motor cortex and supramarginal gyrus lesions. Fragmentation of emboli at the MCA bifurcation or serial strokes are the most likely mechanisms.

Complete MCA Infarction (Superficial and Deep Territory)

Panhemispheric MCA occlusion is often embolic particularly if sudden. If it occurs with a slower or stuttering onset it is most likely due to carotid occlusion. These patients have cerebral swelling usually within 12 hours of infarction that impairs consciousness. Their head and eyes are deviated ipsilaterally, they demonstrate periodic or Cheyne-Stokes respiration, a flaccid contralateral hemiparesis and hemisensory deficit, homonymous hemianopsia and global aphasia (DH), or severe contralateral sensory neglect (NDH). The eyes are usually congruently deviated slightly below the horizontal due to pressure on the center for upgaze (the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF)) that is ventral to the superior colliculus. In stem MCA infarction,

edema is most severe at 3 days. Prior to herniation, patients may demonstrate an ipsilateral sluggish and oval pupil (pressure on the III nerve) as well as ipsilateral or bilateral ptosis (frontal eye field compromise).

Clinical Summary of Complete Superficial Territory Infarction

1. Hemiparesis faciobrachial > leg
2. Hemineglect for space and motor activity (NDH)
3. Anosognosia (NDH)
4. Asomatognosia (NDH)
5. Spatial disorientation (internal/external/geographical) NDH
6. Disorientation NDH > DH hemisphere
7. Depressed reflexes contralaterally (acutely); rarely increased (cortical disinhibition)
8. Babinski sign contralaterally (ipsi or bilaterally if there is increased ICP)
9. Angular gyrus syndrome (DH)
10. Supra marginal gyrus syndrome (DH)
11. Wernicke's aphasia (DH)
12. Broca's aphasia (DH)
13. Conduction aphasia (motor DH)
14. Conduction aphasia (sensory DH)
15. Alexia without agraphia (DH)
16. Ideomotor/limb-kinetic apraxia D > NDH
17. Ideational apraxia (DH)
18. Alien hand syndrome (DH > NDH)
19. Sympathetic apraxia or callosal apraxia (DH)

Superior Division MCA Occlusion (Bifurcation Pattern)

1. Broca's aphasia (DH)
2. Exner's area (severe inability to write) DH; Brodmann's area 45
3. Parietal hand (updraft; loathness to move)
4. Dysarthria
5. Motor conduction aphasia (DH)
6. Limb kinetic/ideomotor apraxia (DH)
7. Alien hand syndrome (area6/DH)
8. Brachiofacial pattern of weakness > leg weakness
9. Depressed reflexes contralaterally
10. Head and eye deviation (ipsilaterally)
11. Babinski sign contralaterally
12. Frontal behavioral syndrome
13. Apathy and abulia
14. Brachiofacial crural weakness (rare)
15. Phonemic paraphasia
16. Rare cheiro oral sensory loss

Inferior Division MCA Occlusion (Bifurcation Pattern)

1. Wernicke's aphasia (DH)
2. Sensory conduction aphasia (DH)
3. Supramarginal gyrus syndrome (DH)
4. Angular gyrus syndrome (DH)
5. Hemineglect for space (NDH)

6. Depressed optokinetic nystagmus (ipsilateral hemisphere)
7. Depressed optic scanning (contralateral space)
8. Constructional apraxia (NDH)

Prosopagnosia (NDH)

1. Loss of higher cortical sensory function (contralateral)
2. Ideational apraxia
3. Posterior type alien hand

Dominant Hemisphere

1. Wernicke's aphasia (DH)
2. Sensory conduction aphasia (DH)
3. Supramarginal gyrus syndrome (DH)
4. Angular gyrus syndrome (DH)

Summary of MCA Infarctions

1. 2/3 of first brain infarcts involve the MCA
2. 1/3 of MCA infarction involves the deep MCA territory
3. 1/10 of MCA infarction involves both superficial and deep territory
4. 50% are branch occlusions

Large Middle Cerebral Artery and Pan Hemispheric Stroke

General Characteristics

1. Definitions:
 - a. The cortical and deep territory supplied by the MCA
 - b. Territory supplied by MCA and ACA
 - c. Territory supplied by the MCA and PCA
 - d. Combination infarction of all three territories including the anterior choroid artery
2. These infarctions often cause severe edema, increased intracranial pressure and cerebral herniation and are termed malignant infarctions
3. Hemispheric stroke accounts for approximately 10% of supratentorial strokes
4. Higher incidence in:
 - a. Women
 - b. Younger patients
 - c. Involvement of the anterior choroidal artery
5. Usual arteries affected are the internal carotid and the proximal MCA (M1)
6. Predisposing features:
 - a. Hypoplasia and rotation of components of the circle of Willis
 - b. Decreased caliber and number of collateral vessels

Clinical Manifestations

1. M1 stem occlusions of the dominant hemisphere cause muteness
2. Initial loss of consciousness is unusual with MCA or hemispheric infarction. The exception is seizure activity
 - a. Deteriorating level of consciousness begins on the third or fourth day concomitant with cerebral edema and herniation

b. Transtentorial herniation in association with:

- i. Central neurogenic hyper ventilation
- ii. Small 2–3 mm pupils that are reactive
- iii. Decorticate to decerebrate posture:
 1. Decerebrate posture contralateral to the lesion and decorticate posture ipsilaterally to the lesion
- iv. Head and eyes to the side of the lesion (frontal eye field involvement) and contralateral severe hemiparesis and hemisensory defect.
- v. Homonymous hemianopia (contralateral to the lesion)
 1. Maybe hard to determine due to level of consciousness
 - a. Secondary to involvement of the optic tract from the stroke
 - b. Compression and infarction of the PCA under the tentorium
- vi. Prior to death, blood pressure falls, the pulse is thready and rapid, Doll's maneuvers fail to move, the eyes, the pupils dilate (and maybe oval) and respiration becomes agonal
- vii. Lateral temporal lobe herniation
 1. Much rarer than diencephalic herniation
 2. IIIrd nerve with pupillary involvement is early; concomitant contralateral decorticate then decerebrate posture
 - a. Rare compression of the contralateral cerebral peduncle against the tentorium producing Kernohan's notch syndrome (ipsilateral hemiparesis due to compression of the CST in the cerebral peduncle; the pyramidal decussation is at C1–C2)

Neuropathology

1. Usually greater than 2/3 of MCA territory is infarcted
 - a. Devastating effect of M1 stem infarction derives from the infarction of the internal capsule
2. If fetal carotid (the PCA takes origin from the ICA) the MCA and PCA are infarcted
3. If there is atherosclerotic involvement of the carotid siphon (T embolus) the anterior cerebral artery may be involved

Neuroimaging

1. 2/3 of MCA territory includes its cortical territory and basal ganglia structures (head of the caudate, insular stripe, and cortical effacement)
2. Cerebral edema with swelling; pineal or interhemispheric dural displacement (anteriorly)
3. ACA or PCA involvement
4. Midline shift of greater than 5–7 mm

Intracranial Atherosclerotic Disease (ICA)

General Characteristics

1. Prevalence of 20–40/100,000 persons worldwide; higher in African Americans and Hispanic than Caucasian patients
2. Intracranial atherosclerotic disease cause 33–37% of ischemic strokes in the Chinese population
3. Severe ICA affects 43% of subjects 65 years and older, 65% in those 60–69 years old and 80% of those 70–79 years old
4. Intracranial arterial disease risk factors:
 - a. Non-modifiable:
 - i. Age
 - ii. Men (younger age and in the basilar artery)
 - iii. Hispanic subjects
 - iv. Chinese subjects
 - v. Angiotensin converting enzyme polymorphism
 - vi. African American subjects
 - vii. Plasma endostatin vascular endothelial growth factor ratio
 - viii. Glutamine S-transferase. Omega-1 gene polymorphism
 - ix. Plasma homocysteine levels
5. Modifiable Risk Factors:
 - a. Hypertension
 - b. Serum beta lipoprotein
 - c. Total serum cholesterol
 - d. Serum LDL-cholesterol
 - e. Serum Apolipoprotein
 - f. Serum HDL-cholesterol
 - g. Sickle cell disease
 - h. Meningitis
 - i. Extracranial carotid stenosis
6. Possibly Modifiable Risk Factors:
 - a. Diabetes mellitus
 - b. Metabolic syndrome
 - c. Alzheimer's disease
 - d. Aortic Plaques
 - e. X-RT (radiotherapy)
 - f. Tuberculosis and cryptococcal meningitis
 - g. Family history of stroke
7. Asymptomatic stenosis (50–99%) of other arteries in a proportion of patients
8. Patients with symptomatic intracranial arterial disease
9. Ischemic stroke, ICH or vascular death (not caused by ischemic stroke) occurred in 22% (WASD trial)
10. Ischemic stroke occurred in the territory of the symptomatic artery (14%); other vascular territories (19%)
11. One year risk of stroke in the territory of a symptomatic stenosis artery (greater than 70%) was 19%

Clinical Manifestations

1. TIA
2. Stroke

3. Recurrent stroke: highest risk within two weeks
4. Rate of recurrence of ischemic events is high regardless of antiplatelet or anticoagulation therapy

Neuropathology

1. Increased insinuation of fibrinogen and LDL-cholesterol in the sub endothelial space
2. Inflammation in the walls of affected arteries

Neuroimaging

1. Spin-echo MRI with contrast demonstrates arterial wall enhancement
2. Intravascular ultrasonography
 - a. Provides real-time dynamic measurements and histology maps of the plaques

Sentinel Differential Diagnostic Features of Large Vessel Stroke of the Anterior Circulation

The hallmark of carotid disease is retinal involvement either embolic from burst plaques or artery to artery. Hollenhorst plaque material at a bifurcation of a retinal artery is pathognomonic. Horner's syndrome associated with a brachycephalic predominant lesion points to the internal carotid artery. Due to the circle of Willis collaterals may save a great deal of the hemisphere. Carotid siphon disease has no ocular pathology, but the anterior cerebral artery may be involved concomitantly with the middle cerebral artery. Emboli from the siphon may occlude the anterior cerebral artery and the inferior branch of the dominant middle cerebral artery sparing the major portions of the motor sensory cortex. This causes a Wernicke's aphasia with shoulder and leg weakness.

The anterior choroidal artery supplies aspects of both anterior and posterior circulations. The hallmark of its infarction is a quadruple sectoranopic defect that spares the central sector. The defect arises from infarction of the lateral geniculate body. Infarction of the uncus and components of its thalamic supply cause a deficit in short term memory and language processing. Hyperesthetic hemiparesis (thalamic) and hyperesthetic ataxic hemiparesis are patterns of infarction.

The usual pattern of anterior cerebral artery infarction is severe weakness and sensory loss of the foot, minimal involvement of the shoulder and face with excellent preservation of hand movement. The patient may be able to wiggle the thumb, but not the arm if the A1 section is involved. If the recurrent artery of Heubner is infarcted, the patient demonstrates facio brachial predominant weakness. Involvement of the supplementary motor area (distal ACA) causes transcortical motor aphasia, mirror writing acquired stuttering and muteness. Muteness is often seen as well with sudden occlusion of the stem of the MCA. Medial frontal lobe infarction often causes euphoria, lability and jocularity. Anterior callosal involvement causes sympathetic apraxia (inability to follow commands with the left hand) and the anterior alien hand syndrome (intermanual conflict).

The major differential distinction of middle cerebral artery disease is that from internal carotid artery occlusion. TIAs in the middle cerebral artery distribution occur on awakening, are less frequent than carotid TIAs and once initiated occur over a shorter time period. They frequently fluctuate or progress over 1–7 days. The mechanism often is distal field ischemia so symptoms often vary with posture. There are no monocular symptoms. Characteristic of superficial territory involvement is hemiparesis and hemisensory deficit with brachycephalic predominance. The frontal eye fields are frequently involved (FEF) with no corresponding visual field deficit. Severe motor neglect and parietal visuospatial deficits are noted if the non-dominant parietal lobe is involved. The angular artery syndrome of Von Gerstmann localizes the lesion to posterior parietal territory if the DH is involved. The pre and frontal superficial branches of the superior division supply Broca's area (Brodman's area 44). The dorsolateral prefrontal cortex (DLPC) is also frequently involved and causes memory retrieval difficulties. Characteristic of inferior division infarction of the superficial territory is Wernicke's aphasia (pathognomonic of embolus if isolated and concomitant with atrial fibrillation) and agitation.

Deep territory middle cerebral artery territory infarction is characterized by internal capsule and basal ganglia infarction. The important differential point from superficial territory and carotid infarction is involvement of the leg, absence of eye deviation and the transient nature of any cortical deficits. This infarction causes a striatocapsular stroke with persistent motor sensory signs. The medial and lateral lenticulostriate group of arteries from the M1 and M2 segments of the MCA of the lateral group is involved. The putamen may be affected causing motor weakness, increased tone and reflexes without sensory loss. The capsular warning and genu syndromes may be seen prior to stroke.

Differential Diagnosis of Posterior Circulation Stroke

The posterior circulation can be considered the arch of the aorta, the innominate and subclavian arteries and vertebral, basilar, posterior cerebral and their derivative arteries.

The arch of the aorta is a rich source of embolic material to the posterior circulation. Its prominence in this regard has recently been accentuated by transesophageal echo cardiography. A mobile grade V plaque is extremely dangerous as a source of embolus. Approximately 30% of emboli to the posterior circulations arise from this source. Emboli to both anterior and posterior circulations arise from the heart or the arch of the aorta in the great majority of cases. The embryologic connections from the carotid to the basilar artery are rare sources of emboli. These include the persistent trigeminal artery, the otic, hypoglossal and proatlantal arteries. The most significant of these arteries is the persistent trigeminal which connects this top of the basilar to the carotid artery just below the siphon.

The vertebrobasilar system can be divided into diagnostic thirds. Each major artery has sentinel features that can guide

diagnosis. Characteristic of a subclavian stenosis proximal to the origin of the vertebral artery is the subclavian steal syndrome. The patient uses the affected arm (left greater than right) which further lowers pressure in the arm (lower than that in the vertebrobasilar system) and blood flows to the arm from the vertebral supply. Most patients have a clear difference in blood pressure between the two arms and a significant decrease of pulse volume and clear lag of the pulse in the affected side. The syndrome usually causes more claudication in the arm than brainstem symptoms. It is rarely significant clinically.

A rare syndrome of ischemia of the brachial plexus and posterior circulation can occur from ischemia of the vertebral and axillary artery (feeds the plexus) that occurs simultaneously. Patients may complain of arm pain in the lateral or medial cord distribution, hand weakness concomitantly with lower brainstem, and cranial nerve symptoms.

Atheromatous occlusion with or without emboli may cause simultaneous carotid and vertebral artery symptoms on the right side. In general, the left carotid takes origin from the aorta and this will not occur on this side.

The common congenital anomaly of the posterior cerebral artery taking origin from the carotid may cause complete hemispheric infarction if that carotid is occluded. The patency of the posterior communicating arteries may determine upper basilar perfusion if there is occlusion of the mid basilar or vertebral arteries.

Proximal vertebral artery disease is most common at the origin from the subclavian artery which is accessible to stenting and angioplasty. The most prominent clinical symptoms are dizziness, diplopia (VIth nerve), dysphagia, oscillopsia, bilateral leg weakness and sensory loss on the trunk. Isolated dizziness especially points to the labyrinth rather than the brainstem. The origin of the posterior inferior cerebellar artery is from the vertebral. It is most commonly involved due to occlusion of the parent artery. The sentinel features of its involvement are dysphagia, nausea and vomiting (out of proportion to dizziness), hoarseness, lateral pulsion to the side of the lesion. These patients have a great deal of difficulty walking which is out of proportion to their ipsilateral ataxia. Seventh nerve weakness (ipsilateral) may occur due to recurrent medullary pyramidal fibers. Ipsilateral facial pain "salt and pepper" in the Vth nerve distribution is characteristic.

Medial medullary infarction is suggested by contralateral flaccid paralysis of the arm and leg (infarction above C2) or ipsilateral flaccid hemiparesis if ischemia involves the cervical medullary junction. Spasticity evolves within days to weeks and causes flexion of the upper extremity and extension of the lower extremities. The motor deficit is more severe distally in the upper extremity which is also typical for pontine infarction. Infarction of the pyramidal decussation may cause a crural paresis. The sensory loss is lemniscal, the face may be involved alone and rarely there is dissociation of position sense and vibratory loss. Upbeat nystagmus

implies pontomedullary junction infarction. Respiratory dysfunction (Ondine's curse), mild ptosis with hypohidrosis and XIIth nerve involvement may occur.

Bilateral medial medullary infarction is manifest by flaccid quadriplegia, paralysis of the tongue, loss of lemniscal sensation, and cardiorespiratory failure.

Combined medial and lateral medullary infarction is suggested by ipsilateral involvement of IX, X, XI, XII a Horner's syndrome, contralateral lemniscal and spinothalamic sensory loss and hemiparesis. Ipsilateral ataxia is apparent if the patient is hemiparetic.

The most common infarction of the pons is ventral and occurs due to occlusion of the anteromedial or anterolateral branches from the basilar artery. These infarctions are suggested by the constellation of facio-branchial crural hemiparesis, brachio-cranial ataxia (homolateral to the motor deficit), ataxic hemiparesis and the dysarthria clumsy hand syndrome. Ataxic hemiparesis and dysarthria clumsy hand occur more often in the middle and upper pons or at the ventro- tegmental junction. Pontine hemiparesis is greater in the distal upper extremity than the lower extremity.

Pontine tegmental involvement is suggested by cranial nerve involvement (Vth, VIth) a depressed level of consciousness and an intranuclear ophthalmoplegia or one-and-a-half syndrome.

Tegmental pontine syndrome from occlusion of short circumferential vessels is heralded by mild motor deficit, cranial nerve involvement Vth–VIIth, and lemniscal (medial) or spinothalamic sensory loss.

The major circumferential artery of the lower pons is the anterior inferior cerebellar artery. Infarction of this artery characteristically causes sudden ipsilateral hearing loss, ipsilateral ataxia arm greater than leg (the reverse of PICA), dizziness, ipsilateral VIIth nerve palsy (small artery to the facial nerve peripherally in the CPA angle) and contralateral loss of pain and temperature of the limbs and trunk.

Mid basilar branch disease is suggested by the motor deficits with a fluctuating and progressive course, the ocular signs of horizontal gaze dysfunction, ataxic hemiparesis (level of the MCP) the clumsy hand dysarthria syndrome and classic lacunar syndromes.

Basilar artery thrombosis may have dizziness as the most frequent early symptom, a herald hemiparesis, alternating levels of consciousness to stupor or coma. Dysarthria, pseudobulbar symptoms, tongue paralysis are common. Pin point pupils and ocular bobbing are diagnostic. The locked in syndrome with maintained consciousness is pathognomonic of ventral pontine infarction.

The top of the basilar (distal 1/3) is commonly involved from embolic disease. The superior cerebellar artery and specific components of the posterior cerebral artery are involved and determine the specific symptoms and signs of the infarction.

The superior cerebellar artery brainstem territory is most often infarcted in conjunction with the posterior cerebral

artery. Severe dysarthria with various degrees of appendicular ataxia are characteristic. The associated components of the posterior cerebral artery often suggest the diagnosis.

The posterior cerebral artery supplies the medial temporal lobe, the midbrain (paramedian branches), the medial and lateral motor sensory thalamus, medial parietal lobe and the occipital cortex. Hippocampal formation ischemia from proximal PCA branch occlusion causes transient global amnesia. A similar amnesic syndrome, much longer lasting may also occur from dorsal medial thalamic ischemia from occlusion of the interpeduncular artery from the top of the basilar artery. Midbrain involvement from paramedian ischemia causes crossed syndromes involving the third nerve. Crossed hemiparesis is Webers syndrome, crossed movement disorder is Benedict's, and Claude's is cerebellar ataxia. Disorders of vertical gaze such as one-and-a-half syndrome, dissociation of vertical and horizontal opticokinetic nystagmus and pupillary abnormalities are characteristic. A peduncular hemiparesis from cerebral peduncle infarction may simulate MCA infarction. The IIIrd nerve is not involved and the face may be spared. Rarely a nuclear IIIrd nerve syndrome is noted with bilateral ptosis, pupillary dilatation and failure of upgaze. Nystagmus retractorius may occur from vascular lesions of the periaqueductal area but is more characteristic of dorsal midbrain pressure. Posterior cerebral artery thalamic involvement is characterized by striking sensory involvement. The patient is aware of a midline split of the sensory deficit. The leg may be involved first (VPL). The fingertip involvement of one hand is diagnostic of thalamic VPI nuclear involvement. Bilateral involvement of intraoral sensation is characteristic of VPM ischemia. Thalamic sensory loss includes vibration. This modality is rarely lost with a cortical lesion, but may be seen with dorsal column nuclear lesions. Thalamic motor involvement may be suspected from a characteristic thumb in the palm drift. Proprioceptive deficits combined with weakness and ataxia of stance is characteristic of thalamic lesions that affect zones of proprioceptive and cerebellar input that converges in VL. Rarely dystonic postures are seen after VA/VL thalamic motor lesions.

Occipital lobe posterior cerebral artery involvement should always be suspected in the face of a dense congruent VF deficit of which the patient is aware. If there is visual neglect the patient has parietal lobe involvement. Deficits in optic scanning and visual gaze coordinative hand function and ocular fixation comprise Bálint's syndrome that overlaps parietal and occipital posterior cerebral artery territories. Anton's syndrome of cortical blindness is manifest by visual confabulation, euphoria and normal pupillary function. Specific field deficits such as a checkerboard field, quadrantic altitudinal deficits, macular sparing and temporal crescent of spared vision all point to PCA occipital lobe branch occlusions.

Lateral posterior choroidal artery infarction is suggested clinically by a homonymous quadrantanopsia. If the lateral geniculate body is involved, patients demonstrate a homonymous horizontal sectoranopia. There may be a concomitant

transcortical aphasia and hemisensory deficit. This infarction is suggested by pulvinar involvement on MRI or CT.

Medial posterior choroidal artery infarction is less common than lateral PchA infarction and is suggested by nystagmus retractorius and a central Horner's syndrome. A mild hemiparesis and lemniscal sensory deficit may occur. CT or MRI of medial pulvinar involvement suggests this arterial territory.

The following is a detailed differential analysis of posterior circulation vascular infarctions.

Posterior Circulation

Occlusion or Severe Stenosis of the Subclavian and Innominate Arteries

Extracranial Vertebral Arteries (ECVA)

1. Arise from the proximal subclavian arteries
2. Subclavian steal syndrome:
 - a. Obstruction of proximal subclavian artery (prior to the origin of the vertebral artery):
 - i. Low pressure system within the ipsilateral vertebral artery
 - ii. Blood supply of the ipsilateral arm is deficient. During exercise these blood vessels dilate which further lowers vascular resistance in the exercised arm
 - iii. Higher pressure system:
 1. Contralateral vertebral artery
 2. Blood flows retrogradely down the ipsilateral VA into the arm (brainstem becomes ischemic)

Clinical Manifestations

1. Most patients are asymptomatic in the face of arterial demonstration of a steal
2. Complaints relate primarily to arm ischemia:
 - a. Fatigue, achiness with exercise, autonomic dysregulation (coolness)
3. Neurologic symptoms are more common with concomitant carotid disease
4. 75% of patients are asymptomatic (demonstrated in Takayasu's disease)
5. Rare neurologic symptoms (usually brief) occur:
 - a. Arm is used repetitively and often overhead
 - b. Blurred vision
 - c. Oscillopsia
 - d. Diplopia
 - e. Vertigo/spinning
 - f. Incoordination and imbalance

Clinical Signs

1. Delayed antecubital and wrist pulse on the stenotic side
2. Smaller pulse volume
3. Supraclavicular bruit (rare)
4. Inflation of blood pressure cuff on the ipsilateral side:
 - a. If the bruit is generated from ECVA the bruit increases as more blood flows through the stenosis (less reversal)

- b. If the bruit is generated from the subclavian stenosis the bruit decreases (increased pressure of ipsilateral system because there is no arm "run-off")
5. Clinical sequelae:
 - a. Stroke is rare with subclavian steal
 - b. Clots can form in a subclavian occlusion
 - i. Embolization to vertebral artery territory
 - c. Raynaud's phenomenon and autonomic dysregulation of the affected extremity may occur

Innominate Stenosis on the Right Side

1. Decrease of carotid flow
2. Exacerbated by cigarette smoking
3. Women > men
4. Associated with other large vessel occlusive disease
5. Right subclavian steal < frequent than left
6. Clot may spread from the innominate into the carotid arteries
 - a. Recurrent arm and brain ischemia
 - b. Floating thrombi within the innominate artery

Differential Diagnosis of Subclavian Artery Disease

1. Takayasu's disease
2. Severe atherosclerosis
3. Aortic arch syndrome
4. Syphilis (chronic aortitis)
5. Cervical rib
6. Giant cell arteritis
7. Athletics that utilize a constant throwing motion

In Takayasu's disease, there is major inflammation and occlusion of the aortic arch vessels. Intermittent claudication of the arm is the most common symptom. Loss of vision with head position (precarious arterial supply to the optic nerve head from posterior ciliary arteries and central retinal artery compromise) and trophic loss of integument of the face and cataracts are common. Most patients with Takayasu's disease are asymptomatic in the face of an arteriographic steal.

Giant cell arteritis may compromise the great vessels at the arch with occlusion and stroke of the carotid artery. A cervical rib most frequently compresses the lower trunk of the brachial plexus with atrophy and weakness of the intrinsic hand muscles.

Vertebrobasilar Infarction

General Characteristics of Lateral Medullary Territory Infarction

Three Major Medullary Divisions

1. Anterior
 - a. Primarily the corticospinal tract that crosses at C2
 - b. Corticobulbar fibers cross at the level of the cranial nerve
2. The tegmentum comprising:
 - a. The respiratory complex
 - b. Cranial nerve nuclei VIII–X; descending VIII–X

- c. Components of the reticular formation
- d. Ascending and descending sensory systems (lemniscal (descending)/spinothalamic (ascending); diffuse nociceptive inhibitory controls DNIC (inhibitory for pain); descending tract and nucleus of V)
- 3. Posterior portion:
 - a. Lemniscal pathways to dorsal column nuclei
 - b. Merges into extension of spinal cord anatomy

Arterial Supply of the Medulla

1. Rostral-paramedian branches of the vertebral arteries (medial)
2. Caudal-paramedian branches of the anterior spinal arteries (vertebral artery origin); medial
3. The anterior lateral medulla is supplied by the circumferential branches of the vertebral arteries
4. Posterior medulla – supplied laterally by the posterior inferior cerebellar artery
5. The posterior dorsal medulla is supplied by branches of PICA (two posterior medullary arteries)

Proximal Vertebral Artery Disease

General Characteristics

1. Most frequent location of extra axial vertebral artery disease (ECVA) is at the origin from the subclavian artery (accessible to stenting and angioplasty)
2. ICA and ECVA stenosis frequently are affected concomitantly
3. Occurs in Caucasians > Asian and African Americans

Clinical Manifestations

1. Most common symptom is dizziness
 - a. Extremely rare for this symptom to be solitary
 - b. TIAs are not precipitated by arm movement as is the case with subclavian-steal syndrome (on rare occasions)
2. Diplopia
3. Dysphagia
4. Oscillopsia (environment moving from nystagmus)
5. Hemiparesis
6. Bilateral leg weakness
7. Sensory loss on the trunk
8. Hypoplastic congenital vertebral and basilar arteries coexist:
 - a. Patient suffers posterior circulation ischemia
 - b. Left vertebral artery 80% of the time dominant over right
 - c. Complete atresia of a vertebral artery is rare

Lateral Medullary Territory (Posterior Inferior Cerebellar Artery)

General Characteristics

1. Direct penetrators from the distal vertebral supply the lateral medulla and cerebellum

2. Posterior inferior cerebellar artery (PICA) supplies the lateral medulla and inferior cerebellum including the floccular nodular lobe
3. Posterior inferior cerebellar artery (PICA) frequently overlaps AICA territory or forms an AICA/PICA artery that supplies both territories
4. Variable: PICA/AICA supply to the lateral medulla or portions of the pons
5. Lateral medullary syndrome: most often occurs from occlusion of the distal perforators of the vertebral artery (VA)
6. If coexisting, AICA involved: middle cerebellar peduncle involved (core territory)
7. If coexisting, PICA involved: lower cerebellum infarcted
8. Dorsal medulla supplied by branches of PICA (two posterior medullary arteries)

Clinical Manifestations

1. General:
 - a. 40% are sudden (ictal)
 - b. 60% a gradual or stepwise pattern over 24–48 hours
 - c. 25% of patients have had a preceding TIA in the same arterial territory
2. Cranial Nerve Abnormalities:
 - a. Dysphagia (rostral nucleus ambiguus)
 - b. Hoarseness (caudal N. ambiguus)
 - c. Crowing cough (N. ambiguus)
 - d. Nausea and vomiting:
 - i. Vestibular nuclei
 - ii. N. tractus solitarius (NTS)
 - iii. Vomiting out of proportion to dizziness
 - e. Ipsilateral Horner's syndrome:
 - i. Descending central sympathetic fibers
 - f. Hiccoughing (singultus; NTS)
 - g. Ipsilateral VII nerve dysfunction:
 - i. Occurs in 33–50% of patients. This is due to two groups of recurrent VII nerve fibers
 - ii. In the upper medulla an origin that recurs through the lateral medulla
 - iii. Fibers that leave the pyramidal tract (at the decussation in the medial medulla and course rostrally to the contralateral tegmentum)
 - h. Lateral medullary infarction lateral recurrent fibers of VII are infarcted
 - i. Dysarthria caused by faciopalatal-glossal dysfunction and cerebellopetal pathways
3. Visual signs and symptoms:
 - a. Blurred vision
 - b. Oscillopsia (with acute infarction)
 - i. Environment appears to move with patient's nystagmus (usually horizontal)
 - c. Vertical, horizontal or oblique diplopia:
 - i. Disruption of the ocular tilt reaction (OTR)
 - d. Incyclotropia:
 - i. Cyclorotation abnormalities (clockwise or counter-clockwise eye rotation)

- ii. Disruption of the vestibulo-ocular response (VOR)
- e. Horizontal and rotary nystagmus is most prominent to the ipsilateral side
- f. Skew deviation-ipsilateral eye down (otic-oculomotor pathways)
- g. Hypermetric saccades to the ipsilateral side (flocculonodular lobe of the cerebellum); hypoactive saccades to the contralateral side
- h. Deviation of the subjective visual vertical (SVV) to the ipsilateral side (internal concept of the body's vertical position)
- 4. Motor signs:
 - a. Ipsilateral hemiparesis (Opalski's syndrome)
 - i. If the pyramidal fibers below the decussation at C2 are involved
 - b. Contralateral hemiplegia occurs with the combined lateral and medial medullary syndrome; no weakness with pure PICA infarction
 - c. Most often there is ataxia without weakness
- 5. Sensory signs and symptoms:
 - a. Ipsilateral facial pain and sensory loss:
 - i. Touch, temperature, pain, cold decreased (ipsilateral descending spinothalamic tract of V)
 - ii. Loss of ipsilateral corneal reflex (V)
 - iii. "Salt and pepper" facial paresthesia and pain (ipsilesional)
 - b. Far lateral medullary infarction of the spinothalamic tract (STT)
 - i. Crossed hemisensory loss to pinprick and temperature on the contralateral body below the clavicle
 - c. More medial infarction of the lateral medullary STT
 - i. Contralateral loss of pinprick and temperature of the face, trunk, and upper limb (the ipsilateral STT from the arm, trunk and leg and the crossed ventroreticulospinal ascending fibers that cross medially in the medulla that subserve the contralateral face)
 - d. Medial medullary infarction of the SST:
 - i. Bilateral facial hypalgesia with variable contralateral sensory loss (dog's nose pattern)
 - ii. "Onion skin" facial sensory loss
 - 1. Nose involved
 - 2. Pre-auricular area spared
 - 3. Maybe seen as well with V nerve entry zone lesions
- 6. Headache:
 - a. Occipital
 - b. Unilateral
 - c. Non-throbbing
 - d. Vth nerve origin of trigeminal pain afferents to the dura, proximal blood vessels and sinuses (somatic visceral convergence)
- 7. Brainstem dysfunction:
 - a. Autonomic dysregulation
 - i. Cardiac arrhythmia
 - ii. Blood pressure variability

- 1. Lateral medullary vasomotor center
 - 2. Most often postural hypotension
- b. Respiration
 - i. Sleep apnea
 - ii. Sleep disordered breathing
- iii. Failure of automatic breathing Ondine's curse
 - 1. Disruption of oscillations of lateral and medial respiratory neurons (Boettinger complex)
 - 2. Afferent disruption of IX and X pulmonary afferents (Hering-Breuer reflex) may be carried centrally in STT
- 8. Cerebellar syndrome:
 - a. Gait and ipsilateral limb ataxia; leg more than arm
 - b. Axial lateropulsion (if restiform body involved from concomitant medial branch infarction); patient is pushed to the side of the lesion

Unilateral Medial Medullary Infarction (Dejerine's Syndrome)

General Characteristics

- 1. Less than 1% of posterior circulation strokes
- 2. Branch occlusion from the VA

Clinical Manifestations

Motor Signs and Symptoms

- 1. Flaccid hemiparesis:
 - a. Contralateral if above C2
 - b. Ipsilateral if the infarction spreads to the cervical medullary junction
- 2. Spasticity within days to weeks:
 - a. Flexion of upper extremities
 - b. Extension of the lower extremities
- 3. Rarely weakness can be minimal or absent
- 4. Rarely upper limb monoparesis:
 - a. Fibers after decussation may be lateral
- 5. Motor deficit is more severe distally in the upper extremity
- 6. Patterns of weakness at the level of the pyramidal decussation:
 - a. Leg fibers may cross anteriorly and then remain lateral to arm fibers
 - b. Some studies – arm fibers decussate anteriorly to leg fibers
 - c. Crural paresis:
 - i. Proximal portion of the limbs affected with finger and toe movements preserved
 - ii. Hemiplegia cruciata:
 - 1. Arm involved ipsilaterally with contralateral leg weakness
- d. Pontine recurrent VIIth nerve pathway may be infarcted with facial weakness

Sensory Signs and Symptoms

- 1. Contralateral lemniscal type sensory loss of the hemibody with or without the face

2. More marked distally
3. May involve the face only
4. Pseudospinal dropped sensory level on the trunk
5. Dissociation between vibration and position loss
 - a. Vibration may be involved with more lateral extension
6. Pain sensation
 - a. Occasionally decreased with preserved temperature, sensation, and mild hypesthesia

Cognitive Dysfunction

1. Medial reticular formation involvement:
 - a. Apathy
 - b. Somnolence
 - c. Hallucinations
 - d. Delirium
2. Differential diagnosis of pathologic laughing and crying that occurs with infarction of:
 - a. Internal capsule
 - b. Pons
 - c. Pyramidal tract (usually bilateral)
 - d. Bilateral temporal lobe (usually trauma)
 - e. Medial frontal lobe (laughing)

Ophthalmologic Signs

1. Upbeat nystagmus:
 - a. Dorsolateral medulla or pontomedullary junction infarction that spares the medial medulla
 - b. Ipsilateral MLF or perihypoglossal nuclei are involved in upgaze
 - c. Horizontal nystagmus (ipsilateral) or multiple directional nystagmus related to vestibular nuclear involvement or their connections to the cerebellum in the lateral medulla
 - d. Rare – ocular bobbing (usually a pontine lesion)

Lateral Pulsion

1. Contralateral lateral pulsion:
 - a. Dorsolateral medulla and cerebellum are not involved
 - b. Patient feels as if he is pushed to the side
 - c. Lesion at the level of the restiform body or olivary nuclei

Respiratory Dysfunction

1. Cluster breathing
2. Decrease of voluntary control of breathing secondary to corticospinal destruction and lack of intercostal muscle control
3. Loss of automatic breathing (Ondine's curse)

Autonomic Dysregulation

1. Mild ptosis with hypohidrosis
 - a. Severe miosis (0.5 mm pupil) with pontine infarction
 - b. Dissociation of ptosis and pupillary sympathetic fibers is due to a somatotopic arrangement of sympathetic fibers around the N. ambiguus
2. Bladder retention or inhibited contractions only occur with bilateral MMI

Cranial Nerve XII

1. Isolated contralateral XII nerve
2. More common with hemorrhage than infarction

Isolated Drop Attacks

1. May progress to stroke over several days
2. Ischemia of:
 - a. Medullary or pontine corticospinal fibers
 - b. Medial reticular formation involvement (loss of tone)

Differential Diagnosis of Vascular Etiologies of Unilateral Medial Medullary Infarction

1. Branch occlusion from VA (upper medulla)
2. Dolichoectasia of vertebrobasilar system
3. Embolus
4. Syphilis
5. Branch occlusion from the anterior spinal artery (lower medulla) secondary to atheroma of the VA or anterior spinal artery

Underlying Associated Conditions

1. Diabetes mellitus
2. Birth control pills
3. Dissection of VA
4. Thrombosis of VA
5. Embolus in 1/4 of patients

Bilateral MMI Infarction

Clinical Manifestations

1. Quadriplegia (flaccid)
2. Associated loss of lemniscal sensation
3. Paralysis of the tongue
4. May have step wise progression
5. Bladder retention or uninhibited contractions
6. Death by cardiorespiratory failure

Differential Diagnosis

1. Anomalous anterior spinal artery from one vertebral artery
2. Occlusion of the ASA after it forms a single vessel

Medial and Lateral Medullary Syndrome (Babinski–Nageotte)

Clinical Manifestations

1. Clinical features of combined LMI and MMI:
 - a. IX, X, XI, XII ipsilaterally
 - b. Horner's ipsilaterally
 - c. V ipsilateral (most often STT modalities)
 - d. Ocular findings (LMI and MMI)
 - e. Contralateral hemiparesis; may be ipsilateral (depending on infarction below decussation at C2)
 - f. Lemniscal and STT sensory loss (contralateral)
 - g. Ipsilateral ataxia
 - h. Reinhold's syndrome

Hemimedullary Syndrome (Reinhold's Syndrome)*General Characteristics*

1. Usually vertebral artery occlusion
2. Combination of both medial and lateral medullary syndromes
3. Hemiparesis may be ipsi- or contralateral

Cestan-Chenoi Syndrome*General Characteristics*

1. Intermediolateral medullary infarction
2. Vertebral artery, PICA, and anterior cerebral artery are involved

Clinical Manifestations

1. Contralateral hemiplegia
2. Paralysis of the larynx and soft palate
3. Horner's syndrome

Neuroimaging

A recent evaluation of 142 patients with medullary infarction (from a total of 3833 patients) demonstrated by diffusion-weighted magnetic resonance imaging revealed:

1. Bilateral medullary infarction in 8.2%
2. Upper medulla sustained infarcts in the anterior medial or lateral territories
3. Lateral infarctions more common in the middle and lower territories
4. 50% stenosis or occlusion of the VA was noted in 52% of patients
5. Large artery atherosclerosis – 34.5%
6. Lacunes and cardioembolism comprised 3.5% and 4.2% respectively
7. Lacunar infarction involved the anterior and anterolateral territories
8. Cardiac emboli involved lateral or posterior territories

In a second study of 77 patients, large artery disease was the most common etiology for both LMI and MMI.

1. LMI – arterial dissection greater than small vessel disease and cardioembolism
2. MMI – more prevalent in younger patients
3. Patients with large artery disease and dissection had positive DWI
4. Patients with large artery disease and dissection had positive DWI

Pontine Infarction*General Characteristics*

1. Most often pontine infarction is associated with atherosclerotic cerebrovascular disease
2. There may be restricted pontine lesions from atheromatous ostial lesions or lipohyalinosis
3. The anteromedial and anterolateral territories are most commonly involved

4. Atheromatous ostial occlusion the most common etiology (> 15 mm lesion on 3 slices); lipohyalinosis (less evidence; smaller lesion)
5. Pontine lesions are 12–27% of posterior circulation strokes

Clinical Manifestations

1. Pontine TIAs are seen in 1/3 of patients. Often preceding stroke onset:
 - a. Pathologic laughter: spontaneous laughing and crying spells – “Fourier prodromique”
 - b. Pontine warning syndrome
 - c. Yawning
 - d. “Salt and pepper” face pain (trigeminal nucleus)
 - e. Herald hemiparesis
2. 5 specific arterial territories

Anteromedial Infarcts (Paramedian)*General Characteristics*

1. Approximately 2/3 of pontine infarcts
2. Arterial territories involved:
 - a. Medial basis pontis – includes the corticospinal tracts, supplied from short midline perforators from the basilar artery
 - b. Long midline perforators from BA supply:
 - i. Medial medial lemniscus
 - ii. IIIth cranial nerve
 - iii. MLF
 - c. Para pontine reticular formation (PPRF) – the center for horizontal gaze
 - d. Infarction may extend to the ventral surface
 - e. Ischemic changes are seen commonly:
 - i. In the midline affecting the legs (gait disturbance)
 - ii. Seen in T2-weighted images as high intensity lesions (pontine sludge)

Clinical Manifestations

1. Pure Motor Hemiplegia
 - a. Arms greater than legs
 - b. Distal greater than proximal muscles
 - c. Seen in 50% (some evidence that arm fibers more lateral than leg fibers)
 - d. Infarcts in middle or caudal pons
2. XIIth nerve; central and lateral palatal muscles – lingual – laryngeal paresis
3. Isolated dysarthria: rare
4. Upper pontine paramedian infarcts dysarthria associated with:
 - a. Hemiparesis
 - b. Brachial monoparesis
 - c. Supranuclear VIIth nerve palsy and hemiataxia
5. Paramedian lesions associated with transitory tegmental signs that include:
 - a. Decreased proprioception and vibration
 - b. Cheiro-oral crural or facial hypoesthesia (rostral pons – central face; caudal pons, pre-audicular area)

6. Neuro-ophthalmological signs:
 - a. One-and-a-half syndrome; PPRF involvement in association with posterior MLF lesion; 8^{1/2} syndrome (VII nerve involved)
 - b. Ocular bobbing (eyes driven down and float up; ocular dipping)
 - c. Primary position downbeating nystagmus
 - d. Skew deviation (down eyeside of the lesion)
 - e. Horner's syndrome (lateral extension)
 - f. VIth nerve palsy (isolated or with contralateral hemiparesis)
7. Ventroregmental junction infarction:
 - a. In middle or upper pons are associated with:
 - i. Dysarthria – clumsy hand syndrome
 - ii. Ataxic hemiparesis (crossing fibers from pontine nuclei to middle proprioceptive zone)
8. Etiology most commonly basilar branch disease from ostial atheromatous plaque

Anterolateral Territory Infarction

General Characteristics

1. Arterial supply – short circumferential arteries from the basilar artery
2. Supplies lateral corticospinal tract and components of the medial lemniscus

Clinical Manifestations

1. Facio-brachial-crural weakness
2. Dysarthria clumsy hand syndrome
3. Ataxic hemiparesis
4. Homolateral gaze paralysis
5. Saccadic substitution for smooth pursuit
6. Horner's syndrome
7. One-and-a-half syndrome
8. Skew deviation
9. Horizontal nystagmus
10. Isolated VIth nerve
11. Etiology is most often basilar atheromatous disease in 50% and lipohyalinosis in 20%

Lateral Territory Infarction

General Characteristics

1. Accounts for 12–30% of pontine infarctions
2. The superior cerebellar arterial branches irrigate the lateral upper pontine structures that include:
 - a. Pontine nuclei
 - b. Dorsolateral corticospinal tract
 - c. Medial lemniscus
 - d. Ventral trigeminothalamic tract
 - e. Middle cerebellar peduncle

Clinical Manifestations

1. Facio-brachial-crural hemiparesis
2. Crural monoparesis (more commonly at upper levels)
3. Contralateral lemniscal or spinothalamic sensory deficits that include the following distributions:
 - a. Brachial crural
 - b. Facio-brachial-crural
 - c. Arm, face and leg hypoesthesia
 - d. Rarely, trigeminal weakness with hypoesthesia
4. Neuro-ophthalmologic signs similar to those seen with medial infarcts and are associated with:
 - a. Contralateral motor and sensory deficits
 - b. Ataxia
5. Lateral dorsal infarcts associated with:
 - a. Fascicular VIth nerve or nuclear VII nerve palsy
 - b. Painful ipsilateral Vth nerve palsy (descending tract and nucleus of V)
6. Caudolateral infarction associated with:
 - a. No oculomotor signs
 - b. May have isolated vertigo that suggests an acute peripheral vestibulopathy
 - i. A cause of contralateral lateral pulsion
7. Small artery disease is the primary etiology

Dorsomedial Pontine Infarction

General Characteristics

1. The arterial territory is supplied by long circumferential arteries from the superior cerebellar artery or AICA

Clinical Manifestations

1. Infarcts often associated with strokes of the cerebellum or brainstem infarction from basilar artery disease
2. Rarely, homolateral cranial nerve palsy

Bilateral Infarction

General Characteristics

1. Associated with extensive brainstem ischemia or extension of prior infarcts
2. Approximately 10% of pontine infarcts

Clinical Manifestations

1. Bilateral motor deficits with tegmental signs
2. Associated neuro-ophthalmological cranial nerves and sensory deficits
3. Ventral infarcts at the middle and caudal level:
 - a. Depressed level of consciousness
 - b. Locked-in syndrome:
 - i. Patients are conscious
 - ii. Unable to move
 - iii. Vertical gaze and eye closure are maintained
 - iv. Variant partial forms are seen
 - c. Motor deficits include:
 - i. Tetraplegia
 - ii. Triparesis

- iii. Paraplegia
- iv. Ataxic tetraparesis
- 4. Acute pseudobulbar palsy

Anteromedial and Anterolateral Infarction

- 1. Large infarcts
 - a. Severe hemiparesis and dysarthria
- 2. Small infarcts
 - a. Dysarthria clumsy hand syndrome
 - b. Ataxic hemiparesis
 - c. Pure motor hemiparesis
- 3. Anterolateral and dorsolateral infarcts
 - a. Crural monoparesis

Summary of Pontine Infarction

Patterns of Weakness in Pontine Hemiparesis

- 1. Greater in the distal upper extremity than lower extremity
- 2. Less commonly the leg has distal weakness greater than the arm
- 3. Crural or brachiorural paresis with preservation of finger and toe movement
- 4. Arm fibers – disrupted by more dorsal lateral lesions
- 5. Ventral tegmental lesions – leg weakness and gait ataxia
- 6. Leg fibers – disrupted by more lateral lesions
- 7. Facial palsy associated with palato-glossal weakness – involvement of pontomedullary bundle
- 8. Severe dysarthria
- 9. Isolated dysarthria and facial weakness are rare
- 10. Some correlation of severity of motor deficits and contralateral ataxia

Rare Signs of Paramedian Infarction

- 1. Pure VI or VII nerve paralysis
- 2. Contralateral hyperhidrosis alone or associated with hemiparesis
 - a. Destruction of inhibitory fibers for thermal sweating
 - i. Lesion noted in middle pons
- 3. Variants of the one-and-a-half syndrome
 - a. Absent horizontal gaze to the side of the lesion; abducting nystagmus of the contralateral eye (MFL lesion); if convergence is intact, the lesion is caudal near the PPRF
 - b. The nine syndrome:
 - i. “Eight-and-a-half” syndrome (cranial nerve VII and one-and-a-half syndrome) plus contralateral hemiplegia and hemihypesthesia
 - c. Non-paralytic pontine exotropia
 - d. WEBINO syndrome (wall eyed bilateral INO)
 - e. Sixteen and one half syndrome associated with ipsilateral supranuclear VII palsy
 - f. Upbeat nystagmus associated with ataxia, INO and hemiparesis
 - g. Millard–Gubler syndrome:
 - i. Ipsilateral VI, VII palsy

- ii. Contralateral hemiparesis
- h. Foville’s syndrome:
 - i. Ipsilateral cranial VI and VII
 - ii. Infarction of the ipsilateral PPRF (ipsilateral horizontal gaze paralysis)
 - iii. Contralateral hemiparesis
- i. REM sleep behavior disorder:
 - i. Periodic limb muscle movements during sleep
 - ii. Contralateral lateral pulsion

Rare Signs of Posterior Pontine Territory Infarction

- 1. Marie-Foix syndrome
- 2. Homolateral cranial nerve palsies
- 3. Central Horner’s syndrome (ipsilesional)
- 4. Hemiataxia (ipsilesional)
- 5. Uveula-palato-pharyngeal myoclonus (ipsilesional)
- 6. Contralateral pain and temperature deficit

Rare Manifestations of Combined Anteromedial and Anterolateral Syndrome

- 1. Raymond-Cestan syndrome:
 - a. Ipsilateral I&O
 - b. Contralateral hemiparesis
 - c. Contralateral hemihypesthesia

Rare Manifestations of Bilateral Infarcts

- 1. Peduncular hallucinations:
 - a. Paramedian rostral pontine infarct
- 2. Freezing of gait and gait ignition deficits
 - a. Disruption of pedunculo-pontine input to the nucleus cuneiformis
- 3. Bilateral horizontal gaze palsy associated with nuclear VII nerve palsy
- 4. Perioral hypesthesia, hypesthesia of the hands and distal arms
 - a. Bilateral tegmental infarcts at the caudal pons

Vertebral and Basilar Artery Stroke

General Characteristics

Posterior circulation strokes are 20% of all ischemic cerebral vascular disease.

- 1. Infarcts are frequently multiple
- 2. Basilar artery irrigates:
 - a. Most of the brainstem
 - b. Occipital lobes (through PCAs)
 - c. Cerebellum (AICA; SCA artery)
 - d. Thalamus (PCA-thalamogeniculate and thalamoperforate arteries)
 - e. Midbrain (top of the basilar interpeduncular arteries)

Neuropathology

Pathogenesis of Vertebrobasilar Disease

- 1. Atherothrombosis is the most common cause of vertebrobasilar disease

2. Emboli occur from:

- a. Cardiac source or arch of the aorta
- b. Artery-to-artery (vertebral to basilar; basilar to P1 and P2 (PCA) or midbrain from interpeduncular artery (arises from top of the basilar))
- c. Middle basilar artery infarction is usually atherothrombotic
- d. Top of the basilar (distal) or proximal basilar are occluded by emboli
- e. Atherothrombotic lesion of the vertebral artery:
 - i. Present in the intracranial portion of the artery and are often occlusive and bilateral
 - ii. There are often concomitant atherosclerotic lesions in the anterior circulation
 - iii. Multiple risk factors are present (particularly HCVD, diabetes mellitus and cardiac insufficiencies)
 - iv. Collateralization is from the posterior communicationings leptomeningeal and anterior spinal arteries
 - v. Dissection most frequently occurs in the vertebral artery (occasionally extending to the basilar artery)
 1. VA dissection occurs with an annual incidence of 97/100,000 patients
- vi. Clinical signs and symptoms are variable due to:
 1. Variation of the arterial supply
 2. Number and extent of lesions in both vessels (VA and BA)
 3. 50% of patients with acute VB stroke have had TIA in the same vascular territory whose characteristics are:
 - a. Waxing and waning pattern due to:
 - i. Distal field ischemia
 - ii. Hemodynamic changes (decreased BP)
 - iii. Head position (occlusion of the contralateral vertebral artery in the trans-cervical canal)
 - iv. Usual symptoms reflect:
 1. Cranial nerve deficits
 2. Vestibulocerebellar dysfunction
 3. Motor deficits
 - vii. Premonitory and progressive signs and symptoms suggest atherothrombosis. Ictal signs and symptoms suggest emboli (particularly with top of the basilar topography). Less frequently proximal vertebral or mid basilar topography of sudden stroke suggests an embolism from a unilateral VA
 - viii. Most vulnerable VA territories:
 1. Lateral medulla supplied by perforating arteries from the intracranial VA
 2. PICA (cerebellar perfuses area)
 - ix. The vestibular nuclei and connections to the vermis:
 1. Supplied by the intracranial VA
 2. Common signs of hypoperfusion are vertigo and ataxia

Clinical Manifestations

Major Clinical Patterns of VB Ischemia (New England Medical Center Classification)

1. Lower territory:
 - a. Medulla and PICA fed by intracranial vertebral arteries and their branches
2. Middle territories irrigated by the BA and its branches:
 - a. Pons
 - b. Lower midbrain
 - c. Aica (arterial territory)
3. Distal territory irrigated by the distal BA; superior cerebral artery branches:
 - a. Upper midbrain
 - b. Thalamus
 - c. SCA arterial territory
 - d. Temporal, medial and occipital lobes
4. Multiple infarcts in VB territory are due to:
 1. Bilateral VA atherosclerotic narrowing or occlusion
 2. Proximal BA stenosis or occlusion
 3. BA branch occlusion including the posterior cerebral arteries

Clinical Sign and Symptoms of Basilar Artery Thrombosis

1. May be acute, a progressive stroke or preceded by prodromal symptoms
2. Vertigo and nausea (54–73%)
3. Facial weakness and hemiparesis (40–67%)
4. Dysarthria (30–63%)
5. Headache (40–42%) – basi-occipital
6. Diplopia (21–33%); VI cranial nerve; I & O
7. Confusion, changes in consciousness (17–33%) may alternate and may progress to stupor
8. Pseudo bulbar symptoms
9. Ocular bobbing and dipping, dysfunction of the ocular tilt reaction, skew deviation
10. Bilateral hearing loss
11. Pathologic laughter
12. Pontine warning syndrome

Differential Diagnostic Points Between Basilar Artery vs Vertebral Artery Stroke

1. BA at any location tends to have motor and oculo-motor signs and symptoms particularly in the face of altered consciousness
2. Vertigo and cerebellar symptomology suggest VA disease

Midbrain Infarction*General Characteristics*

Midbrain infarctions are 2% of all cerebral infarcts and 8% of those that occur in the posterior circulation. The midbrain is usually infarcted in association with the thalamus and pons or the superior cerebellum and temporal occipital cortex. There are four major vascular territories. The most commonly involved is the paramedian (anteromedial) followed by the anterolateral which supply the middle and upper midbrain. The major consequence of infarction in this territory is abnormalities of vertical gaze.

Paramedian (Anteromedial) Territory

1. This territory is supplied by:
 - a. Perforators from the top of the basilar (the interpeduncular artery)
 - b. Superior cerebellar perforating arteries
 - c. The thalamo-subthalamic paramedian artery from the P1 segment of the posterior cerebral artery (origin is medial to the posterior communication artery)
2. The major oculomotor structures affected and involved with vertical gaze are:
 - a. The rostromedial nucleus of the medial longitudinal fasciculus (riMLF), the posterior commissure and the periaqueductal area

Clinical Manifestations

1. Occur from both bilateral and unilateral infarction of the upper midbrain
2. Oculomotor deficits are rarely isolated
3. Unilateral or bilateral thalamic infarcts cause vertical eye movement dysfunction with associated deficits that include:
 - a. Down and in eyes
 - b. Decreased levels of consciousness (waxing and waning)
 - c. Short term memory loss and aphasia
4. Complete bilateral ophthalmoplegia with:
 - a. Bilateral ptosis
 - b. Bilateral infarction at the mesodiencephalic junction
5. Supranuclear conjugate gaze palsies from infarction of the paramedian rostral midbrain:
 - a. Vertical palsies that can be either up or down
 - b. Complete ophthalmoplegia with ptosis
 - c. Dorsal midbrain syndrome (Parinaud's syndrome)
 - i. Failure of upgaze
 - ii. Associated with impaired hearing (if the inferior colliculus is involved)
 - iii. Dissociated optokinetic nystagmus (loss of vertical component)
 - iv. Bilateral ptosis (central caudal nucleus)
 - v. Bilateral mydriasis (Edinger – Westphal nucleus; mid-dilated pupil)
 - vi. Skew deviation (vertical diplopia)
 - vii. Accommodation spasm on attempted upgaze
 - viii. Pupillary light-near dissociation
 - ix. Spasm of convergence
 - d. Convergence-retraction nystagmus
 - e. See-saw nystagmus
 - f. Pseudoabducens palsy (slower movement of the abducting eye than the adducting eye during horizontal saccades)
 - g. Bilateral down-gaze palsies (dorsomedial to the red nucleus; rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF)); supranuclear disconjugate gaze palsies:

- i. Double elevator palsy (weakness of the superior rectus and inferior oblique; contralateral pretectal supranuclear fibers that subserve the superior rectus subnucleus of the IIIrd nerve complex)
- ii. Vertical one-and-a-half syndrome (supranuclear down gaze paralysis with monocular elevation palsy)
 1. Bilateral infarction at the thalamo-mesencephalic junction; region of the upper medial red nucleus
 - a. Efferent tracts of the riMLF are affected bilaterally
 - b. Lesion of the premotor fibers to the contralateral superior rectus subnucleus and ipsilateral inferior oblique sub-nucleus (pre or post decussation in the posterior commissure)
 - c. Skew deviation (down eye opposite the infarction)
 - d. Prenuclear syndrome of the oculomotor nucleus

Non Neuro-Ophthalmologic Signs of Midbrain Rostral Infarcts

1. Pure motor hemiparesis:
 - a. Simulating MCA infarction (perforating arteries from the PCA; no facial involvement; infarction of medial 3/5 of the cerebral peduncle)
 - b. Isolated gait ataxia
 - c. Body lateral pulsion (falls to the side of the lesion; involvement of the ascending fibers of the crossed dentatorubrothalamic tract near the red nucleus)

Paramedian Middle Midbrain Infarction

1. Nuclear III (with hemiparesis or ataxia):
 - a. Ipsilateral IIIrd nerve with central SR palsy (failure of upgaze)
 - b. Bilateral ptosis (central caudal nucleus that innervate the levator palpebrae)
 - c. Bilateral mid-brain mydriasis (Edinger-Westphal nucleus)

Unusual Middle Midbrain Signs

1. Dysarthria is found in approximately 50% of patients with pure midbrain infarction usually with other signs and symptoms
 - a. Isolated dysarthria from a medial ventral substantia nigral lesion
2. Acquired stuttering
3. Isolated IIIrd, IVth nerve palsy may be caused by giant cell arteritis, neoplasm or pituitary apoplexy (IIIrd and IVth with pituitary apoplexy)
4. Divergence paralysis:
 - a. Lesion is in the vicinity of the PAG; possible medial reticular formation
5. Plus-minus eyelid syndrome with ataxia:

- a. Ptosis on one side and eyelid retraction on the other
 - i. IIIrd nerve infarction ipsilaterally
- b. Nucleus of the posterior commissure (inhibits the levator palpebrae)

Anterolateral Territory Infarction

General Characteristics

1. Subservd by P2 branch mesencephalic arteries

Clinical Manifestations

1. Peripheral type of IIIrd most usual (more severe ptosis than with aneurysm of P-COM)
2. IIIrd nerve palsy with hemiparesis (Weber's syndrome)
 - a. Patients are awake; hypotonic, hyporeflexic
 - b. Subdural hematoma patients: lethargic; spastic hemiplegic
3. IIIrd nerve palsy plus cerebellar signs:
 - a. Claude's syndrome:
 - i. Involvement of dentatohalamic fibers
 - b. Benedict's syndrome:
 - i. IIIrd nerve palsy and contralateral movement disorder
 - ii. Tremor (rubral, large amplitude at right angle to the line of movement); chorea from infarction of the red nucleus and dentatohalamic fibers. In general, the closer the infarction is to the red nucleus, the greater the tremor and failure of proximal extremity fixation
 - c. Ataxic hemiparesis or hypesthetic ataxic hemiparesis
 - d. Rarely – hemiparkinsonism particularly of the lower extremities
 - i. Substantia nigra pars compacta (SNPc) involvement
 - e. Unilateral or bilateral infarction of the SNPc may cause peduncular hallucinosis

Paramedian Caudal Midbrain Infarction

General Characteristics

1. Unilateral or bilateral INO (MLF involvement associated with limb and gait ataxia, dysarthria and rubral tremor (Wernekinck's commissure which is the decussation of the superior cerebellar peduncle))
2. Bilateral INO
3. Rarely – pathologic laughter may be premonitory. This sign is most often associated with dysarthria and hemiparesis
 - a. Interruption of basal ganglia projections to the forebrain

Lateral Territory Infarction

General Characteristics

1. The rostral level of the caudal territory is supplied by the posterior choroidal artery
2. The caudal 2/3 of the laterodorsal region is perfused by short circumferential branches of the SCA

Clinical Manifestations

1. The clinical signs derive primarily from involvement of the medial and trigeminal lemniscus and include:
 - a. Cheiro-oral and cheiro-oral pedal large fiber sensory loss associated with hemiataxia and hemiparesis

Dorsal Territory Infarction

General Characteristics

1. Often infarction due to concomitant involvement of SCA territory

Clinical Manifestations

1. Clinical signs include:
 - a. Isolated IVth nerve
 - b. Ipsilateral Horner's syndrome
 - c. Contralateral ataxia
 - d. Isolated hemihypesthesia

Unusual Patterns of Midbrain Infarction

1. Bilateral infarction of upper paramedian territories:
 - a. Associated ischemic thalamic involvement
2. Vertical gaze dysfunction:
 - a. Plus-minus syndrome with ataxia
 - b. Divergence Paralysis
3. Locked-in syndrome:
 - a. Bilateral cerebral peduncle infarction

Neuropathology

Mechanism of Midbrain Infarction

1. In a 74 patients with pure mesencephalic infarction:
 - a. Basilar artery stenosis or occlusion was most common (43%)
 - b. Small artery disease (30%)
 - c. Cardiac embolism (11%)
 - d. Not determined (15%)
 - e. An embolic source is suspected if ischemia involves the thalamus, superior cerebellum and temporo-occipital cortex
 - i. Artery-to-artery (VA > BA)
 - ii. Cardiac source

Rare Stroke Syndromes from Midbrain Infarction

1. Subthalamic small deep infarcts:
 - a. Abnormal movements and asterixis
 - b. Unilateral or bilateral ballistic movements (>2/3 of the corpus Luysi; STN has to be infarcted)
 - c. Blepharospasm
2. Cerebellar syndromes:
 - a. Rostral and lateral red nucleus area infarcts with rubral tremor
 - b. Unilateral ataxia with superior cerebellar infarct (SCA) with rostral midbrain signs
 - c. Superior cerebellar decussation syndrome (ataxia of all extremities) at the level of the IVth nerve at the inferior colliculus

3. Masugi's syndrome:
 - a. Ipsilateral IIIrd and IVth nerves
 - b. Ipsilateral ataxia (SCP)
 - c. Contralateral hemiparesis
 - d. Contralateral sensory defect
 - e. Caused by infarction of the superior cerebellar artery or branches of the lateral and medial posterior choroidal arteries

Summary of Midbrain Infarction

1. Paramedian arteries:
 - a. Isolated third nerve palsy
 - b. Nuclear third nerve: bilateral ptosis; bilateral pupillary dysfunction (large); bilateral failure of upgaze (superior rectus palsy and inferior oblique)
2. IIIrd nerve and contralateral hemiplegia (Weber's syndrome):
 - a. Supranuclear gaze palsy; mydriatic or miotic pupil depending on sympathetic involvement; occasional sensory dysfunction: P1 segment of the PCA is infarcted (medial 3/5 of the cerebral peduncle infarcted); patients are awake; hemiparesis may spare the face
 - b. Concomitant thalamic and occipital lobe involvement may occur
3. IIIrd nerve plus cerebellar signs:
 - a. IIIrd nerve palsy and contralateral cerebellar dysfunction is Claude's syndrome. Basilar paramedian artery (dentatothalamic projections are involved)
 - b. IIIrd nerve palsy plus contralateral abnormal movements (Benedict's syndrome). Tremor (rubral, large amplitude at right angle to the line of movement); chorea (paramedian artery; infarction of the red nucleus, dentatothalamic fibers often with third nerve paralysis)
 - c. The closer the infarction is to the red nucleus, the greater the tremor and failure of extremity postural fixation
4. Supranuclear conjugate vertical gaze palsy:
 - a. Median or paramedian infarction of the upper midbrain
 - b. Superior cerebellar artery: infarction; destruction of:
 - i. Periaqueductal gray matter
 - ii. Posterior commissure
 - c. Single trunk (paramedian thalamic mesencephalic artery of Percheron) infarcts involves the medial and subthalamic (STN) areas bilaterally as well as the upper midbrain
 - d. Upgaze paralysis:
 - i. Posterior commissure, riMLF (rostral interstitial nucleus of the MLF); PAG
 - e. Down-gaze palsy:
 - i. Bilateral upper midbrain infarction; more caudal than upgaze palsy (above the red nucleus; Pasik's syndrome)
 - f. Combined up and down gaze palsy:
 - i. Bilateral or unilateral midbrain infarcts

- ii. Unilateral lesion of the riMLF may decrease conjugate vertical gaze
- g. Supranuclear disconjugate vertical gaze palsies:
 - i. Monocular elevation palsy
 - ii. Vertical one-and-a-half syndrome
- iii. Infarction of paramedian upper midbrain

Unusual Neuro-Ophthalmological Deficits

1. Skew deviation (lesion is on the side of the down eye)
2. Tonic ocular-tilt reaction (incyclotropia or excyclotropia dysfunction)
3. Intermittent corectopia (pupillary size changes)
4. Upper lid retraction (Collier signs; increased upper lid retraction on down gaze; central caudal nucleus of the IIIrd nerve involved)
5. Ptosis with intranuclear ophthalmoplegia
6. Convergence retraction nystagmus (PAG; and involvement of the periaqueductal gray area)
7. Dissociated vertical gaze palsies

Associated Clinical Midbrain Signs

1. Gaze palsies with:
 - a. Coma and hypersomnia
 - b. Akinetic mutism
 - c. Disorientation to time and place
 - d. Antegrade amnesia
 - e. Motor and multimodal neglect
 - f. Faciobrachial hypesthesia
 - g. Transcortical motor aphasia
 - h. Delayed athetoid or clonic movements

Specific Midbrain Stroke Syndromes

1. Classic lacunar syndromes from midbrain infarcts
 - a. Weber's
 - b. Claude's
 - c. Benedict's
 - d. Masugi's
2. Lateral midbrain involvement of the cerebral peduncle (P1-PCA) pure motor stroke
3. Dorsolateral midbrain:
 - a. Hemiparesis
 - b. Hypesthesia
 - c. Ataxia
4. Eye movement deficit

Midbrain Locked-In Syndrome

1. Bilateral lateral midbrain infarction
2. Midbrain hematoma-pure sensory stroke (rare)

Hemiplegia with Posterior Cerebral Artery Occlusion

1. Proximal P2 infarction:
 - a. Hemiplegia
 - b. Visual disturbance
 - c. Neuropsychological abnormalities
 - d. Mimics MCA occlusion

Rare Stroke Syndromes from Midbrain Infarction

1. Subthalamic small deep infarcts
 - a. Abnormal movements and asterixis
 - b. Unilateral or bilateral ballistic movements
 - c. Blepharospasm
2. Cerebellar syndromes
 - a. Rostral and lateral red nucleus infarcts with cerebellar syndromes
 - b. Unilateral ataxia with superior cerebellar infarct (SCA) with rostral midbrain signs
 - c. Superior cerebellar decussation syndrome (ataxia of all extremities); infarction of the decussation of the brachium conjunctivum (Windekink's commissure; level of the IVth nerve at the inferior colliculus)
3. Masugi's syndrome
 - a. Ipsilateral IIIrd, IVth nerve
 - b. Ipsilateral ataxia (SCP)
 - c. Contralateral hemiparesis
 - d. Contralateral hemisensory defect
 - e. Infarction of the superior cerebella artery or branches of lateral and medial posterior choroidal arteries
4. Peduncular Hallucinoses
 - a. Vivid visual hallucinations; objects moving (kaleidoscopic); peculiar dress
 - b. Rarely auditory hallucinations
 - c. Often occurs at sundown

Thalamic Stroke*Overview*

The thalamus is a major relay to the cerebral cortex and is pivotal for: 1. arousal and consciousness; 2. sensory functions both spinothalamic and lemniscal; 3. cognitive function and 4. oculomotor function. It can be conveniently thought of as an egg (anatomically) with an anterior, medial, lateral, and posterior arterial supply. It is frequently involved from embolic stroke as it receives a great deal of its blood supply from the top of the basilar artery (particularly the paramedian territory).

*Infarcts in the Territory of the Tuberothalamic Artery***General Characteristics**

1. Origin is the middle third of the posterior communicating artery

Clinical Manifestations

1. Left hemisphere lesions cause
 - a. Deficits in retrieval or acquisition of visual or verbal memory
 - b. Disorientation for time (DM lesion)
 - c. Acalculia and thalamic aphasia
2. Amnesic syndrome lesions caused by:
 - a. Lesions of the mammillothalamic tract and the amygdala thalamic projections
 - i. Disconnects the anterior nuclei from the amygdala and hippocampal formation

- ii. Thalamic aphasia (not completely defined) consists of:

1. Amnesia (dichotomy between visual or auditory presentation)
2. Decreased fluency
3. Impaired comprehension
4. Fluent paraphasias
5. Oral reading relatively preserved
6. Decreased reading comprehension
7. Retained ability to repeat

- iii. Non-dominant hemisphere lesions cause:

1. Visual memory deficits
2. Mild cognitive impairment
3. Apathy, abulia, anosognosia

3. Bilateral infarctions cause:

- a. Severe abulia and memory deficits

*Infarction of the Paramedian Territory (Interpeduncular Artery)***General Characteristics**

1. Interpeduncular artery arises from the top of the basilar (P1)

Clinical Manifestations

1. Acute infarction causes decreased and fluctuating levels of consciousness (similar to subdural hematoma)
2. May evolve to agitation, confusion, aggression or apathy which may become permanent
3. Disturbances in arousal and vigilance caused by lesions of the intralaminar nuclei and rostral midbrain reticular formation
4. Oculomotor dysfunction:
 - a. Up and down gaze palsy: often the patient is looking at the tip of his nose with one or both eyes
 - b. Skew deviation: down eye is opposite the lesion (brainstem: the down eye is ipsilesional)
 - c. Pure down-gaze paresis (only bilateral lesion)
 - d. Horizontal gaze palsy (rare)
 - e. Rarer ophthalmological signs:
 - i. Bilateral INO
 - ii. Loss of convergence
 - iii. Miosis (2 mm pupils)
 - iv. Acute esotropia
 - v. Pseudo VIth nerve palsy
 - vi. Photophobia
5. Chronic paramedian territory deficits
 - a. Amnesia
 - b. Short term memory/learning deficits
 - c. Abnormal movements (contralateral)
 - i. Uni- or bilateral asterixis
 - ii. Tremors (dentate-rubro-thalamic tract)
 - iii. Dystonia (VL nucleus)
 - iv. Thalamic hand (down drift, flexion of the wrist, adduction of the thumb)
 - v. Blepharospasm

*Bilateral Paramedian Territory Infarction***General Characteristics**

1. A single peduncle supplies both territories from P1 (thalamic peduncle of Percheron) and the rostral mid-brain

Clinical Manifestations

1. "Thalamic dementia"
2. Akinetic mutism
3. Utilization behavior
4. Disinhibition
5. Abulia
6. Personality change

*Inferolateral Territory Artery Infarction***General Characteristics**

1. The thalamogeniculate arteries takes origin from P2 of the PCA (a peduncle of 6 to 12 arteries)

Clinical Manifestations

1. Pure sensory stroke:
 - a. The sensory deficit respects the midline (as if a line were drawn down the middle of the body)
 - b. There is bilateral sensory loss around the umbilicus
 - c. VPM involvement produces bilateral intraoral sensory deficit (numbness)
 - d. In general, thalamic (VPL) sensory loss causes an active deficit. Patients have disturbing paresthesias as if insects were crawling on their skin – formication; burning sensation or in 15% numbness
 - e. All sensory modalities (including vibration) are involved; occasionally touch, temperature and pin-prick are spared)
 - f. Patients may develop decreased touch with pain (anesthetic douloureux)
2. Sensorimotor stroke:
 - a. Infarction of VPL and the posterior limb of the internal capsule:
 - i. Thalamic sensory loss
 - ii. Hemiparesis
 - b. Large inferolateral infarction described by Dejerine and Roussy include:
 - i. Cerebellar outflow tremor
 - ii. Dystonia, chorea, athetosis
 - iii. Thalamic astasia
 1. Lesion of proprioceptive projections to VL nucleus
 - iv. Loss of the sense of the subjective visual vertical (SVV):
 1. Patients tilt to the side of the lesion and push themselves back to the midline
 2. "Pusher syndrome"
 3. Most often seen with posterior thalamic infarction
 - v. Hand jerks associated with hemidystonia, severe sensory loss and ataxia:
 1. Thalamic hand may be seen
 2. Executive dysfunction: rare

3. Auditory illusions

- a. Medial geniculate involvement
- b. Anosognosia with right sided lesions

Infarction of the Lateral Posterior Choroidal Artery (L PchA)*General Characteristics*

1. PchA Arterial Territories Involved:
 - a. Lateral geniculate body (LGD)
 - b. Pulvinar and posterior thalamus
 - c. Hippocampus and parahippocampal gyrus

*Clinical Manifestations***Clinical Syndromes of Lateral PchA Infarction**

1. Homonymous quadrantanopsia
2. With or without hemisensory loss
3. Homonymous horizontal sectoranopia (lateral LGD)
4. Memory loss
5. Delayed movement disorder
6. Transcortical aphasia

Visual Field Deficits

1. PchA – Homonymous horizontal sectoranopia
2. AchA – middle horizontal sector is spared
3. Quadruple sectoranopia is characteristic
 - a. Lower or upper quadrantanopsia
4. Complete homonymous hemianopia
5. Superior quadrantanopsia-may have macular sparing
6. Homonymous hemianopia
 - a. Sparing of the horizontal sector
 - b. Inferior lateral LGD infarction
7. Homonymous superior-quadrantanopsia
 - a. Lateral geniculate infarction
 - b. Infarction of:
 - i. Optic tract
8. Origin of the geniculocalcarine tract
9. Sectoranopia visual field deficits
 - a. Lateral geniculate body infarction

Specific Visual Field Deficits

1. Wedge or tubular homonymous sectoranopia with delayed sectorial optic atrophy
2. Lower or upper quadrantanopsia more common but less specific with LGD infarction
3. Wedge or tubular sectoranopia also possible with AchA, MCA, PCA infarction
4. Visual field deficits with concomitant anatomical lesions of the LGD

Ocular Motility Deficits

1. Impairment of ipsilateral pursuit
2. Poor contralateral saccades

Sensory Symptoms

1. Involvement of thalamic radiations of the internal capsule or damage to ventroposterior nucleus (caudal part)

Motor Symptoms

1. Damage to corticospinal or corticobulbar fibers in the internal capsule (PchA)
2. AchA more severe hemiparesis than PchA

Aphasia and Higher Cortical Deficits

1. Transcortical motor aphasia – pulvinar damage
2. Transient visual and verbal memory disturbance
3. Disorientation for time without confusion or confabulation
 - a. May also be seen following thalamic stereotactic surgery
4. Abulia
5. Non-dominant hemisphere lesion:
 - a. Visual spatial processing deficit with dorsal lesions

Thalamic Stroke with PchA Infarction

1. Neuropsychologic deficits
2. Pulvinar infarction on CT/MRI
3. Paramedian infarction; tuber thalamic artery involvement (concomitant)

Visual Hallucinations

1. Paramedian thalamic infarction

Correlative Anatomy of the Lateral Geniculate Body

1. Anterolateral LGD subserve lower quadrants
2. Anteromedial LGD subserve medial quadrants
3. Posterior LGD subserve the macula
4. Central LGD: supplied by lateral posterior choroidal artery
 - a. VF defect: homonymous horizontal sectoranopia
 - b. Supplied by PchA
5. AchA also supplies the LGD

Unusual Features of Thalamic Infarction

1. Simultaneous ptosis and astasia:
 - a. Anteromedial infarction
2. Emotional synesthesia:
 - a. Specific sensory stimuli are associated with emotional responses
3. Left thalamic infarction:
 - a. Aphasia (anterior ventral nucleus)
 - b. Amnesia; recent memory impairment
 - c. Frontal lobe dysfunction by diaschisis

Medial Posterior Choroidal Artery (MPchA)**General Characteristics**

1. Territory supplied: medial pulvinar; dorsomedial thalamus; anterior thalamic nuclei
2. Less common than lateral PchA infarcts

Clinical Manifestations**Ocular Signs (Midbrain Involvement)**

1. Nystagmus retractorius

2. Upgaze or horizontal gaze paralysis
3. Meiosis
4. Central Horner's syndrome

Sensory Loss (MPchA)

1. Lemniscal or spinothalamic

Motor Symptoms

1. Mild hemiparesis

Neuropathology**Pathogenesis (MPchA)**

1. HCVD and DM
2. Cardiac embolism, large artery disease, migrainous stroke, catheter induced thrombosis

Differential Diagnosis**Differential Diagnosis of MPchA vs PchA vs AchA**

1. M PchA:
 - a. Sensory loss is noted acutely with later onset of pain and abnormal movements
2. Movement disorder:
 - a. Choreoathetotic myoclonic syndrome
 - b. Pseudobulbar tremor
 - c. Dystonic posture of the fingers
 - d. Dystonic thalamic hand worsened by voluntary activity
 - e. Akathisia
3. L PchA infarct
 - a. Sectoranopia VF deficit
4. AchA infarct:
 - a. Quadruple sectoranopia VF deficit
 - b. Greater hemiparesis than L PchA stroke

Posterior Circulation Major Artery Strokes (Long Circumferential Arteries)**Cerebellar Artery Infarction****General Characteristics****General Features of Cerebellar Artery Infarction**

1. Infarction of the cerebellum is approximately 7.5% of all ischemic strokes
2. Major clinical manifestations are: vertigo/dizziness, gait instability, headache, nausea and vomiting. They are non-specific and are often misdiagnosed
3. Serious complications are worsening edema and consequent brainstem compression
4. Superior cerebellar arterial territory:
 - a. Superior cerebellar peduncle
 - b. Tentorial surface
5. Anterior inferior cerebellar artery territory is:
 - a. Middle cerebellar peduncle (core territory)
 - b. Flocculus
 - c. Petrosal surface of the cerebellum
6. Posterior inferior cerebellar artery perfuses:
 - a. Inferior cerebellar peduncle
 - b. Suboccipital surface to the horizontal fissure

Epidemiology (Perugia Hospital-Based Stroke Registry)

1. Cerebellar infarction accounts for about 3.4% of all cerebral infarctions
2. Mean age of 72 years; 3:1 males to females
3. Unilateral in 86%; bilateral in 14%
4. Bilateral infarctions: emboli to the top of the basilar
5. Superior cerebellar artery region – 36%
6. Anterior inferior cerebellar artery region – 12%
7. Posterior inferior cerebellar artery region – 40%
8. Multiple vascular region involvement – 12%
9. Approximately 52% have associated brainstem infarctions

Clinical Manifestations

1. Dizziness/vertigo in approximately 50%:
 - a. Lasts for more than 72 hours
 - b. Moderate to severe imbalance
 - c. Differential is often acute peripheral labyrinthine disease
2. Severe ataxic gait:
 - a. Anterior lobe involvement
 - b. “Martinet gait”:
 - i. Disinhibited anterior lobe projections to lateral vestibular nuclei (increased extensor tone)
3. Lateral pulsion to ipsilesional side:
 - a. Involvement of ascending gravicentric fibers
4. Nausea and vomiting:
 - a. Vomiting more severe than vertigo suggests brainstem ischemia
 - b. Present in 50% of patients
 - c. Ischemia and/or pressure on the vomit center of the floor of the IVth ventricle; involvement of the nucleus solitarius and vestibular connections
5. Headache occurs in approximately 40% of patients:
 - a. Usually homolateral in the basiocciput
 - b. May project to C2 territory (the meninges of the posterior fossa are innervated by C2; C2 projects to the nucleus caudalis of the Vth nerve which may sensitize all the distributions of the nerve)
6. Overshoot and increasing oscillations as the target is approached (cerebellar outflow tremor) may be more prominent than limb ataxia
7. Dysarthria is present in 50% of patients (scanning speech is produced from the inability to coordinate speech and breathing; abnormal prosody)
8. Upbeat nystagmus occurs from lesions of the superior vermis or pontomedullary junction
9. Eye movement abnormalities include:
 - a. Saccadic substitution for smooth pursuit
 - b. Ocular overshoot or undershoot on attempted fixation
 - c. Hypometric saccades

Neuropathology**Pathogenesis of Cerebellar Infarction**

1. Large artery atherosclerosis – 41%
2. Small artery disease – 24%

3. Cardioembolism – 9.8%
4. Varied etiologies occur in 7.3% and include:
 - a. Vertebral artery dissection
 - b. Vasculitis
 - c. Hypercoagulable state
 - d. Drug abuse (cocaine, methamphetamine)
5. Indeterminate etiology – 17%

Superior Cerebellar Artery (SCA) Infarcts**General Characteristics**

1. Rarely involves the brainstem territory of the SCA; usually partial; good outcome; 50–60% of cerebellar infarctions
2. Early and delayed edema (one week); brainstem compression with tonsillar herniation if edema is severe (4–7 days; pseudotumoral presentation)
3. Associated infarction in other territories with complete SCA infarction (usually that of PCA):
 - a. Rostral territory of the basilar artery
 - b. Unilateral or bilateral occipitotemporal lobe infarction
 - c. Thalamic; subthalamic and mesencephalic infarcts
 - d. Rare upper ventral pontine infarction
 - e. 1/3 occur with PICA and AICA infarction
 - f. Partial SCA infarcts most frequently involve the rostral superior cerebellar artery territory
 - g. Some SCA infarcts occur with MCA infarcts due to emboli

Clinical Manifestations**Clinical Features of Superior Cerebellar Artery: 6 Clinical Patterns**

1. Classic SCA:
 - a. Occur in 3% of infarctions
 - b. Involves the brainstem territory of SCA
 - c. Ipsilateral limb dysmetria
 - d. Ipsilateral Horner’s syndrome
 - e. Contralateral IVth nerve involvement
 - f. Contralateral loss of pain and temperature
2. Unusual signs and symptoms of classic SCA infarction:
 - a. Ipsilateral loss of mimetic facial
 - b. Unilateral or bilateral hearing loss (nucleus of lateral lemniscus)
 - c. Sleep disorder (locus coeruleus)
 - d. Ipsilateral choreiform, athetotic or coarse tremor
 - e. Head tremor or unsteadiness of the head
 - f. Palatal myoclonus; may be associated with myoclonus of the tongue, vocal cord, jaw and face
 - g. Cerebellar cognitive affective disorder:
 - i. Visual dyslexia/surface dysgraphia
 - ii. Personality behavioral deficit
3. SCA infarction with top of the basilar artery involvement:
 - a. Vomiting, dizziness, visual field deficits, diplopia, paraesthesia, ataxia, weakness and drowsiness
 - b. Occipitotemporal lobe concomitant involvement:
 - i. Cortical blindness and hemianopsia (Anton’s syndrome)

- ii. Bálint's syndrome
- iii. Memory loss or confusion
- c. Thalamic-mesencephalic infarction:
 - i. Thalamic multimodal sensory loss; latter possibly Dejerine Roussy syndrome (VPL)
 - ii. Contralateral Horner's syndrome
 - iii. Appendicular ataxia (ataxia of stance); involvement of cerebellar thalamic projections
 - iv. Behavioral abnormalities: abulia, contralateral spatial neglect, memory loss, transcortical motor aphasia
- d. Midbrain infarction (concomitant):
 - i. Claude's, Benedict's, Weber's, Nothnagel's Syndromes, Masugi's
 - ii. Parinaud's syndrome
 - iii. Pseudo VIth nerve, gaze paresis or deviation, Collier's sign, pupillary abnormalities (light-near dissociation, inverse Argyll-Robertson pupil, miosis or mydriasis, corectopia)
 - iv. Drowsiness, peduncular hallucinosis, confusion
 - v. Hemiballismus (subthalamic involvement)
- 4. Coma at initial presentation:
 - a. Tetraplegia and IIIrd nerve palsy
 - b. Embolic occlusion of basilar tip
- 5. SCA involvement with ICA infarction:
 - a. Aphasia
 - b. Brachiofacial sensorimotor hemiplegia
 - c. Cardiac embolism; occlusion of innominate artery with embolism to right MCA and vertebral artery with propagation to SCA
- 6. Cerebellar vestibular syndrome:
 - a. Occipital headache and gait ataxia
 - b. Dizziness and vomiting
 - c. Nystagmus (most often horizontal to affected side) or contralaterally; rarely vertical
 - d. Dysarthria-cardinal symptom of SCA infarct
 - e. Hemiparesis in 25%
- 7. Lateral SCA syndrome (anterior rostral territory):
 - a. Arm and leg dysmetria
 - b. Ipsilateral axial lateropulsion
 - c. Dysarthria
 - d. Nystagmus; saccadic overshoot (ipsilaterally)
- 8. Medial SCA syndrome:
 - a. Most medial branch: unsteadiness of gait
 - b. Lingula, culmen, centralis lobules (anterior cerebellar lobe) appendicular ataxia (legs affected > arm), head tilt (ipsilateral)
 - c. Paravermal involvement: dysarthria; left-sided paravermal zone of rostral cerebellum causes consistent dysarthria

Neuropathology

Differential Diagnosis of Causes of Superior Cerebellar Artery Infarction

1. Cardiac embolic source

2. Artery-to-artery embolus:
 - a. Vertebral artery
 - b. Aortic arch
3. Vertebral dissection
4. In young patients:
 - a. SCA dissection
 - b. Fibromuscular dysplasia (FMD)
 - c. Patent foramen ovale (PFO)
 - d. Cocaine and methamphetamine abuse

Anterior Inferior Cerebellar Artery Infarction

General Characteristics

1. Origin: first 1/3 of the basilar artery
2. Brainstem signs at presentation
3. Involved territory: lateral caudal pons; middle cerebellar peduncle (always involved)
4. Supplies the inner ear: internal auditory artery from which derive the anterior vestibular artery; common cochlear artery
5. 70% involve the anterior inferior flocculus
6. AICA and PICA may arise from a common trunk from the vertebral or basilar artery
7. Anastomosis between the AICA and PICA – constant when both arteries have equal dominance
8. AICA dominance on one side; then consequent ipsilateral vertebral PICA hypoplasia
9. Infarction of the inferolateral pons; may extend up to the middle third of the lateral pons or down to the superior part of the lateral medulla
10. AICA infarction: may be associated with PICA and SCA infarction with consequent ventromedial pontine infarction

Clinical Manifestations

1. Prodromal vertigo (minutes); dizziness, dysarthria
 - a. Ipsilateral peripheral VIIth nerve (small artery to facial nerve in CPA angle)
 - b. Hearing loss (sudden) ipsilaterally
 - c. Ipsilateral Vth nerve involvement
 - d. Horner's syndrome (ipsilaterally)
 - e. Ipsilateral appendicular dysmetria (arm > leg)
 - f. Contralateral loss of pain and temperature of the limbs and trunk
 - g. Delayed facial paralysis

Unusual Signs

1. Ipsilateral conjugate or lateral gaze palsy (floccular involvement)
2. Dysphagia (superior part of the lateral medulla)
3. Ipsilateral motor weakness (involvement of the corticospinal tract in the pons or mesencephalon contralaterally)
4. Periodic alternating nystagmus

Coma

1. Tetraplegia (massive ventromedial infarction of the basis pontis)

2. Cerebellar infarction PICA/AICA/SCA distribution
3. Isolated vertigo mimicking labyrinthitis; infarction of the internal auditory artery or its superior vestibular division
4. Isolated cerebellar signs

Differential Diagnosis

Differential Diagnosis of AICA Infarction

1. Atherosclerotic lower basilar artery occlusion (AICA)
2. Occlusion of the vertebral artery above PICA
3. Pure AICA: a basilar branch occlusion; plaque in the basilar artery extends to occlude its origin; microatheromata block the origin of the artery
4. Migraine (Bickerstaff variant)

Vascular Anomalies of the Vertebrobasilar System

1. Persistent trigeminal artery with embolus from carotid system
2. Dolichoectasia of the basilar artery
3. Hypoplastic vertebral artery

Extracranial and Intracranial Vertebrobasilar Dissection

1. Intradural dissection:
 - a. Subadventitial hematoma of the basilar artery causes:
 - i. Subarachnoid hemorrhage
 - ii. Brainstem stroke
 - iii. Pseudoaneurysm
 - iv. May occur silently
2. Extracranial dissection
 - a. Hematoma within the media or intima
 - b. Emboli at the site rather than a blood flow limiting process cause symptoms

Post Operative Cerebellar and Brainstem Stroke

Signs and Symptoms

1. Altered consciousness; stupor, restless agitation
2. Vestibulocerebellar syndrome

Differential Diagnosis

1. Neck positioning during or after surgery
2. Thrombus that embolized from compressed arteries

Hypercoagulability After Surgery

1. Increased thrombin activity
2. Increased fibrinogen
3. Increased factor VIII
4. Decreased fibrinolytic activity
5. Altered platelet function

Posterior Inferior Cerebral Artery – See Lateral Medullary Infarct (PICA)

Posterior Cerebral Artery (PCA) Infarction

General Characteristics

1. Major blood supply of: midbrain, thalamus, occipital lobes, part of the posterior inferior parietal lobe

2. The arterial segment prior to the posterior communicating artery fusion with the basilar artery is the P1 segment:
 - a. 10% of PCAs take origin from the carotid artery (fetal origin). If this occurs, there is a concomitant hypoplastic P1 from the basilar artery
3. 29% of patients have large or (24%) unusually small PCA arteries
4. Accounts for 5–10% of all ischemic strokes

Vascular Territory Supplied by the PCA

1. Vascular supply of the P1 segment (peduncular or precommunal segment; between the tip of the basilar artery and the posterior communicating artery) is:
 - a. Medial midbrain; posteromedial thalamus
 - b. Origin of the paramedian mesencephalic arteries (take off is the top of the basilar)
2. Tuberothalamic (polar arteries)
 - a. Origin is the posterior communicating artery
 - b. Anterior and anterolateral thalamus
 - c. Tuber thalamic artery may be absent. Its territory is then supplied by the thalamic subthalamic artery (thalamoperforating arteries)
3. P2 segment is the origin of the peduncular perforating (PPA); thalamogeniculate arteries (TGA)
 - a. Thalamoperforate artery supplies:
 - i. Lateral midbrain
 - ii. VA and VL of the motor thalamus
 - iii. Part of the internal capsule
 - iv. VPL, VPM of the thalamus
 - b. Thalamogeniculate artery supplies the ventrolateral thalamus: arteries arise from the ambient portion of the PCA
 - c. Anterior temporal artery arises from the ambient portion of the PCA and supplies the medial temporal lobe
 - d. Posterior temporal artery (origin between the tentorium and the medial temporal lobe)
 - e. Parieto-occipital artery: originates from the ambient segment; supplies the occipital and medial inferior parietal lobe); this branch is the origin of the posterior pericallosal artery
 - f. Calcarine artery:
 - i. Usually arises as a single branch of the PCA
 - ii. In 16% of patients the calcarine artery arises from the parieto-occipital artery
 - g. P3 and P4 are the distal segments with their cortical branches
 - i. Infarction of P2 and P2 cause 25% of PCA infarction as does P3 and P4
 - ii. Combined deep and superficial arteries occur in 50% of patients

Clinical Manifestations

Clinical Symptoms and Signs of Unilateral PCA Ischemia and Infarction

1. PCA Stenosis:
 - a. TIA's precede infarction with PCA stenosis is causative
 - b. Usually atherosclerotic narrowing

General Features of PCA Infarction

1. Ambient section is affected most frequently which causes a hemispheric branch occlusion
2. P1 segment – 13% of PCA occlusions
3. PCA with thalamic involvement – 37% of infarctions
4. Occipital, parietal and posterior temporal branch arteries are frequently involved concomitantly
5. Anatomic areas involved: medial midbrain, posteromedial thalamus, lateral thalamus, and posterior hemisphere
6. Penetrating arteries from the top of the basilar artery may arise from one PCA (artery of Percheron) and therefore the thalamic infarction may be bilateral and paramedian:
 - a. Infarctions are usually embolic from the heart, proximal aorta and the proximal vertebral arteries (to the top of the basilar artery)
 - b. Patients that have suffered rostral paramedian tegmental mesencephalic and posteromedial thalamic infarcts are comatose, hyper somnolent and may demonstrate vertical gaze palsies and an amnesic state

The distinguishing features of proximal PCA infarction (P1 precommissural branch) are:

1. Hemiplegia, infarction of the cerebral peduncle (medial 3/5); may spare the face
2. Paramedian mesencephalic and PPA arteries are involved (cognitive deficit; hypersomnolence)
3. Partial or complete IIIrd nerve palsy
4. Nuclear IIIrd nerve signs include:
 - a. Bilateral ptosis (central caudal nucleus)
 - b. Failure of upgaze bilaterally (superior rectus is bilaterally innervated)
 - c. Dilated pupils
 - d. Skew deviation:
 - i. Skew deviation is seen with vertical IIIrd nerve paresis if the nuclei of Cajal and Darkschewitsch are involved with cortico-mesencephalic or mesencephalic tracts themselves are lesioned
5. Midline infarctions: patients are lethargic and abulic
6. Involvement of DM and the wall of the IIIrd ventricle
7. One paramedian artery may supply both medial thalamic territories (the thalamic peduncle of Percheron)
8. Paramedian thalamic clinical triad:
 - a. Hypersomnia and fluctuating levels of consciousness (intralaminar nuclei; Dorsomedial nucleus)
 - b. Cognitive dysfunction:
 - i. Short term memory deficits (DM nucleus)
 - ii. Transcortical motor aphasia (DM nucleus)
 - c. Oculomotor deficits
 - d. Often associated with thalamic signs

Thalamogeniculate Artery Infarction (TGA)*General Characteristics*

1. Infarction of the lateral thalamus and posterior temporal lobe is known as the syndrome of Foix–Hillman
2. Pathogenesis: trunk PCA occlusion (multiple penetrating branches involved) or single atheromatous branch occlusion

Clinical Manifestations

1. Sensory symptoms:
 - a. Leg may be involved most severely; pattern of face, arm and leg
 - b. Conscious perception that the symptoms bisect the body (face, trunk, penis)
 - c. Intraoral involvement (may be bilateral)
 - d. Quality of sensation: tingling, pricking, crawling, burning (active dysesthesias and paraesthesias)
 - e. Loss of pinprick, touch, or thermal sensation. May lose vibration sensibility which is rarely lost with cortical infarction. The other location for vibratory loss is the dorsal column nuclei
 - f. If medial, ventrolateral or thalamoparietal projections are involved:
 - i. Proprioceptive, thermal sensory loss, decreased pain
 - g. Tips of the fingers of the contralateral hand (VPI nucleus); spinothalamic afferents to each finger
2. Slight hemiparesis
3. Clumsiness and ataxia (dentate thalamic projections)
4. Choreiform and ataxic limb movements (contralateral)
5. Thalamic hand posture
6. Clinical symptomatology of thalamic pain:
 - a. Delayed onset (months after VPM/VPL infarction)
 - b. Hyperpathic pain
 - c. Mechanical and thermal hyperalgesia and allodynia of the affected area
 - d. Spontaneous
 - e. If provoked-not stimulus bound
7. Associated infarcts in the temporal and occipital lobes if midbrain and thalamus are involved

Ambient Segment (P2) Infarction (Thalamoperforating Artery)*General Characteristics*

1. Occlusion is proximal to the origin of the thalamogeniculate artery:
 - a. Vascular supply to the motor thalamus
 - i. Ventroanterior, ventrolateral nuclei
 - ii. VOA, VIM, VOP (stereotactic nomenclature, part of VL)
 1. VIM is the target for stereotactic surgery to relieve tremor

Clinical Manifestations

1. Motor symptoms
 - a. Contralateral 4–6 HZ tremor
 - b. Usually sudden onset of choreoathetosis:
 - i. Frequent arterial involvement in diabetic patients
 - c. Rare contralateral dystonia
 - d. Thalamic hand
 - e. More medial lesions in this territory cause thalamic ataxia
 - i. Interrupt cerebellar projections (dentatorubral loop)
 - ii. “Ataxia of stance”

Posterior Cerebral Artery (PCA) Hemispheric Infarction (P3 and P4 Infarction)

General Characteristics

1. The anterior and posterior temporal arteries arise from P3 (rarely from distal P2) and supply the medial temporal lobe
2. The 3 main branches of P3 are:
 - a. Occipitotemporal
 - b. Calcarine
 - c. Occipital parietal

Anatomy of the Visual Radiations

1. The PCA and its branches supply the lower component of the geniculocalcarine radiations; the MCA supplies the upper
2. The more posterior and closer to the cortex, the more congruent the VF deficit

Clinical Manifestations

Visual Field Loss

1. Most common defect – contralateral homonymous dense VF loss
2. Infarction may occur in: lateral geniculate body, optic radiations, or the striate cortex
3. 50% of patients are aware of the deficit
4. If unaware of the deficit there is parietal lobe involvement
5. Acute or with resolution of VF defect:
 - a. Photopsias, colors, and hallucinations in the affected field
6. Usual VF deficits: congruent contralateral hemianopia, inferior or superior quadrantanopsia
 - a. Macular sparing often noted (middle cerebral artery supply compensates)
 - b. Involvement or sparing of the contralateral visual temporal crescent (inferior lip of the calcarine fissure subserves the most peripheral temporal field)
 - c. Homonymous central scotoma (occipital pole infarct)
 - d. “Checker board” deficit (one inferior quadrant with contralateral superior quadrant)
7. Complex visual phenomena

Visual Perseveration

1. Objects seen in sighted field-then noted in the defective hemifield although gaze fixation maintained
2. Object in the sighted field appears in the defective hemifield after gaze is shifted to defective field
3. Palinopsia (perseveration of an object)
4. Motion detection in blind field but no ability to discriminate (Riddoch’s object phenomena)
5. Defects in distance, depth and localization in the defective hemifield
6. Micropsia and macropsia

Sensory Symptoms of PCA Hemispheric Infarction

1. Paresthesia, numbness or loss of pain; thermal or positional sense loss

Higher Cortical Deficits from Hemispheric Infarction

1. Dominant Hemisphere: parieto-occipital and/or temporal branch occlusion:
 - a. P3 and P4 segments
 - b. Alexia without agraphia patients; write, speak, and spell normally. They cannot read words or name colors (damage must include left occipital cortex and splenium of the corpus callosum). Can read letters and numbers. Cannot access Wernicke’s area
 - c. Alexia with agraphia:
 - i. Angular gyrus or white matter of the inferior parietal lobule involved
 - ii. Abnormalities of reading, writing, and spelling
2. Inferior parietal lobule infarction:
 - a. Decreased ability to read letters and paragraphs
 - b. Decreased spelling and writing
 - c. Components of Gerstmann’s syndrome are noted: dyscalculia, finger agnosia, right left confusion, and dysgraphia and conduction aphasia. The latter may be accompanied by paraphasia
 - d. Transcortical sensory aphasia
 - e. Aggressive behavior
3. Paralexia or hemidyslexia:
 - a. Dominant hemisphere: reading errors to the right side of words
 - b. Non-dominant hemisphere: reading errors at beginning of words
4. Visual agnosia:
 - a. Dominant hemisphere
 - b. Concomitantly with alexia and agraphia and decreased color naming
5. Amnesia:
 - a. Involvement of left hippocampus and adjacent white matter
6. Sensory Symptoms:
 - a. Lesions of the thalamic projections to the sensory cortex; concomitant supply from the MCA territory (central sulcal, anterior and posterior parietal branches of the superior division of MCA)

Non-Dominant Hemisphere – PCA Infarction

1. Neglect of contralateral visual field
2. Constructional apraxia (parietal and temporal lesions)
3. Right posterior parietal lesion-disorientation for geographical space
4. Reduplicative paramnesia (two versions of a geographic location)
5. Prosopagnosia (usually bilateral lesions required)
 - a. Inability to recognise faces

Neuropathology

Mechanisms of Unilateral PCA Infarction

1. Embolism: cardiac, proximal vertebral artery, arch of aorta, fetal origin of PCA

2. Emboli arise from the end of atheromatous plaques of recently occluded proximal vertebral artery
3. African Americans and Asians patients: infarction is more frequent in context of stenosis with in situ thrombosis
4. Migraine
5. Coagulopathy
6. Transtentorial herniation – temporal and calcarine branches compressed against the tentorium
7. If 2 PCA branches and the posterior chorioidal artery are affected if there is severe small vessel disease

Bilateral PCA Infarction

General Characteristics

1. Infarcts often restricted to bilateral inferior or superior calcarine branches

Clinical Manifestations

1. Cortical blindness (Anton's syndrome):
 - a. Bilateral infarction of the striate cortex:
 - i. Anton's syndrome:
 1. Denial of blindness
 2. Maneuver around objects (visual crescent remains, bilateral hemianopsias or scotoma)
 3. Visual confabulation
 4. Normal pupillary reaction to light
 5. Euphoria
2. Bálint's syndrome (superior parietal and occipital lobe involvement):
 - a. Simultagnosia (patients see objects piecemeal); cannot describe the entire object)
 - b. Optic ataxia (lack of coordination of hand eye movements; usually under reaching the object)
 - c. Apraxia of gaze (inability to look at an object on command)
 - d. Difficulty in breaking fixation of gaze
 - e. Poor visual scanning of areas of interest
 - f. May be limited to one visual field
3. Amnesia:
 - a. Bilateral infarction of the temporal lobe
 - b. Amnesia occurs concomitantly with visual sensory loss and acute depression of level of consciousness
4. Emboli and infarction (below calcarine fissure):
 - a. Upper quadrant altitudinal defect
 - b. Abnormal color perception
 - c. Difficulty in recognizing faces (prosopagnosia)
 - d. Inability to revisualize the form of an object; able to revisualize direction and place relationships of objects
 - e. Agitated delirium (involvement of the lingual and fusiform gyri, inferior temporal lobe)
 - f. Central achromatopsia (may perform adequately on Ishihara plates) unable to match hues or colors
 - g. Agitated delirium (left posterior inferior temporal lobe)
 - h. Emboli to tip of the basilar artery have predilection for inferior calcarine branches

5. Bilateral superior bank infarction
 - a. Severe hypotension (MCA/PCA border zone) is the usual mechanism
 - b. Less common than lower bank infarcts
 - c. Disorientation to place, difficulty in revisualization of locations (where people and places are topographically)

Neuropathology

Pathogenesis of Bilateral PCA Infarction

1. Serial infarction; stenosis of arteries from atherosclerosis
2. Simultaneous; embolus to top of the basilar artery or from thrombus in the basilar artery
3. Capillary-leak syndrome (primarily white matter) of the occipital lobe
 - a. Hypertensive encephalopathy
 - b. Cyclosporine and FK 506 (tacrolimus)
 - c. Uremia
 - d. Eclampsia
 - e. Dissection of distal basilar artery
 - f. PRES

Clinical Manifestations of PCA Progressive Occlusion

1. Progressive stenosis of PCA following anterior augmentation surgery for Moyamoya disease:
 - a. Often is delayed following original revascularization surgery
2. Vertebral artery calcification:
 - a. Associated with distal PCA segment stroke
3. Transneuronal retrograde degeneration of the optic nerve following PCA occipital lobe lesions
4. Posterior cerebral laterality is favorable sign for recovery in middle cerebral artery occlusion
5. Occlusion of the artery of Percheron causes bilateral thalamic infarction:
 - a. Single artery arises from one cerebral artery to perfuse the paramedian thalamic territory (usually arises from the top of the basilar artery)

Border Zone Infarction

Overview

Border zone infarctions occur between two or three arterial territories during prolonged periods of hypotension or cardiac arrest. The infarction may occur between pial conducting vessels or internally between ascending vessels that are feeding deep nuclear structures and descending penetrating vessels. They tend to be symmetric and occur in characteristic areas. There are internal laminar infarctions between the capillaries that are the functional metabolic columns of the brain. An O₂ molecule diffuses approximately 10 μ from the hemoglobin of its 7 μ RBC. These 10 μ constitute the functional intercapillary metabolic zones of the brain. Patients less than 40 years

of age have infarctions in the anterior circulation while older patients tend to infarct the border zones of the posterior circulation. Specific syndromes have been described for many of these infarctions. The “man in the barrel” suggests an anterior cerebral/middle or cerebral artery border zone infarction. The shoulder on upper arm components of the homunculus are involved. These patients have preserved intrinsic hand muscle function. Posterior MCA/PCA infarction may cause Bálint’s syndrome of infarction of the superior parietal lobule. These patients have a simultagnosia, poor optic scanning, failure to break fixation and optic ataxia. Ascending lenticulostriate and penetrating medullary vessels from pial conducting vessels cause the periventricular vascular stripe. Leg fibers may be preferentially affected. Isolation of the speech area suggests cortical hypoxia, carbon monoxide poisoning or hypotension. Ischemia of the optic nerve head from poor perfusion of the central retinal artery and posterior ciliary artery with giant cell arteritis and prolonged hypotension. Border zone infarcts of the brainstem do not demonstrate clear patterns of anatomical localization as those of the anterior circulation.

The following discussion is of the differential diagnosis and characterization of border zone infarcts.

General Characteristics

The major cerebral arteries have superficial pial branches that anastomose at the junction of their territories and perforating centripetal vessels. The deep ascending branches of the major vessels supply the parenchyma and do not anastomose. The territories between a superficial vessel and its ascending deep perforators define border zone areas of the deep circulation. These areas are known as the distal fields of the particular vascular territory and may suffer decreased:

1. Cerebral blood flow
2. Perfusion pressure
3. Increased oxygen extraction

These areas are susceptible to hemodynamic changes principally hypotension. It has also been postulated that microemboli from the heart, aorta or vessels from vessel atherosclerotic plaque debris preferentially lodge in these boundary areas. Hemodynamic parameters in border zone areas decrease the washout of embolic material and increase the susceptibility to infarction. Infarction between two or three arterial territories are defined as border zone (termino-terminal) if there is no arterial collateral circulation between the two arterial territories. There are two types of border zone infarct:

1. Cortical – between major arteries of the cerebral cortex or cerebellar cortex (possible microembolic mechanism)
2. Internal border zone infarction:
 - a. Occurs in deep cerebral or cerebellar white matter or the brain stem
 - b. Probable hemodynamic mechanism

Cerebral Border Zone Infarction

1. Territory between the ACA/MCA:
 - a. Frontal parasagittal cortex from the anterior horn of the lateral ventricle to the frontal cortex
2. Territory between the MCA and PCA:
 - a. Cortex between the posterior horn of the lateral ventricle to the parieto-occipital cortex

Cerebral Internal Border Zone Infarction

1. Localized between the superficial (long medullary perforators from MCA branches and the lenticulostriate arteries)
 - a. Affects the corona radiata
2. Junctional territories between perforators of the ACA/MCA
 - a. Affects the centrum semiovale
 - b. Arm area anteriorly; leg posteriorly and the bladder fibers next to the ventricle
3. Junctional territory between the lenticulostriate (carotid branches), paramedian territory and the inferior lateral thalamic territory (thalamogeniculate artery)

Cerebellar Border Zone Infarction

General Characteristics

1. Superficial territories between the PICA and superior cerebellar arteries:
 - a. Affects the cerebellar hemispheres
2. Internal border zone infarction:
 - a. Affects deep cerebellar white matter

Brainstem Internal Watershed

1. Junctional arterial territories between the paramedian perforators of the basilar arteries and the lateral perforators of the short circumferential branches of the cerebellar arterial supply

Clinical Manifestations

1. Precipitating features if the mechanism is hemodynamic:
 - a. Arising from a supine position
 - b. Physical exercise
 - c. Post prandial
 - d. Valsalva maneuvers (decreased CBF)
 - e. Coughing (decreased CBF)
 - f. Systemic hypotension (often after change in antihypertensive medications)
 - g. Anesthesia
 - h. Cardiac or other prolonged surgery
 - i. Hypervolemia (bleeding or anemia)
2. Symptoms and MRI findings are often bilateral and symmetrical
3. Concomitant carotid or vertebral artery partial occlusion are often present:
 - a. Concomitant carotid stenosis in a high percentage of patients

4. Loss of consciousness at the onset of border zone stroke more frequent than in thromboembolic disease
5. Early onset of seizures (if there is cortical ischemia)

Specific Syndromes of Border Zone Infarction

1. Carotid hypoperfusion
 - a. Unilateral shaking TIA (bilateral if in VB circulation)
 - i. Hemodynamic precipitants
 - b. Optico-cerebral syndrome
 - i. Rare
 - ii. Amaurosis fugax ipsilesionally with contralateral hemiparesis
 - c. Retinal claudication
 - i. Monocular transitory loss of vision when exposed to bright light
 1. Failure of retinal pigment regeneration due to ischemia
 - d. Mild cognitive impairment
 - i. Particularly with bilateral disease
 - ii. Chronic hypoperfusion

ACA/MCA Border Zone Stroke

1. Contralateral hemiparesis
2. Facial sparing
3. If cortical, arm involvement is greater than leg involvement
4. The wrist and hand can be preferentially involved as can the shoulder
5. Bilateral involvement causes:
 - a. "Man in the barrel" syndrome
 - b. Bilateral arm weakness (proximal greater than distal)
 - c. Patient can walk
 - d. Subcortical lesions:
 - i. Leg greater than arm weakness
 - ii. If bilateral, both legs are involved and can appear as "pseudo-spinal"
 - e. Dominant hemisphere:
 - i. Transcortical motor aphasia
 - ii. Affected area usually above Broca's area
 1. Disconnection of supplementary motor cortex from Broca's area
 - f. Non-dominant hemisphere:
 - i. Transitory mood disturbance
 1. Euphoria or apathy
 2. Apathy can be severe
 - a. Akinetic mutism
 - b. Loss of frontal lobe executive function

Posterior Border Zone MCA/PCA Infarction

1. Optic radiation ischemia (the geniculate body to the calcarine cortex)
 - a. Peripheral visual field constriction
 - b. Homonymous inferior quadrantanopsia (emboli often cause superior quadrantanopsia)
 - c. Hemianopsia

Bilateral Cortical MCA/PCA Border Zone Infarction

1. Anton's syndrome
 - a. Can distinguish light from dark
 - b. Can avoid large objects while walking; possible preservation of peripheral retinal projections
 - c. Normal pupillary reflexes
 - d. Visual confabulation
 - e. Euphoria
2. Bálint's syndrome
 - a. Under reaching (inability to reach a target (superior longitudinal fasciculus damage; connects the superior parietal lobule with frontal eye fields); visual navigation deficit)
 - b. Simultanagnosia – inability to see objects as a whole (can identify pieces of a face – eyes, nose, mouth but can't perceive these components as a face; superior parietal lobule)
3. Optic apraxia (delayed volitional saccades)
 - a. Poor initial scanning of a visual scene
 - b. Inability to break fixation and follow a moving object
 - c. Optic ataxia (visual navigational deficit)
 - i. Inability to point at a target volitionally
4. Cortical involvement (dominant hemisphere)
 - a. Wernicke's aphasia
 - i. Lesion between Wernicke's area (BA22/BA23) and posterior parietotemporal association areas (BA39, BA40, BA41)
 - ii. Parietal sensory loss and hemihypesthesia
 1. Non-dominant hemisphere: hemineglect and anosognosia
 2. Dissociation of primary sensory area (SI) from primary sensory association areas of the posterior parietal lobe
 - iii. Brachiofacial hemiparesis or no motor loss subcortical
5. Hemispheric internal border zone infarction
 - a. Ischemic territory between deep and cortical perforators of the MCA
 - b. Ischemic zones between internal capsule and thalamus (lenticulostriate and thalamogeniculate and thalamoperforate arteries)
 - c. Clinical manifestations:
 - i. Brachiocephalic paresis
 - ii. Cortical sensory loss
 - iii. Dominant hemisphere aphasia
 - iv. Vascular stripe on MRI
 1. Periventricular (1 cm from the ventricle) increased T2-weighted signal

Border Zone Cerebellar Infarction

General Characteristics

General Features of Arterial Territories

1. Less than 2 cm in diameter
2. Between SCA and PICA boundary zones

3. Between left and right SCAs on the cortex
4. Between SCA and PICA branches in the deep cerebellar white matter

Deep Cerebellar Watershed Territory of Arterial Territories

1. Caudal cerebellum
2. Deep boundary zones of AICA–lateral PICA, medial PICA–lateral SCA and medial SCA territories
3. Appear as round holes above the dentate nucleus

Clinical Manifestations

Clinical Features of Border Zone Cerebellar Infarction

1. Similar to territorial infarcts
2. Rarely: transient loss of consciousness; usually dysequilibrium
3. May represent low flow state of the posterior circulation

Brainstem Border Zone Infarction

General Characteristics

1. Usually prolonged hypotension
2. Arterial territories
 - a. Symmetrical necrosis of the tegmentum:
 - i. Territory involved between pontine penetrating vessels and short and long circumflex arteries

Clinical Manifestations

1. Cranial nerve, oculomotor and brainstem dysfunction
2. Coma

Rare Clinical Border Zone Infarctions

General Characteristics

1. Isolation of the speech areas (Perisylvian):
 - a. Anterior and posterior aphasia
 - b. Can only repeat

Neuropathology

1. Severe cortical hypoxia (cardiac arrest)
2. Carbon monoxide poisoning
3. Prolonged hypotension
4. Isolation of the speech areas from much of the cortex (perisylvian border zone)

Deep Cerebral Infarcts Extending to the Subinsular Region

General Characteristics

1. Involved territory is between the lateral ventricle and subinsular region
2. The paraventricular region in the centrum semiovale is involved and extends for greater than .5 cm
3. The at risk territory of the subinsular cortex is 1/3 of the anterior posterior extent of the insula

Clinical Manifestations

1. Hemiparesis
2. Transcortical conduction aphasia
3. Dysarthria
4. Dysphasia

Neuropathology

1. Stenosis or occlusion of extracranial arteries
2. Initiating factors: bradycardia, high hematocrit, systemic hypotension, drop in cerebral perfusion pressure
3. Systemic hypotension due to:
 - a. Cardiac surgery
 - b. Bilateral symmetrical distributions
 - c. More common in posterior watershed zones (MCA/PCA)
4. Systemic disease
 - a. Artery-to-artery cholesterol microemboli
 - b. Sick cell anemia
 - c. Polycythemia vera

Granular Cortical Atrophy

1. Multiple small foci of cortical infarction in all border-zones
2. Gray matter involvement
3. Pial arteries supplying the cortex
4. Cortical microinfarcts

Multiple Infarctions

Overview

The differential diagnosis of multiple infarctions is usually suggested by the clinical setting. Not surprisingly many patients in the course of their evaluation for their first clinical stroke are found to have had either asymptomatic prior strokes or concomitant strokes in territories other than that suspected by their clinical presentation. The major categories of illness that cause multiple infarctions are:

1. Atherosclerosis
2. Cardiac emboli
3. Angiopathies
4. Hematologic disorders
5. Hypoperfusion and venous infarction

Patients with poorly controlled diabetes, hypertension and similar history have an overwhelming probability of suffering both large and small vessel disease. Lacunes are expected in the basal ganglia, pons, internal capsule, thalamus and centrum semiovale. Accelerated and disseminated large vessel atheroma will be seen at the carotid bifurcation, siphon, and at M1 and M2. Calcified and thick, vertebral, carotid and basilar arteries are expected on CT. Severe hypertension will produce dolicoectasia. In situ thrombosis, flow limiting ischemic stenosis greater than 70% and cholesterol laden plaques will

be seen asymmetrically in both anterior and posterior circulations. Accelerated atherosclerosis will be seen beyond bifurcations of the great vessels and intracranially in the fields of X-ray therapy.

Cardiac emboli from clots formed from an ischemic myocardium, arrhythmias, dilated myocardial failure, valve disease, embolize primarily to the MCA circulation that receives the most CBF. Emboli tend to go to the same territory due to flow and viscosity characteristics. They often occur in showers in which two circulations are involved simultaneously. Emboli from atrial fibrillation often occlude the temporoparietal occipital branch of the inferior division of the MCA. Carotid distribution and superior cerebellar artery concomitant stroke suggest an embolic cardiac origin. Occlusion of the top of the basilar artery is most often embolic often from a cardiac source in which the midbrain, thalamus and posterior cerebral arteries are involved. An embolic event in younger patients in two distinct circulations over a long time course suggests a patent foramen ovale with or without an atrial septal aneurysm. Peripheral aneurysms in two distal circulations suggest atrial myxoma. Rhabdomyosarcoma is to be expected with tuberous sclerosis. A shower of emboli in a cancer patient suggests non-bacterial thrombotic emboli. Severe migraine with visual aura and stroke in two circulations is strong evidence for the anticardiolipin syndrome.

Small strokes in pial conducting vessels of all territories of the cerebral cortex occur with active and severe collagen vascular disease. SLE is the most prominent of these illnesses.

Hematologic illness such as leukemia and lymphoma, particularly when the white cell count approaches $250,000/\text{mm}^3$, is attended by strokes in multiple territories. Polycythemia most frequently occludes the posterior circulation. Disseminated intravascular coagulation may strike large extracranial vessels as well as conducting intracranial vessels. Sickle cell disease affects large and small vessels of both anterior and posterior circulations.

Hypoperfusion causes strokes by distal perfusion failure in affected arteries as well as by circulatory compromise between vascular territories. This complication is to be expected and is routine with cardiac pump surgery and following cardiac arrest.

Venous infarction is immediately suggested in the setting of pregnancy and delivery, dehydration and a hypercoagulable state. Bilateral thalamic infarction easily seen on CT or MRI is characteristic of superior sagittal sinus thrombosis. Severe seizures accompany cortical vein thrombosis.

Multiple infarctions other than that from atherosclerosis suggest internal medical and cardiac disease as the source. The younger the patient the more this is true.

General Characteristics

Concomitant Infarction

1. 33% of patients when diagnosed with first stroke have multiple infarcts in the carotid territory

2. 2% of multiple infarcts are in vertebrobasilar territory
3. 2% of patients at first infarct have had prior strokes in both territories (carotid and vertebrobasilar territories)

Asymptomatic Infarction

1. Occurs in 10–38% of stroke patients
2. Often occurs in non-critical areas and are small
3. Right-sided deep hemisphere and basal ganglia lesions more common than left-sided if non-lacunar
4. Risk is the same in multiple and single lesions

Neuropathology

Atherosclerosis

1. Atherosclerosis: large and medium-sized arteries
2. Small vessel disease:
 - a. Lipohyalinosis (penetrating vessels); HCVD
 - b. Spread of atheromatous plaque to occlude adjacent origins of major vessels
 - c. Atheroma at origin of penetrating vessels
 - d. Emboli: artery to artery; cardiac or arch of the aorta are sources

Cardiac Embolism

1. Nonrheumatic atrial fibrillation (AF) most common source of cardiac embolism
2. AF with emboli 10% per year (if untreated):
 - a. Multiple pial territory infarction suggests cardioembolic source
 - b. Bilateral anterior circulation infarcts are more common in patients with emboligenic heart disease

Angiopathies

1. Isolated angitis of the CNS (cerebrum, cerebellum)
2. Granulomatous vasculitis
3. Herpes zoster
 - a. Affects small and medium-sized vessels
 - b. Infarction more common than hemorrhage
 - c. Localized lesions: cerebrum, cerebellum, brainstem in >75% of patients
 - d. May occur in carotid MCA territory if V1 involved. Occurs 2 weeks after onset of skin lesions or may be delayed

Differential Diagnosis

Differential Diagnosis of Non-Inflammatory Angiopathies with Multiple Strokes

1. Eales disease (arterioles and venules involved)
2. Sneddon's syndrome (livedo reticularis)
3. Moyamoya syndrome (carotid occlusion at siphon with collaterals)
4. MELAS (mt DNA) mitochondrial encephalopathy with lactic acidosis and stroke
5. Cerebral amyloid angiopathy (associated dementia)
6. Intravascular lymphoma (angiotrophic endovascular lymphomatosis); dural involvement
7. Arterial dissection of intracranial and cervical arteries (diseases of collagen)

Hematological Disorders

1. Thrombotic thrombocytopenic purpura (TTP):
 - a. Multiple occlusions of small vessels
 - b. Large artery occlusion
 - c. Hallucinations
 - d. Renal failure
 - e. Focal cortical deficits
 - f. Seizures
2. Polycythemia vera:
 - a. Posterior > anterior circulation stroke
 - b. Megakaryocyte proliferation greater than one million has a high incidence of stroke
 - c. Hemoglobins of 18–22 g/dl
 - d. Rheological abnormalities (dysfunction of laminar flow)
3. Sickle Cell disease (HbSS):
 - a. Stroke occurs in 3–17% of patients
 - b. Ischemic stroke 15%
 - c. Large and small vessels involved
 - d. Strokes <15 years of age; border zone, and subcortical areas
 - e. Hemoglobin C: strokes in pregnancy; aseptic necrosis of the hip
 - f. Severe abdominal and joint pain
4. Disseminated intravascular coagulations (DIC):
 - a. Small and large vessel strokes (often concomitantly)
 - b. Encephalopathy
 - c. Non-bacterial thrombotic emboli (NBTE) frequently associated
 - d. SAH
5. Systemic lupus erythematosus:
 - a. Vasculopathy affecting:
 - i. Small arteries
 - ii. Arterioles
 - iii. Capillaries
 - iv. Pathology is fibrinoid neurosis
 - b. Vasculitis
 - i. Pathologically similar to hypersensitivity vasculitis
 - ii. Approximately 10% of patients
 - c. Microangiopathy:
 - i. 50% of SLE patients
 - ii. Circulating antiphospholipid antibodies (APA's)
 - iii. 2 mm to 3 cm infarction size
 - d. Clinical manifestation of stroke:
 - i. May occur at any time during course of the disease
 - ii. Caused by APA's (antiphospholipid)
 1. Titer may fluctuate and is not tightly correlated with systemic disease activity
 2. Circulating IgG and IgM antibodies associated with the thrombotic events
 3. APA's that bind to the phospholipid on factor V and X
6. Inhibits conversion of prothrombin to thrombin
7. Anticoagulant properties in vitro (lupus anticoagulant; LAC)
8. Some LAC are procoagulant
9. High titers of anticardiolipin antibodies (ACL):
 - a. Greater specificity for thrombotic events
 - b. IgG > association with thrombosis than IgM
 - c. Stroke risk with secondary APA's in SLE is increased with:
 - i. Oral contraceptives
 - ii. Smoking
 - iii. Hypertension
10. Stroke types:
 - a. Branch occlusion most common
 - b. Multiple infarcts
 - c. Centrum semiovale strokes
 - d. Cardioembolic from Libman-Sacks endocarditis
11. Vasculitis in SLE:
 - a. Ischemic and hemorrhagic stroke
 - b. Intracranial hemorrhage
 - i. Parenchymal
 - ii. SAH
 - iii. Most associated with vasculitis
 - c. Most likely cause of stroke if:
 - i. Active systemic disease
 - ii. Normal TEE
12. Associated collagen vascular disease
13. Hyperviscosity syndromes:
 - a. Bing-Neel syndrome (poor cerebral perfusion from high viscosity)
 - b. Bleeding gums
 - c. Myeloproliferative and dysglobulinemia states (IgM particularly severe)
 - d. Multiple occlusions of small blood vessels
 - e. Petechial hemorrhage
 - f. Waldenström's macroglobulinemia
 - i. Petechia below the knee
 - ii. Acrocyanosis

Hypoperfusion

1. Severe hypotension (cerebral perfusion pressure of less than 70 mm systolic)
2. Prolonged hypoxemia
3. Cardiac circulatory failure (no reflow phenomena of specific microcirculations)
4. Symmetrical and asymmetrical watershed infarcts
5. Infarcts in deep and superficial MCA territories
6. Cerebellar watershed infarcts
7. Multiple clinical syndromes depending on involved circulations

Venous Infarction

1. Hemorrhagic
2. Specific circumstance: pregnancy, prothrombotic state, cancer, Behçet's disease
3. Gray matter (basal/thalamus); subcortical white matter

Lacunar Stroke

Overview

Lacunae are small ovoid lesions 1–2 mm in size noted in deep nuclear gray matter of the basal ganglia and thalamus as well as the internal capsules, centrum semiovale and pons. They are found in the setting of poorly controlled diabetes and hypertension. They are caused by fibrinoid necrosis of the endothelium and adventitia of the single perforating arterioles. The infarct is limited to the territory of deep perforators and is caused by in situ infarction. The process may also be caused by atheromatous occlusion of the mouth of these blood vessels. If a series or a group of perforators are involved simultaneously emboli are suspected as causal (this most often occurs in the lenticulostriate territory).

Discrete clinical syndromes are noted with infarctions of these perforators which outline their territory and allow anatomic localization.

Involvement of arm, face, and leg suggests lacunar infarction of the middle 1/3 of the posterior limb of the internal capsule. Genu involvement is suggested by more face than arm involvement and severe dysarthria. The posterior 1/3 of the capsule may be selectively involved with hemisensory numbness. Occasionally, a single extremity may become weak from involvement of the medullary stria arteries that perfuse the centrum semiovale. The motor and sensory fibers are separated in the fiber deep into the brain. The dysarthria clumsy hand syndrome occurs from posterior ventral 1/3 pontine infarction in which the corticobulbar fibers, speech and arm fibers are closely opposed. Ataxic hemiparesis suggests pontine lacunar involvement at the midpontine level.

Lacunar infarctions rarely ever are associated with headache, VF cut or aphasia. Pure motor, pure sensory and mixed deficits are common. There are no cortical sensory or behavioral manifestations which differentiates this from pial artery stroke. Pure motor hemiparesis with III nerve pattern (Weber, Benedict; Claude's and Nothnagel's) places the lesion in the midbrain. Rarely hemiballisms occurs from lacunar infarction of the subthalamic nucleus due to paramedian thalamic involvement. Lacunes of basilar artery territories are suggested by dizziness, diplopia, and intranuclear ophthalmoplegic without weakness.

General Characteristics

1. Lacunes are the result of small vessel disease and are usually ovoid lesions
 - a. No evidence of cerebral cortex involvement
 - b. Imaging evidence of a lesion less than 15 mm
 - c. Often concomitant hypertensive cardiovascular disease or diabetes mellitus
 - d. Overlap both in risk factor profile and clinical symptoms with large artery disease
 - e. Lacunes are defined as occlusions of a single perforating artery:
 - i. Large lacunae are 15–20 mm in diameter
 - ii. Small lacunae are 3–4 mm
 - f. Generally, large lacunes have more symptoms; small lacunes are symptomatic if in a critical location of a sensory or motor tract
2. If a specific clinical syndrome is present there is an 87% chance the patient has suffered a lacunar stroke
3. Some series demonstrate a 40–50% incidence of concomitant ischemic heart disease
4. Predictive value for lacunar stroke:
 - a. Pure sensory stroke 100%
 - b. Highly correlated
 - i. Ataxia, hemiparesis
 - ii. Sensorimotor stroke
5. 25% of lacunes are due to a non-lacunar mechanism
 - a. Atherosclerosis
 - b. Cardiac source of emboli
 - i. 10–15 perforators are occluded
 - ii. Larger size than those from small vessel disease
6. May have stuttering course over 2–3 days
7. No cortical sensory loss
8. May have behavioral changes; minimal cognitive deficits
9. No visual field deficit
10. Involvement of the territory of one single perforating arteriole
11. <1.5 cm lesion on CT or MRI; (ovoid in shape)
12. Infarct is limited to the territory of the deep perforators
13. Caused by in situ small vessel disease
14. Infarcts limited to the territory of deep perforators may occur with:
 - a. Cardiac emboli
 - b. Ipsilateral internal carotid artery stenosis or occlusion
15. Diabetes is a major risk factor for lacunes
16. The most suggestive clinical syndrome for lacunar infarction:
 - a. Pure motor hemiparesis with face, arm and leg involvement
17. Arterial networks that supply subcortical territories:
 - a. Deep perforating branches form the ACA
 - i. Recurrent artery of Huebner (A2)
 - ii. Direct anterior lenticulostriate branches
 - b. Deep perforating branches from the anterior choroidal artery
 - c. Thalamic arteries from P1 and P2 segments
 - i. Interpeduncular (top of the basilar)
 - ii. Thalamoperforate
 - iii. Thalamogeniculate
 - iv. Posterior choroidal artery
 - v. Tuberothalamic artery (from the posterior communicating artery) These arteries are perforators, but have collateral branches and are not terminal branches
 - d. White matter medullary arteries
 - i. Originate from the superficial (pial) branches of the MCA > ACA > PCA

- ii. 2–5 cm long
- iii. Selective territories
- iv. No collaterals
- v. Subserves the centrum semiovale
- vi. Do not anastomose with the deep perforators (lenticulostriate arteries)
- e. Cortical arteries with subcortical territories that supply:
 - i. U-fibers
 - ii. Extreme capsule
 - iii. External capsule
 - iv. Claustrum
- f. Most commonly found:
 - i. Centrum semiovale
 - ii. Basal ganglia
 - iii. Thalamus
 - iv. Midbrain
 - v. Pons
 - vi. Medulla
- g. Infarction in these territories are often not lacunar (i.e., from one perforator) but may be secondary to distal field ischemia (carotid stenosis) or cardiac thromboembolism
- 6. Mesencephalic; decreased upgaze (Nothnagel's syndrome)
- 7. Thalamic dementia (DM, AV nuclei)
- 8. PMH with horizontal gaze palsy – lower 1/3 of pons, PPRF (para pontine reticular formation)
- 9. PMH with III nerve (Weber's syndrome)
- 10. PMH with III nerve and ataxia – Claude's syndrome (midbrain)
- 11. PMH with III and movement disorder (Benedict's) (mid-brain)
- 12. PMH with VI nerve palsy (Ramon's syndrome); pons
- 13. PMH with confusion (brainstem RF; thalamus AV/DM)
- 14. Sensorimotor stroke (thalamic-capsular)
- 15. Hemiballism – (STN; paramedian mesencephalic vessels)
- 16. Lacune of basilar territory (dizzy, diplopia, gaze dysfunction)
- 17. Lateral medullary partial infarction (penetrators from the vertebral artery)
- 18. Lateral pontomedullary territory (partial AICA)
- 19. Loss of memory (DM nuclei of thalamus); paramedian perforator)
- 20. Locked in syndrome (infarction of ventral pons; bilateral cerebral peduncles)
- 21. Unusual lacunar syndromes:
 - a. Weakness in one leg with falling (corona radiata; ventral portion of ventral pons)
 - b. Pure dysarthria – posterior 1/3 of ventral pons
 - c. Acute dystonia (thalamoperforate artery to basal ganglia)
 - d. Lacunar strokes and cognitive deficit
 - i. Late onset of bipolar disease
 - ii. Silent lacunar infarct with:
 - 1. Brain atrophy
 - 2. Multiple subcortical sites
 - 3. Enlarged ventricles
 - iii. Decreased executive function
 - iv. Decreased visuospatial ability

Clinical Features of Lacunar Stroke

Clinical Presentation of Lacunar Stroke

1. Occur more commonly during sleep
2. Arm, face, leg may be affected separately (corona radiata and pons most common areas of infarction)
3. Pure motor, pure sensory or mixed clinical patterns
4. Rare aphasia (a differential point against lacunar stroke)
5. No headache
6. No visual field deficit
7. May have stuttering course over 2–3 days
8. No cortical sensory or behavioral manifestations (strong differential point for lacunar stroke)
9. Cause of multi-infarct dementia (état spongiosus)

Clinical Patterns of Lacunar Stroke

1. Pure sensory stroke (PSS) (primarily thalamus)
2. Pure motor hemiparesis
 - a. Corona radiata
 - b. Middle internal capsule
 - c. Cerebral peduncle (medial 3/5)
 - d. Ventral pons
 - e. Medullary pyramidal
 - i. At decussation with cruciate pattern (ipsilateral arm; contralateral leg)
3. Ataxic hemiparesis (AH) (pontine gray – MCP and descending CST)
4. Dysarthria clumsy hand syndrome (pons)
5. Pure motor hemiparesis sparing the face (farther posterior in the middle 1/3 of the posterior limb of the internal capsule)

Clinical Presentation and Patterns of Pure Motor Hemiparesis (PMH) and Sensory Stroke

1. Motor Cortex
 - a. Hand and arm representation is in the precentral gyrus "motor knuckle"
 - i. C5–C6 roots are represented medially
 - ii. C8–T1 are more lateral
 - b. Infarction frequently appears as a pseudo radial palsy (wrist drop)
 - c. Embolic pathogenesis from the internal carotid artery
 - d. Rare that face is involved in isolation
 - e. Cranial nerve III or VI involved with pure hemiparesis, ataxia or movement disorder
 - f. Medullary pyramid-flaccid hemiparesis that spares the face

Pure Motor Stroke (PMS)

1. The most common lacunar syndrome
 - a. 45–57% in 3 major stroke registries
2. Territories involved:
 - a. Anterior limb of the internal capsule
 - i. Facial brachial pattern of weakness
 - b. Leg weakness – the lesion is more posterior in the internal capsule
 - c. Distal upper limb – pontine infarction
 - d. Medullary pyramid – flaccid hemiparesis that spares the face
3. Mechanism
 - a. Occlusion (atheroma at ostium) of deep perforating end artery
 - b. Lipohyalinosis of perforator: fibroid necrosis of media of the perforating arteriole
 - c. Embolus to a group of perforators
 - d. Basilar artery branch disease in pontine infarction due to atherosclerosis of the basilar artery

Pure Sensory Stroke

1. Lacune in the centrum semiovale (deep penetrating medullary arteries)
 - a. Usual feeling of numbness or heaviness
2. Infarction of ventrobasilar thalamic complex (VPM or VPL):
 - a. Patients may describe numbness, paraesthesias, formication or pain
 - b. Bilateral intraoral loss of sensation (VPM). This is to be differentiated from a vascular brainstem stroke in which patients may feel numbness on one side of the tongue. VPL involvement may present as numbness of the trunk and extremities in 20% of patients. Dysesthetic, paraesthetic and burning occurs more often in the involved territory. Later this territory may be associated with the hyperpathia of Dejerine-Roussy syndrome (thalamic pain). Associated thermal and mechanical allodynia and hyperalgesia are frequently present concomitantly with this syndrome. Thalamic lesions respect the midline and may involve vibration sensibility. Exception is bilateral decreased periumbilical sensation
3. Thalamic-capsular lacunar infarction most often causes sensorimotor stroke. Feeling loss is perceived as numbness and heaviness
4. Involvement of the ventral medial spinothalamic tract (quintothalamic tract) by lacunar infarction at medullary levels causes unilateral or bilateral facial pain or numbness (onion skin distribution)
5. Smallest of the symptomatic deep infarcts
6. Approximately 6% of lacunar strokes
7. Territories involved:
 - a. Posterior limb of the internal capsule
 - b. Thalamus (VPL)
 - c. Anterior thalamic radiations

- d. Rostral pontine tegmentum that involves:
 - i. Medial lemniscus
 - ii. Lateral spinothalamic tracts
- e. 9.5% of pure sensory strokes are not due to lacunar infarction

Ataxic Hemiparesis

1. Ataxic Hemiparesis or Corticobulbar Dysfunction
 - a. Infarction of the descending corticospinal tracts and pontine crossing fibers (comprises the middle cerebellar peduncle)
2. Anatomical locations:
 - a. Internal capsule – 39%
 - b. Thalamus – 13%
 - c. Corona radiata – 13%
 - d. Lentiform nucleus – 8%
 - e. Cerebellum – 4%
 - f. Frontal cortex – 4%

Clinical Features of Ataxic Hemiparesis

1. Hemiparesis or corticospinal signs associated with ipsilateral cerebellar signs:
 - a. Lesion topology
 - i. Lesions in the white matter of the corticospinal (motor cortex to pontine nuclei)
 - ii. Afferents to the middle cerebellar peduncle that project to the cerebella afferent zone for proprioception
 - iii. Thalamic cerebellar nuclei
 - iv. 3a of SI in the sensory cortex that projects back to MI. There are subtle differences with lesions at each level of this pathway
 - b. Partial hemiparesis, nystagmus, dysarthria – suggest an infratentorial lesion
 - c. No facial involvement, dysarthria, sensory loss is more cortical lesion site
 - d. Painful ataxic hemiparesis
 - i. Edema or ischemia of the internal capsule
 - ii. Pain and ataxia
 1. VPL of the thalamus
 2. Cerebellar proprioceptive zone in VL
 - e. Ataxic hemiparesis from:
 - i. Frontal infarction and contralateral cerebellar diaschisis (demonstrated by SPECT scan)
 - f. Ataxic hemiparesis accounts for between 9–18% of lacunar strokes

Dysarthria (Clumsy Hand Syndrome)

1. Corticobulbar fibers to the Xth and XIIth cranial nerves with contralateral ataxia of the hand and arm
2. IIIrd nerve palsy with contralateral ataxia (Claude's syndrome); contralateral movement disorder (Benedict's); failure on upgaze Nothnagel's)

Sensorimotor Stroke Syndrome

1. Territories involved:
 - a. Thalamic capsule component of the corona radiata and putamen
 - b. Ventral posterior lateral thalamus and internal capsule
 - c. Cortical infarction anterior to the Rolandic fissure
 - d. In the Stroke Data Bank Study, lesions were seen:
 - i. Posterior limb of the internal capsule – 3%
 - ii. Corona radiata – 22%
 - iii. Genu of the internal capsule – 7%
 - iv. Thalamus – 9%
 - v. Anterior limb of the internal capsule – 6%

Hemiballism

1. Infarction of at least 2/3 of the corpus Luysi (subthalamic nucleus. Usually thalamoperforate or paramedian thalamic penetrating artery is occluded.)

Tetraplegia (Locked-In Syndrome)

1. Patients are fully awake
2. Quadriplegic
3. Able to blink and look up and down on command
4. Unable to perform lateral eye movements
5. Involvement of the basis pontis (basilar artery) or the cerebral peduncles (bilaterally)
 - a. P1 segment of the PCA's

Unusual Patterns of Lacunar Weakness

1. Weakness in one leg with falling
 - a. Basis pontis (ventral portion of ventral pons)
 - b. Posterior corona radiata fibers
2. Pure dysarthria: corona radiata, internal capsule, cerebral peduncle; basis pontis
 - a. No difference in dysarthria
 - b. Imprecise articulation of labials and glottals
 - c. Monotonous voice
 - d. Slowed rate
 - e. Pontine or medullary areas have more severe dysarthria
 - f. Left paravermian cerebellar lesions
 - i. Coordination of articulation and respiration is disrupted
3. Acute dystonia
 - a. Thalamus (VA, VL or VIM)
 - b. Putamen

Rarer Lacunar States

1. Loss of memory
 - a. Anterior thalamic nuclei
 - b. Anterior limb of internal capsule that involves anterior thalamic efferent fibers
2. Thalamic dementia (dorsal medial nucleus from paramedian infarction)

3. Pure motor hemiparesis sparing the face
4. Multiple lacunar infarctions:
 - a. Primarily in the basal ganglia
 - b. "État" Lacunaire
5. Dysarthria, facial, lingual paresis
 - a. Genu capsular syndrome
6. Cerebellar lacunes
 - a. Unusual small round lesions in the watershed between SCA, PICA, AICA
 - b. One case of giant lacune in the cerebellum
 - c. SCA greater deep territory supply from AICA or PICA
 - d. Large artery occlusion, cardiac embolic, end artery lesion

Differential Diagnosis by Arterial Territory and Anatomical Structure of Pontine Stroke with Lacunar Infarction

1. Paramedian arteries:
 - a. Medial basis pontis
 - b. Ventral tegmentum
 - i. Corticospinal tract
 - ii. VIth cranial nerve fibers as they exit
 - iii. Facial nerve fibers as they exit
 - iv. Rare PPRF (para pontine reticular formation by extension)
2. Short circumferential arteries
 - a. Lateral 3/5 of the pons involved
3. Long circumferential arteries
 - a. Lateral tegmentum
 - b. Tectum:
 - i. Cerebellar projections
 - ii. Vth and VIIIth cranial nerves
 - iii. Part of sensory lemniscus infarcted
4. Large bilateral pontine infarcts
 - a. Basilar artery lesions
 - i. PPRF, one-and-a-half syndrome
 - ii. Ocular bobbing and dipping
 - iii. <0.5 mm pupils
 - iv. Decreased consciousness
 - v. Decerebration
 - vi. Hyperactive reflexes
 - vii. Babinski signs

Differential Diagnosis Between Pontine Hemorrhages vs. Infarction

1. Ischemic:
 - a. Prior TIA
 - b. Stuttering clinical course
2. Hemorrhage:
 - a. Abrupt headache
 - b. Nausea and vomiting
 - c. Meningeal irritation
 - d. Rapid decrease of consciousness

3. Lacunar syndrome may be due to hemorrhage or infarction; isolated small hemorrhage may be associated with:
 - a. Dysarthria clumsy hand syndrome
 - b. Pure sensory stroke
 - c. Ataxic hemiparesis

Small Vessel Disease

Small Vessel Disease Overview

Small vessel disease is a major component of cerebral vascular disease that is manifest by lacunar infarction, microhemorrhages both in the cortex and basal ganglia, dilated Virchow Robin spaces and white matter intensities (identified on T2-weighted MRI) that may be generalized or topographic. There are monogenic conditions that present primarily as small vessel disease such as: retinal vasculopathy with cerebral leukodystrophy (RVCL) that has recently been mapped to chromosome 3p21 and may have 3 variants: 1. Hereditary Retinal Vasculopathy (HRV), 2. Cerebroretinal Vasculopathy (CRV) and Hereditary Endotheliopathy, 3. Retinopathy and Nephropathy (HERNS). An infantile syndrome that is similar but does not map to 3p21 is: Hereditary Infantile Hemiparesis with Arteriolar Retinopathy and Leukoencephalopathy (HI-HARL). Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is well recognized as a genetic cause of small vessel disease. Less recognized in Western populations is the autosomal recessive small vessel disease Cerebral Autosomal Recessive Arteriopathy with Subcortical Infarction and Leukoencephalopathy (CARASIL). There are multiple mutations in the genes encoding type IV collagen (COL4A1 and A2), a major component of basement membrane that cause multi system involvement (eye, brain, kidney) as well as cerebral aneurysms, hemorrhages and severe small vessel disease. Hereditary Angiopathy with Nephropathy, Aneurysms, and muscle Cramps (HANAC) is a specific variant. Fabry's disease is now being increasingly diagnosed as a cause of small vessel disease. It is clear that migraine is common in several monogenic causes of small vessel disease and has been shown in and of itself to be causative of cerebral ischemia (vasospasm or secondary ischemia from spreading cortical depression). Intracranial small vessel disease from atherosclerosis is a major subcategory of small vessel disease. Poorly controlled hypertension, diabetes and dyslipidemia are the most common causes of small vessel disease. White matter hyperintensities (WMH) that are a concomitant of normal aging are associated with cognitive dysfunction and are increased in migraine, some monogenic forms of SVD, hypertension, diabetes and dyslipidemia. They are topographic such that symmetry, density, periventricular and specific lobe involvement suggests a specific leukoencephalopathy, Alexander's disease, frontal variant of adrenar leukodystrophy, metachromatic leukodystrophy (periventricular) that affect the frontal lobe to a greater

degree than hypertension or diabetes. The genetic forms of amyloid angiopathy occur in specific populations (Icelandic, Dutch, Iowa kindred, Volga Germans) while sporadic congophilic angiopathy is a major cause of sporadic small vessel disease in the elderly.

The clinical symptomatology of small vessel disease from all causes is convergent but there are seminal features that help in differential diagnosis.

Clinically, small vessel disease (SVD) is associated with lacunar infarction, microhemorrhages and white matter hyperintensities on T2-weighted MRI sequences. If severe, the multiple small vessel infarctions cause vascular dementia characterized by subcortical type apraxia and slowness of information processing. SVD occurs very frequently in association with Alzheimer's disease so the cognitive decline noted may be multifactorial. Severe disease may cause pseudobulbar palsy gait disorder and spasticity. Uncontrolled diabetes and hypertension are almost universally associated with SVD. There are controversial arguments as to the pathologic relevance of lipohyalinosis atheroma at the origin of penetrating perforators or hyaline degeneration of the arterial media in SVD. Chronic kidney disease clearly exacerbates both large and small vessel disease. Calcifications of larger vessels are common. Less sympathetic control of posterior cerebral artery blood flow may be causative of posterior occipital lobe SVD as noted with eclampsia, reversible vasoconstriction syndrome and hypertensive encephalopathy. Family history may suggest a monogenetic cause of SVD. Migraine in young patients may have scattered white matter hyperintensities while microhemorrhages in the cortex will be seen in elderly patients with CAA. Microhemorrhages in the basilar ganglia are more characteristic of hypertension. An associated lobar hemorrhage supports the diagnosis of CAA if the microhemorrhages are cortical. A single microhemorrhage, either cortical or deep, is significant.

General Characteristics and Definitions for Small Vessel Disease

1. Small Vessel disease causes:
 - a. Lacunar infarcts
 - b. White matter hyperintensities (WHM)
 - c. Microinfarction (smaller than lacunes)
 - d. Dilatation of perivascular spaces
 - e. Microbleeds
2. Small Vessel disease often occurs in association with atherosclerosis and affects large and medium-sized arteries
 - a. By intimal proliferation and accumulation of lipids and cholesterol within the vessel wall
 - b. Plaques form at bifurcations of arteries and in areas of blood flow derived shear stress (stenosis of the lumen)
 - c. Plaques rupture occurs from:
 - i. Local thrombosis (primarily due to endothelial dysfunction)

- ii. Emboli from both cholesterol plaque material and fibrin-platelet clots
3. Vessel wall changes of small artery arteriosclerosis occur in 200–800 μm sized blood vessels
 - a. Similar to atherosclerosis but the vessels do not calcify
4. Lipohyalinosis:
 - a. Occurs in arteries of 30–300 μm size
 - b. Asymmetric fibrosis and hyalinosis associated with foam cells and accumulation of blood derived lipids and proteins within the vessel wall
5. Arteriolosclerosis
 - a. Occurs in arterioles between 50–150 μm in diameter
 - b. A concentric hyaline thickening of the vessel wall with stenosis
6. White matter hyperintensities (most easily seen on MRI) and associated with sporadic and familial SVD:
 - a. Most common in the elderly and may be seen frequently in normal subjects
 - b. White matter changes are characterized by:
 - i. Demyelination axonal loss
 - ii. Astrogliosis
 - iii. Often severe in the deep white matter
 - iv. Spares U-fibers
 - v. Associated with microglial activation
 - c. White matter lesion progression:
 - i. Growth of existing lesions
 - ii. WMH are surrounded by regions of milder injury ('penumbra')
 - iii. Gradual spatial spreading
 - iv. New lesions accrue in approximately 20% of patients in addition to growth of prior lesions
 - d. Study of CADASIL patients (pure SVD) reveals that:
 - i. Lacunes develop at the edge of white matter hyperintensities along the course of perforating vessels
7. Leukoaraiosis
 - a. Age related (as well as disease caused) white matter hyperintensities
 - i. Major risk factors are age and hypertension
 - b. Pathology:
 - i. Demyelination/axonal loss/gliosis/infarcts
 - ii. Fibrohyalinosis of small vessels (30–150 μm) in size
 - iii. Venous collagenosis
8. Microinfarcts:
 - a. Smaller than lacunar infarcts (1 mm or less)
 - b. In SVD occurs in the white matter
 - c. In CAA they occur in the cortex
 - d. Watershed microinfarcts:
 - i. Occur in hyper perfused areas between two vascular territories

Clinical Features

Lacunar Infarction

1. Round, usually 1 mm (maybe up to 3 mm); the territory served by a penetrating arteriole

2. Differentiated from a Virchow-Robin space (surrounding a penetrating arteriole). These spaces (often not ovoid) are increased in number and size by uncontrolled hypertension. They are more frequent in specific locations
3. Most patients have multiple lacunes with SVD
4. Lacunes most frequently involve the centrum semiovale, the, basal ganglia and the pons
5. Multiple penetrating arterioles are involved from both the anterior and posterior circulations. Descending arterioles from cortical conduction vessels cause large lacunar infarctions in the centrum semiovale
6. Large lacunes (>25 mm) may involve multiple perforating arterioles and may be embolic

Extensive Lacunar Infarction

1. Cystic lesions of the basal ganglia, thalamus, anterior and posterior limbs of the internal capsule, brainstem and pons are known as "état lacunaire"
2. Traditional clinical features of "état lacunaire"
 - a. Pseudobulbar palsy:
 - i. Emotional dyscontrol: "laughter without mirth, crying without tears", inappropriate to the social environment (bilateral cortical spinal tract involvement at any level from the internal capsule to the medullary pyramids)
 - ii. Difficulty with swallowing combined with a hyperactive gag reflex (poor fractionated pyramidal control of bulbar musculature for swallowing innervated by cranial nerve V, IX, X and XII)
 - iii. Gait dysfunction
 1. Small (decreased swing phase), unsteady guarded gait (Well's dementia gait)
 - iv. Subcortical dementia (apraxia and decreased processing speed)
 - v. Spasticity (often with bilateral Babinski sign)
 - vi. Mild focal motor and sensory deficits
 - vii. Cortical release reflex (forced grasp, parietal hand, palmomental)

Clinical Features of All Patients with Small Vessel Disease

1. Decreased information processing speed:
 - a. Areas of involvement that correlate with this deficit are the left medial frontal cortex and anterior thalamic radiations
 - b. The medial frontal cortex (MFC):
 - i. Pivotal for a short reaction time
 - ii. Response adjustment
 - iii. Receives projections from the anterior thalamus
 - iv. Microinfarctions in this circuitry is the characteristic pathology which causes retrograde degeneration of the medial frontal cortex
2. Effects of periventricular white matter demyelination
 - a. Frontal cortical thinning
 - b. Decreased executive function

3. Occipital and temporal cortical thinning also noted with SVD
 - a. Exact functional loss has not been determined
4. Role of frontal subcortical circuits is essential for processing speed, praxis, executive function and possibly episodic memory

Gait Disorders with Small Vessel Disease

Clinical Manifestations

1. Lower gait velocity
2. Shorter stride length (swing phase)
3. Broader stride width

Neuroimaging

MRI

1. Lesions that correlate with gait deficiency
 - a. Centrum semiovale lacunes
 - b. Periventricular white matter hyperintensities in the frontal lobe
 - c. Genu of the corpus callosum (lacunes)
 - d. Fibers interconnecting bilateral areas of the prefrontal cortex
2. Utilizing fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), radial diffusivity (RD) and MRI sequences:
 - a. Mobility is correlated with FA and AD of the inferior cerebellar peduncle (ICP) and the superior cerebellar peduncle (SCP)
 - b. Measures of fiber tract integrity of both myelinated and unmyelinated axons are demonstrated
3. T2-weighted and FLAIR sequences on a 3 Tesla magnet are excellent for location and anatomy of lacunar infarction, 7 Tesla magnets are being utilized in major centers which will certainly bring new understanding of lesion correlation with functional deficits in lacunar states
4. Gradient ECHO MRI and Susceptibility Weighted imaging are the present standard for detection of microbleeds and hemorrhages

Functional MRI (fMRI)

1. Functional connectivity and network function:
 - a. Dependent on white matter structural integrity
 - i. Demonstrated with diffusion tensor tractography and functional connectivity within all networks. The major nodes of the default mode network (DMN) are the medial frontal cortex, posterior cingulate gyrus, precuneus, hippocampus and inferior parietal lobule. This network is active during introspection and important for consciousness
2. SVD associated with minimal cognitive impairment (MCI) has deactivation failure or deficient functional connectivity in the default mode network (DMN) associated with cognitive task performance
 - a. Impaired deactivation of the precuneus and posterior cingulate gyrus

3. MCI patients without SVD
 - a. Relative hyper activation during vigilance and hypo activation of the salience network at high working memory load

Monogenetic Causes of Small Vessel Disease

1. CADASIL (central autosomal dominant angiopathy with subcortical infarction and leukoencephalopathy)
 - a. Notch 3 gene
2. CARASIL (cerebral autosomal recessive angiopathy with subcortical infarction and leukoencephalopathy)
 - a. HTRA-1 gene
3. Fabry's disease
 - a. Lysosomal α -galactosidase A deficiency
 - b. X-chromosome
4. COL4A1/A2 (collagen 4a and a2)
 - a. Chromosome 13q34 collagen IV gene
 - b. Hereditary angiopathy with Nephropathy Aneurysm and Muscle cramps (HANAC)
5. Amyloid Angiopathy (Genetic Variants)
 - a. Dutch
 - b. Icelandic
 - c. Kindred variants (founder mutations)
 - d. Specific mutations
 - e. Iowa variant
 - f. Flemish variant
 - g. Italian variant
 - h. Familial British and Danish Dementia
6. Retinal Vasculopathy with Cerebral Leukodystrophy (RVCL)
 - a. TREX 1 gene mutation
7. Chromosome 3p21 causes of retinal vasculopathy with cerebral leukodystrophy
 - a. Cerebroretinal Vasculopathy (CRV)
 - b. Hereditary Vascular Retinopathy (HVR)
 - c. Hereditary Endotheliopathy, Retinopathy and Nephropathy (HERNS)
8. Non-chromosome 3p21 variant
 - a. Hereditary Infantile Hemiparesis with Arteriolar Retinopathy and Leukoencephalopathy (HIHARL)
9. Pontine Autosomal Dominant Microangiopathy and Leukoencephalopathy (PADMAL)
10. Hereditary Angiopathy with Nephropathy, Aneurysm and Muscle Cramps (HANAC)
 - a. Mutations in COL4A1 gene
11. Swedish Hereditary Multi Infarct Dementia (SHMID)
 - a. Hypertension
 - b. Diabetes
 - c. Dyslipidemia

Sporadic and Hereditary Cerebral Amyloid Angiopathies (CAA)

Overview

1. Amyloid fibrils deposit primarily in the walls of arteries and arterioles

2. Veins and capillaries are affected less frequently
 - a. Amyloid- β peptide is the most common amyloid subunit deposited in both sporadic and hereditary CAA
 - b. Other proteins deposited in familial forms of CAA include:
 - i. A Bri and A Dan in British and Danish dementia (BR1₂ gene related dementia)
 - ii. Variant cystatin C (hereditary cerebral hemorrhage with amyloidosis-Icelandic type)
 - iii. Variant transthyretin (meningovascular amyloidosis)
 - iv. Prion associated amyloidosis (premature stop codon mutation)
 - v. Gelsolin mutation (A Gel) in familial amyloidosis Finnish type
2. Perivascular inflammatory response
 - a. Activates microglia and astrocytes cause:
 - i. Seizures, focal neurologic deficits, headaches
3. Cerebral infarction, lobar hemorrhages and diffuse white matter changes occur irrespective of the type of vascular amyloid deposited
4. Cerebral amyloid angiopathy (CAA) is:
 - a. Defined by the deposition of amyloid proteins in the walls of cerebral vessels
 - b. Overproduction or abnormal degradation of circulating precursor proteins is causative
 - c. Tissue or organ affinity is present for each type of amyloid
 - i. Amyloid- β (A β) and cystatin C are most commonly associated with CAA
 - ii. Amyloid A β
 1. 40–43 amino acid proteolytic product of amyloid- β precursor protein (APP)
 2. Several isoforms (derived from alternate splicing); the gene is located on chromosome 21; most prominent in neuronal tissue
 - a. A β deposits are found:
 - i. In the walls of cerebral vessels in patients with sporadic CAA
 - ii. Dutch type hereditary ICH (HCHWA-D)
 - iii. Alzheimer's disease
 - iv. Down syndrome
 - v. Cystatin C colocalizes with:
 1. A β in vessel walls of AD
 2. HCHWA-D
 3. Sporadic CAA
 4. Not in senile plaques

Amyloid Formation

1. Aggregation and polymerization of soluble circulating proteins:
 - a. Conformational change from coiled protein to toxic β sheet configuration
2. Increase of protein conformers to a critical level
3. Protofibrillar intermediate state
4. Formation of amyloid fibrils

Precondition of Amyloid Formation

1. Proteolytic processing of a larger precursor protein:
 - a. β and γ -secretases act on the amyloid precursor protein (APP) in Alzheimer's disease to produce amyloid- β (A β peptide)
 - b. Mutated BRI₃ precursor protein
 - i. Processed by furin enzyme
 - ii. Releases A Bri or A Dan amyloid proteins in familial British and Danish familial dementia

Mechanisms That Destabilize the Secondary Structure of Soluble Native Proteins

1. Genetic and posttranslational modifications that include:
 - a. Missense mutation in gene coding region
 - b. Consequent amino acid substitution in the protein changes the rate of conversion of soluble native protein to a fibrillary conformer
2. Increased concentration of the soluble protein:
 - a. Trisomy of Down's syndrome
 - b. Duplication of the APP gene of early onset AD
3. Amyloid-associated proteins:
 - a. Pathological chaperones
 - b. Binding may facilitate misfolding of the soluble protein

Cerebrovascular Amyloid Deposition

1. A staged process:
 - a. A β first deposited in the tunica media
 - b. Intimal layers are affected
 - c. Amyloid replaces smooth muscle cells
 - d. Degenerative changes in the vessel wall

Sporadic A β CAA

General Characteristics

1. A β CAA is primarily sporadic and found in:
 - a. Normal elderly patients
 - b. Alzheimer's disease and Down syndrome
 - c. Long-standing repeated head injury (dementia pugilistica)
 - d. Post anoxic encephalopathy
2. Annual incidence of lobar hemorrhage in patients greater than 70 years old is 30–40/100,000 persons of which 30% are caused by A β CAA
 - a. Women greater than 80 years have a higher incidence than men and this increases with age
 - b. Alzheimer's Dementia patients (autopsy series) with A β CAA (25%–100%)

Genetics

1. 2/3 of patients demonstrate:
 - a. ApoE ϵ 2/cystatin C has been implicated
 - b. Polymorphisms associated with sporadic CAA or CAA-related ICH include:
 - i. Presenilin-1 (PS1)
 - ii. ApoE
 - iii. α 1-antichymotrypsin (ACT)
 - iv. Neprilysin (NEP)
 - v. Transforming growth factor β 1 (TGF- β 1)

Clinical Manifestations

1. Most sporadic CAA is asymptomatic
2. Cerebral microbleeds associated with lobar hemorrhages:
 - a. Temporal and occipital lobes are affected to a greater degree than the frontal lobe in location; rarely are there cerebellar or pontine bleeds
 - b. May have TIA features with focal deficits prior to the bleed
 - c. Headache, seizures and recurrent bleeds occur
 - d. Cerebral and subarachnoid siderosis are seen:
 - i. Linear streaks in the cortex
 - ii. Adjacent to lobar hemorrhage
3. Cerebral ischemia
 - a. Small cortical infarcts that are silent or associated with focal deficits
4. Dementia
 - a. Associated with infarcts, hemorrhages and generalized leukoencephalopathy
 - b. Concomitant Alzheimer's disease and stroke
 - c. Rapid onset of dementia may be caused by association with angiitis (inflammation)
5. Reversible acute leukoencephalopathy:
 - a. Rapid progression of signs and symptoms followed by rapid clinical and radiologic recovery
 - b. Suggested by MRI; signs of white matter edema and microbleeds (cortical predominant)

Pathology

1. A β CAA involves small and medium-sized arteries and veins in the cortex, leptomeninges and capillaries
 - a. Deposits are in the external layers of the vessels
 - b. Eosinophilia and thickening of vessel walls occurs
 - c. Loss of smooth muscle cells
 - d. Diminution or occlusion of the vascular lumen
 - e. Cystatin may co-localize
 - f. Hippocampal vessels are rarely involved and the spinal cord vessels are spared
2. 2/3 of patients demonstrate:
 - a. Fibrinoid necrosis
 - b. Microaneurysms
 - c. Fibrinoid necrosis, the degree of amyloid deposition and the involvement of white matter vessels are associated with ICH

- d. Vasculitis (chronic inflammation) is seen in some patients which causes loss and de-differentiation of smooth muscle cells
- e. Associated pathologies include:
 - i. Senile plaques, neurofibrillary tangles and dystrophic neurons
- f. Leukoencephalopathy:
 - i. Isolated or associated with ICH
 - ii. Associated with A β 40
 - iii. Associated with lacunar infarction and WMH

Neuroimaging**MRI**

1. MRI in 2/3 of patients demonstrate:
 - a. MRI (gradient-echo or susceptibility weighted images) to detect paramagnetic hemosiderin deposits in macrophages (microhemorrhages)
 - i. Cortical lobar location; deep microhemorrhages are associated with hypertension
 - ii. One or more previous ICHs
 - iii. Temporal and occipital lobe predominance
 - iv. Hemorrhage cluster
 - v. Fibrillary A β is the only amyloid that induces MRI T2 changes

Dutch Variant of Hereditary Cerebral Hemorrhage with Amyloidosis**General Characteristics**

1. Autosomal Dominant
2. Mutation at codon 693 of APP gene that replaces the glutamate (E) by a glutamine (Q); E22Q

Clinical Features

1. An aggressive clinical phenotype
2. Recurrent stroke
3. Valvular dementia in the absence of neurofibrillary plaques
4. Cerebral hemorrhage
5. Dementia may develop in the absence of ICH

Pathology

1. Massive amyloid deposition in leptomeningeal and cortical vessels
2. Parenchymal mature plaques are rare but diffuse preamyloid deposits are common – particularly in young patients
3. High ratio of A β 40 to A β 42

Neuroimaging

1. Cortical microbleeds
2. Cortical ICH
3. Increased superficial siderosis
4. Large centrum semiovale perivascular spaces

Flemish Variant**General Characteristics**

1. Described in one family
2. Mutation is in the APP gene at codon 692; A692G

Clinical Manifestations

1. Early onset Alzheimer's disease
2. Intracranial hemorrhage at young age (approximately 40 years) in the cortex

Pathology

1. A β CAA identified in one autopsied patient; diffuse A β deposits were noted but no neurofibrillary tangles and few senile plaques were seen

Neuroimaging

1. Cortical microhemorrhages
2. Ischemic leukoencephalopathy

Familial CAA with APP Mutations*General Characteristics*

1. Variations in the same gene can occur:
 - a. Rare familial forms
 - b. Common sporadic forms of the same disease
2. There is a rare autosomal dominant pattern
3. Most affected families have:
 - i. β amyloid peptide (A β) coding region mutations in the gene for APP
 - ii. Duplications of chromosomal segments containing APP
4. Familial mutations are generally more severe phenotypically and may have an earlier onset
 - i. Common variants often are less severe phenotypically than rare variants
5. Variants of the APP mutations within the A β sequence include:
 - a. "Italian" variant
 - i. E693K
 - b. "Arctic" variant
 - i. E693G
 - c. "Japanese" variant
 - i. E693 Δ
 - d. "Iowa" variant
 - i. D694N
 - e. L705V mutations

Clinical Manifestations

1. Mixed AD/severe CAA phenotype
2. Pure CAA/cerebral hemorrhage phenotype

Pathology

1. The pathology of these mutations is similar to either Dutch or Flemish APP pathology
 - a. Pure CAA/cerebral hemorrhage phenotype or
 - b. Mixed Alzheimer's disease – CAA/cerebral phenotype
2. Italian APP and APP L705V mutations with predominant CAA phenotype with or without recurrent cerebral hemorrhages
 - a. Also similar to Dutch APP mutations

- i. No neurofibrillary tangles in APP L705V carriers or they were minimal and restricted to the archicortex
3. The Arctic and Iowa variant genotypes are similar to the Flemish APP genotype with a mixed AD/severe CAA phenotype without hemorrhagic strokes. The Arctic genotype also demonstrates parenchymal, ring-like plaques
4. Intragenic A β mutations near the β -secretase and γ -secretase sites of APP, such as APP A713T, cause multiple strokes and progressive dementia. The pathology is consistent with severe Alzheimer's disease, CAA and brain infarcts
5. The APP A673V mutations near the β -secretase site of APP are associated with autosomal recessive inheritance and dementia of the Alzheimer's site

Neuroimaging

1. Leukoaraiosis
2. Cortical microhemorrhages
3. Perivascular space enlargement of the cortex and centrum semiovale
4. Cerebral siderosis

Genes with Familial Early Onset Alzheimer's Disease and CAA*General Characteristics*

1. Presenilin-1 on chromosome 14
2. Presenilin 2 on chromosome 1
3. Duplication of APP locus on chromosome 21
4. Volga German families have PSN gene 2 mutation
5. Finnish family (4 generations):
 - a. No gene determined
 - b. ICH and dementia are the clinical expression

Clinical Features

1. Progressive dementia associated with A β vascular deposition (primarily A β (1-40))

Pathology

1. Increase in the extracellular concentration of A β peptides
2. Ratio of A β (1-42) is increased relative to A β (1-40)
3. A β (1-42) is the principal component of amyloid deposits. It has rapid nucleation and aggregation kinetics

Neuroimaging

1. Leukoaraiosis
2. Cerebral microhemorrhages
3. Enlarged perivascular spaces
4. Voxel based tensor imaging reveals diffusion alterations in gray and white matter areas
5. Earliest clinical stages (memory deficit):
 - a. Deficits in the mesial temporal lobe anterior thalamus and mammillary bodies as well as the posterior cingulate gyrus

Hereditary Cystatin C CAA (Icelandic Type; HCHWA-I)*General Characteristics*

1. AD; chromosome 20
 - a. Glutamine for leucine amino acid substitution at codon 68 of the cystatin C gene
 - b. Cystatin C protein is a type II family cysteine protease inhibitor
 - i. Produced by neurons and other cell types

Clinical Manifestations

1. Early onset of cerebral hemorrhage (20 to 30 years of age) at the corticomedullary junction
2. Condition may stabilize: death before 50
3. Infarcts are rare; vascular dementia occurs

Pathology

1. Cystatin C protein is deposited as vascular amyloid in the leptomeninges, cerebral cortex, basal ganglia, brainstem and cerebellum
2. The deposited protein is an N-terminal degradation product of the mutated cystatin C protein
3. Characteristic feature of HCHWA-I is that in addition to CAA:
 - a. Amyloid deposits are seen in lymphoid organs, skin, salivary glands and testes
4. Extensive ICH that occur at varying time periods and amyloid deposition in leptomeningeal and cerebral vessels
5. Involvement of distal microvasculature including capillaries
6. Demyelination is noted; no Alzheimer's disease pathology

Neuroimaging

1. Recurrent lobar cerebral hemorrhage
2. Rare infarcts
3. Leukoaraiosis

Gelsolin Mutation (A Gel) Amyloidosis (Finnish Type)*General Characteristics*

1. Autosomal Dominant; mutations of the gelsolin gene on chromosome 9q32-34
2. G654A and G654T mutations; the G654A is characteristic of the Finnish population
3. Gelsolin is an actin-binding protein
4. A protein subunit isolated from amyloid fibrils

Clinical Features

1. Dementia
2. Mood disorders
3. Dermatologic (sagging facial skin; cutis laxa)
4. Ophthalmologic (lattice corneal dystrophy)

Pathology

1. Gelsolin deposited:

- a. Gray and white matter vessels of the brain and spinal cord
- b. Basement membranes
- c. Amyloid angiopathy in systemic organs
- d. CNS

Neuroimaging

1. Leukoaraiosis
2. Cortical microhemorrhage
3. Small vessel infarction

CAA Due to Deposition of Variant Transthyretin (TTR)*General Characteristics*

1. Familial amyloid polyneuropathy due to:
2. Multiple mutations of the TTR gene located on chromosome 18; AD
3. Amyloid subunit is composed of 60 known variants of the protein transthyretin
4. Involved in the transport of retinol and thyroid hormone
5. Endemic foci in Japan and Portugal

Clinical Manifestations

1. Hemiplegic migraines
2. Dementia
3. Seizure
4. Stroke
5. Visual loss
6. Familial sensorimotor polyneuropathy with or without ANS involvement
7. Vitreous, meningeal and leptomeningeal involvement in some variants
8. CAA

Pathology

1. Amyloid fibrils may be composed of full length TTR concomitantly with C and N terminal degradation fragments
2. TTR fragment derived from the retinal epithelium or choroid plexus
3. Some variants have vitreous, leptomeningeal and meningeal deposition of amyloid transthyretin

Neuroimaging

1. Leukoaraiosis
2. Small vessel stroke
3. Microhemorrhage

CAA in Human Prion Disease*General Characteristics*

1. Prion protein gene is located on chromosome 20
 - a. Disease associated prions recruit normal cellular prion protein and facilitate its conversion to disease associated prion protein isoform (PrP^{Sc})
 - i. Protease resistant protein causes polymerization and amyloid fibril formation

- ii. In general, PrP^{Sc}-CAA is not a feature of prion diseases that include:
 1. Creutzfeldt-Jakob disease (CJD)
 2. Gerstmann-Sträussler-Scheinker syndrome
 3. Fatal familial insomnia
 4. Kuru
 5. Variant CJD
- iii. Rare hereditary disease forms:
- iv. Premature stop codon mutation of PRPN gene (T to G mutation at codon 145) causes:
 1. Extensive PrP-positive CAA with perivascular PrP deposition
 2. Neurofibrillary tangles
- v. Cerebrovascular amyloid deposition
- 3. Neurofibrillary tangle pathology
- 4. Ability to form ion-channel-like structures in cell membranes may be related to its neurotoxicity
- 5. CAA is extensive and involves blood vessels of the leptomeninges, cerebral cortex, white matter, deep gray nuclei, brainstem, cerebellum and spinal cord
- 6. There is astrocytic, microglial and complement activation in both the classical and alternate pathways in amyloid lesions
- 7. Vascular systemic deposits of ABri are found in peripheral tissues

Neuroimaging

1. White matter ischemic change secondary to CAA is widespread

Clinical Manifestations

1. One patient manifested dementia but possibly symptomatology was due to underlying prion disease

Pathology

1. In a pedigree in which there is a T to G mutation at codon 145 which causes an early stop codon (Y145STOP)
 - a. Extensive PrP-positive CAA with parenchymal perivascular PrP deposition noted along with neurofibrillary tangles
 - b. There is frequent co-deposition of PrP^C in A β amyloid plaques in Alzheimer's disease

Hereditary CAAs in Familial British Dementia (BR12 Gene)

General Characteristics

1. FBD (Familial British Dementia)
 - a. Mutation of the BR12 gene located on chromosome 13; autosomal dominant
 - b. Encodes:
 - i. Type II transmembrane protein that undergoes furin-like proteolysis that releases 23-aa C-terminal peptide
 - ii. Interacts with APP and modifies its processing
 - iii. Possible tumor suppressor and has proapoptotic properties
 - iv. Mutation (T to A) of the normal stop codon of the BR12 gene underlies FBD

Clinical Manifestations

1. Clinical onset in the fifth decade; course approximately 10 years
2. Associated with progressive dementia, spasticity and ataxia
3. Rare: clear clinical stroke

Pathology

1. Parenchymal ABri amyloid and parenchymal plaques
2. Widespread ABri-CAA

Danish Familial Dementia (FDD)

General Characteristics

1. 10-nt duplication insertion mutation between codons 255–256 is causative
2. 34aa long C-terminal peptide cleaved from the mutated precursor protein form amyloid fibrils; toxicity may also occur from production of ion-channel structures in cell membranes
3. Mutation in the BRI2/ITM2B gene
 - a. Loss of Br12 protein
 - b. Inhibits processing of A β PP

Clinical Manifestations

1. Cataracts
2. Deafness
3. Ataxia
4. Dementia

Pathology

1. Anatomical distribution of A Dan deposition is similar to FBD
2. Parenchymal lesions are granular, sparsely fibrillary protein deposits
3. CAA is extensive in blood vessels of the leptomeninges, cerebral cortex, basal ganglia, brainstem and cerebellum
4. Vascular involvement occurs in other organs

Neuroimaging

1. Generalized widespread vascular changes in the white matter similar to ABR12

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)

General Characteristics

Genetics

1. Mutation of the NOTCH 3 gene; chromosome 19
2. Expressed only in arterial smooth muscle cells

3. Mutations are in exon 3 and 4 (70%) which encodes a transmembrane receptor with epidermal growth factor repeats
4. Regulates differentiation and maturation of vascular smooth muscle cells

Clinical Features

1. Migraine with aura starting between 20 to 40 years of age may be the initial presentation
2. Cerebral ischemic events supervene between 4th and 5th decade associated with behavioral changes and cognitive dysfunction
3. Dementia is apparent between age 50 to 60
4. Approximately 50% of patients suffer atypical migraine auras that include basilar hemiplegia or long duration. A few suffer coma
5. 60 to 85% of patients suffer TIAs or strokes. 2/3 of ischemic events are classic lacunar strokes. TIAs and strokes may occur in the absence of classical risk factors
6. 5 to 10% of patients have seizures that may be focal or generalized
7. Apathy is common while aphasia, apraxia or agnosia is rare
8. Dementia is associated with corticospinal tract signs, gait disturbance and urinary incontinence. Pseudobulbar palsy is demonstrated in approximately 50% of patients

Pathology

1. Diffuse hemispheric demyelination with sparing of U-fibers and periventricular and centrum semiovale predominance
2. Lacunar infarction is noted in the thalamus and basal ganglia
3. Deep infarcts and dilated Virchow-Robin spaces are frequent
4. Walls of cerebral and leptomeningeal arterioles are thickened
5. Granular material within the media (glycoproteins) while the endothelium is spared
6. Smooth muscle cells are swollen and degenerated
7. Dense granular osmophilic deposits are seen in the media close to the cell membranes of smooth muscle cells
8. The dense granular osmophilic deposits are seen in the media of arteries in internal organs (spleen, liver, and kidney) as well as skin and muscle

Neuroimaging

1. MRI reveals widespread T2-weighted signal in white matter with focal hyperintensities in the basal ganglia, thalamus and brainstem
2. Younger patients have a periventricular predominance
3. External capsule and anterior temporal lobe lesions are distinctive
4. Corpus callosal lesions occur. Pontine lesions predominate in the brainstem

5. Lacunar lesions and enlarged Virchow-Robin spaces are prominent
6. Gradient-echo sequences detect microhemorrhages in 30 to 50% of patients

Cerebral Autosomal Recessive Angiopathy with Subcortical Infarction and Leukoencephalopathy (CARASIL)

General Characteristics

1. More prominent in Asian and Japanese populations
2. Mutations of the HTRA1 gene
 - a. A serine peptidase/protease

Clinical Features

1. Ischemic stroke (ictal events) or stepwise neurologic deterioration
2. Premature baldness and spondylosis and disc disease

Pathology

1. Vascular fibrosis and overgrowth of the extracellular matrix
2. Intense arteriosclerosis of small penetrating arteries (without granular osmophilic material or amyloid as is seen in CADASIL)
3. Intimal thickening
4. Dense collagen fibers
5. Loss of vascular smooth muscle
6. Hyaline degeneration of the media
7. Putative mechanism
 - a. Failure to repress TGF-beta signaling
 - b. Increased TGF-beta found in cerebral small vessels along with fibronectin and versalan

Neuroimaging

MRI

1. Multiple lacunar infarctions of the basal ganglia and thalamus
2. Diffuse white matter leukoencephalopathy

Retinal Vasculopathy with Cerebral Leukodystrophy (RVCL)

Overview

The RVCL spectrum presents primarily as small vessel disease. Three variants that have been mapped to chromosome 3p21 are: Hereditary Retinal Vasculopathy (HRV), Cerebroretinal Vasculopathy (CRV) and Hereditary Endotheliopathy, Retinopathy and Nephropathy (HERNS).

An infantile syndrome that is similar but does not map to 3p21 is: Hereditary Infantile Hemiparesis with Arteriolar Retinopathy and Leukoencephalopathy (HIHARL).

Cerebroretinal Vasculopathy (CRV), HERNS and Hereditary Retinal Vasculopathy (HRV)

General Characteristics

1. Genetics
 - a. All three diseases are linked to a locus on chromosome 3p21
 - b. Autosomal Dominant
2. Causative gene mutations of TREX 1
 - a. Encodes a 3'-5' DNA repair exonuclease
 - b. Frame shift mutation
3. Other diseases with TREX-1 mutations that have clinical similarity but distinct clinical features:
 - a. Aicardi-Goutières syndrome (AGS)
 - b. Familial Chilblain Lupus (FCL)
 - c. Systemic Lupus Erythematosus (SLE)
4. The truncated protein from the mutation retains exonuclease activity but loses perinuclear localization
5. Hereditary systemic angiopathy (HSA) has recently been described and is also suggested to be on the retinal vasculopathy with cerebral leukodystrophy spectrum

Clinical Manifestations

1. Middle age at onset (4th–5th decade)
2. Predominant CNS involvement
3. TIA, stroke, focal motor and sensory deficits
4. Depression
5. Headaches
6. Cognitive dysfunctions
7. Decreased renal function
8. G.I. bleeding
9. Increased alkaline phosphatase
10. Migraine
11. Raynaud's Phenomena
12. 100% mortality in 5–10 years due to neurologic deficits

Neuropathology

1. Coagulative necrosis secondary to obliterative vasculopathy
2. Minimal inflammatory infiltrate
3. Fronto-parietal cortex motor involvement; lesions also occurs in the basal ganglia, cerebellum and pons
4. One third of patients have hepatic and renal involvement
5. Thickening and reduplication of the retinal capillary basal lamina

Neuroimaging

1. Retinal fluorescein angiography:
 - a. Capillary drop-out (macular region; decreased central vision)
 - b. Prominent juxtafoveolar capillary obliteration and telangiectasia
2. Lesions are most prominent in the fronto-parietal lobes
 - a. Lesions enhance

Differential Diagnosis of RVCL

1. Variants of RVCL with linkage to 3p21 (3p21 mutations)
 - a. CRV (Cerebral Retinal Vasculopathy)
 - b. HVR (Hereditary Vascular Retinopathy)
 - c. HERNS (Hereditary Endotheliopathy Retinopathy with Nephropathy)
 - i. Brain, kidney, GI tract and skin are involved
 - ii. Pathology (by electron microscopy) reveals multilaminated vascular basement membrane
 - d. HIHARL (Hereditary Infantile Hemiparesis with Arteriolar Retinopathy and Leukoencephalopathy)

HIHARL (Hereditary Infantile Hemiparesis with Arteriolar Retinopathy and Leukoencephalopathy)

General Characteristics

1. Not linked to 3p21

Clinical Manifestations

1. Migraine with aura
2. Hemiparesis
3. Retinal hemorrhage and tortuosity

Pathology

1. Vascular endothelial dysfunction
2. Possible increased susceptibility to decreased cerebral blood flow from cortical spreading depression

Neuroimaging

1. Cortical microbleeds
2. Dilatation of perivascular spaces

Collagen 4A1 and A2 Mutations

General Characteristics

1. Type IV collagen is pivotal for the structural integrity and function of the basement membrane:
 - a. Which surrounds vascular smooth muscle cells in the media
 - b. COL4A1 is the most abundant form of type IV collagen
 - c. COL4A2 (collagen IV alpha 2 chain) forms heterotrimers with COL4A1; an obligatory protein partner of COL4A1
 - d. Gene is localized on chromosome 13q

Clinical Manifestations

1. COL4A1 mutations:
 - a. Ocular, renal, muscular defects in addition to CNS vasculopathy
 - b. Ocular abnormalities:
 - i. Cataracts (congenital or juvenile onset)
 - ii. Retinal arteriolar tortuosity and hemorrhages
 - iii. Juvenile onset glaucoma
 - iv. Axenfeld-Rieger syndrome
 1. FOXC1 (eye) and PITX2 (eye and systemic) genes are mutated

2. Anterior segment dysgenesis with glaucoma
3. Optic nerve dysgenesis
4. Renal cysts and renal agenesis

Neurologic Manifestations

1. Sporadic and recurrent intracranial hemorrhages
2. Porencephaly from germinal matrix hemorrhages (COL4A2 > COL4A1)
3. Infantile hemiplegia

Pathology

1. Focal interruptions or expanded and thickened fragmented basal membranes of capillaries

Neuroimaging

MRI

1. Diffuse or periventricular leukoencephalopathy and calcifications
2. Lacunar infarctions both supra and infratentorial areas

Hereditary Angiopathy with Nephropathy, Aneurysms and Muscle Cramps (HANAC)

General Characteristics

1. Mutation of COL4A1 gene; chromosome 13q
 - a. CB3 encodes the integrin binding site

Clinical Manifestations

1. Multiple and complex carotid siphon aneurysms
2. Renal cysts, cramps or elevated CPK; retinal arteriolar tortuosity
3. Cerebral hemorrhages
4. Lacunar infarction
5. Cerebrovascular lesions are often asymptomatic

Pathology

1. Skin biopsy
 - a. Alterations of the basement membrane at the dermoepidermal junction
 - b. Expansion of extracellular matrix between smooth vascular cells in the arteriolar wall
 - c. Multi-lamination, thickening of basement membranes
2. White matter changes affecting subcortical, periventricular and pontine regions

Neuroimaging

MRI

1. Leukoaraiosis
2. Subcortical microbleeds
3. Lacunar infarction
4. Dilated perivascular spaces
5. Highest lesion load in the frontal and parietal white matter

Pontine Autosomal Dominant Microangiopathy and Leukoencephalopathy (PADMAL)

General Characteristics

1. Large German kindred evaluated as the basis of the syndrome
2. Mutated gene not determined

Clinical Manifestations

1. Age at onset (15–77 years)
2. Pontine lacunar infarctions
3. Generalized cognitive decline
4. Gait disorder
 - a. Broad based; short swing phase; slow velocity

Pathology

1. Sclerotic index demonstrates:
 - a. Subcortical white matter affected to a greater degree than gray matter
 - b. Glucose transporter (GLUT-1) protein immunoreactivity (indicates capillary degeneration in white matter) is affected
 - c. Frontal lobe is most the severely affected
 - d. Density of COL IV immunoreactivity is increased

Neuroimaging

MRI

1. Pontine lacunar infarcts
2. Subcortical and periventricular leukoencephalopathy
3. Temporal lobe involvement in 16% of patients
4. Cerebral microbleeds in 16% of patients

MRA

1. No atherosclerotic changes

Swedish Hereditary Multi-Infarct Dementia (SHMID)

General Characteristics

1. Gene has not been characterized

Clinical Manifestations

1. Recurrent lacunar infarction
2. Cognitive deficits
3. Gait disorder

Pathology

1. Sclerotic index not as severe as CADASIL, HERNs or PADMAL
 - a. No osmophilic material in skin biopsy or autopsy material

Neuroimaging

MRI

1. Lacks the hyperintense signals detected in the anterior temporal pole and external capsule as noted in CADASIL

Hereditary Vascular Leukoencephalopathy Mapping to Chromosome 20q13

General Characteristics

1. Two sisters and 21 relatives underwent clinical and genetic testing; pathological data was examined from one patient
2. Mutation was mapped to chromosome 20q13

Clinical Manifestations

1. Five of 14 patients were symptomatic; 9 of 14 demonstrated white matter lesions but were asymptomatic (ages 26–60 years)
2. Gait disturbance
3. Stroke
4. Cognitive decline
5. Transient movement disorder
6. Progressive and age related natural history

Pathology

1. Cerebral arteriopathy affecting small pre terminal arterioles
2. Pathology is more prominent in the hemispheres than the brainstem

Neuroimaging

MRI

1. Symmetric white matter hyperintensities of the hemispheres and brain stem

Summary of Monogenetic Causes of Small Vessel Disease

1. CADASIL
2. CARASIL
3. CAA
 - a. Dutch
 - b. Icelandic
 - c. Kindred founder mutations
 - d. Other mutations
4. Retinal vasculopathy with cerebral vasculopathy (RVCL)
 - a. Hereditary retinal vasculopathy (HRV)
 - b. Hereditary endotheliopathy, retinopathy and nephropathy (HERNS)
 - c. Cerebroretinal vasculopathy (CRV)
 - d. Hereditary infantile hemiparesis with arteriolar retinopathy and leukoencephalopathy (HIHARL)
5. COL4A1/COL4A2 mutations
 - a. Hereditary angiopathy with nephropathy aneurysm and muscle cramps (HANAC)
 - b. Hereditary porencephaly from germinial matrix hemorrhage (COLA2 mutation)
6. Swedish hereditary multi infarct dementia (SHMID)
7. Hereditary Vascular Leukoencephalopathy mapping to chromosome 20q13

Fabry's Disease

General Characteristics

1. X-linked disorder of glycosphingolipid metabolism:
 - a. Enzyme deficiency of a lysosomal alpha-galactosidase A that leads to:
 - i. An accumulation of neutral glycosphingolipids – predominantly globotriaosylceramide in the lysosomes of endothelial and smooth muscle cells in blood vessels
 - ii. Common polymorphisms of angiotensinogen (AGT), AGT promoter and angiotensinogen II receptor type I (AGTRI)
 1. AGT promoter and AGTRI genotypes are noted in Fabry's phenotypes in .6% of high risk populations
2. Prevalence 1:40,000 males
3. Heterozygotes present with no symptoms or a milder disease
4. Heterozygous females:
 - a. Asymptomatic or a milder disease phenotype
 - b. Occasionally they are as symptomatic as males
5. Cerebrovascular manifestations are common in both hemizygote and symptomatic heterozygote groups
 - a. 4% of cryptogenic strokes may have mutations in the α -galactosidase A gene

Clinical Manifestations

1. Early in the disease course:
 - a. Episodic crises of severe neuropathic pain
 - i. Precipitated by exercise, fever or increased ambient temperature
 - ii. Minute to hour duration
 - iii. Primarily acroparesthesias
 - b. Heat intolerance
 - i. Autonomic dysfunction with anhidrosis (infiltration of ceramide trihexoside in the autonomic ganglia and similar infiltration of 1 μ autonomic fibers to sweat glands)
2. Heterozygous males
 - a. Angiokeratomas (cherry red papules) are seen in the periumbilical area, extensor surfaces of elbows, knees and genitals (bathing suit distributions)
 - b. Corneal and lenticular opacities
 - c. Dilatation and tortuosity of conjunctival vessels
 - d. Retinal vessel abnormalities
 - e. Hypohidrosis (with heat intolerance)
 - f. Cardiac dysfunction
 - g. Renal failure
3. Heterozygote females
 - a. Lumbosacral degeneration
 - b. Some patients are asymptomatic
 - c. Some signs/symptoms similar to male patients

Cerebrovascular Disease

1. Male hemizygotes
 - a. Ischemic strokes in the fourth decade

- b. Anterior and posterior circulation involvement; posterior circulation more frequently involved than anterior
- c. Small vessel disease
- d. Cause of vascular dementia for patients less than 65 years old
2. Heterozygote women
 - a. Cerebrovascular symptoms a decade later than males
 - b. 50% involvement in vertebrobasilar system; 10% carotid involvement
 - c. Headaches are seen more commonly in females than males
 - d. Central retinal vein occlusion
3. Greater involvement of posterior circulation whose putative mechanisms are:
 - a. Vertebrobasilar dolichoectasia
 - b. Thickening and luminal compromise of medium and small arteries
 - c. Deep small cerebral infarcts
4. Cardiogenic embolism
 - a. Coronary artery disease (left ventricular wall dysfunction)
 - b. Valvular heart disease (mitral valve)
 - c. Mitral valve prolapse
 - d. Hypertrophic cardiomyopathy (especially in heterozygote women)
 - i. Often associated with atrial fibrillation
 - ii. Occurrence in women greater than men
5. Carotid artery atherosclerotic plaque
 - a. Less than controls
 - b. Greater intima to media thickness
6. Orthostatic hypotension due to autonomic nervous system dysfunction
7. Prothrombotic state:
 - a. Activation of platelets by endothelial dysfunction due to deposition of glycosphingolipids
8. Endothelial cell dysfunction with increased:
 - a. Soluble intercellular adhesion factors-1
 - b. Vascular cell adhesion molecule-1
 - c. P-selection
 - d. Plasminogen activator inhibitor
 - e. Integrin CD11b
 - f. Decreased thrombomodulin
9. Approximately 35% of patients have a factor V Leiden mutation
10. Intrinsic vascular abnormalities:
 - a. Down-regulation of nitric oxide pathway
 - b. Increased oxidative stress which leads to:
 - i. Accelerated atherosclerosis
 - ii. Vasodilatation
11. Intracranial arterial dolichoectasia causes:
 - a. Neurovascular compression syndromes
 - b. Triventricular hydrocephalus
 - c. Isolated III, V, VIII, XIIth nerve palsy by compression from the basilar or vertebral arteries
 - d. Cranial Nerve II compression from dolichoectatic supraclinoid carotid arteries

Pathology

1. Infarcts of:
 - a. Superficial hemispheric pial arteries
 - b. Small deep perforating vessels
 - c. Brainstem and cerebellum
2. Rare intracerebral hemorrhage
3. Narrowing of lumen secondary to glycosphingolipid deposits in lysosomes of both endothelial cells and smooth muscle of the arterial wall
4. Putative mechanism:
 - a. Deposition of glycosphingolipids in the lysosomes of smooth muscle of arterial walls
 - b. Possible cause of ICH (loss of structural integrity of vessel walls)
 1. Hypertension from concurrent vessel disease
 2. Both hemi and heterozygotes

Neuroimaging

MRI

1. Superficial territorial and deep perforating artery infarction of the hemispheric brainstem and cerebellar circulations
2. Dolichoectasia of the basilar and vertebral arteries
3. Small vessel disease pattern in patients older than 54 years
4. Approximately one third of younger patients may have no lesions

MRS (Magnetic Resonance Spectroscopy)

1. NAA/creatine and phosphocreatine were decreased
 - a. Suggestive of neuronal loss

Clinical Differential Diagnosis of Monogenic Small Vessel Disease

CADASIL

1. Severe and clearly genetic (AD)
2. Migraine headaches, behavioral disorders and cognitive deficits prominent in addition to stroke
3. MRI: extensive leukoencephalopathy: extreme capsule and anterior temporal pole are involved

CARASIL

1. Autosomal recessive
2. Early alopecia, disc disease and prominent lumbar spondylosis
3. More prominent in Asian populations (Japanese)
4. Lacunar infarctions prominent in basal ganglia and thalamus

Fabry's Disease

1. Severe acroparesthesias and neuropathy
2. Bleeding following minor surgical procedures
3. Heat intolerance (decreased sweating)
4. Kidney and heart involvement
5. MRI: pulvinar lesions as well as stroke
6. Characteristic angiomas in the genital areas

Congophilic Angiopathy (CAA)

1. Genetic and sporadic forms
2. Lobar hemorrhages that are superficial and may be multiple
3. Cerebral microbleeds are prominent in the cortex
4. Severe leukoencephalopathy with cortical microbleeds
5. May have TIA presentation

Retinal Vasculopathy with Cerebral Leukoencephalopathy

1. All variants have severe retinal arterial tortuosity and some with concomitant retinal artery obliteration and central visual loss
2. Secondary glaucoma (following hemorrhage)
3. Kidney as well as cerebral and ocular vessel involvement

COL4A1/A2 Mutations

1. Porencephalopathy (familial) is most suggestive of COL4A2
2. Migraine and Raynaud's phenomenon
3. Gastrointestinal bleeding
4. HANAC – almost pathognomonic carotid siphon aneurysms, muscle cramps
5. Severe ocular deficits including anterior segment defects and juvenile cataracts

PADMAL

1. Pontine lacunar infarctions with generalized cognitive decline
2. No atherosclerotic blood vessel changes

Summary of Pathologic Involvement in Monogenetic Small Vessel Disease by the Sclerotic Index

1. The sclerotic index measures:
 - a. Density of collagen IV immunoreactivity (basement membranes of blood vessels)
 - b. The number of perivascular macrophages
 - c. Glucose transporter-1 (GLUT-1) protein immunoreactivity (indicates capillary degeneration); white matter affected more than gray matter
2. Cortical Sclerotic Index of Severity of Small Vessel disease
 - a. CADASIL > HERNs > PADMAL > Swedish hMID > sporadic SVD
3. Basal Ganglia Sclerotic Index:
 - a. CADASIL > HERNs > Swedish hMID > PADMAL > sporadic SVD

General Characteristics and Definitions for Small Vessel Disease

1. Small Vessel disease cause:
 - a. Lacunar infarcts
 - b. White matter hyperintensities (WMH)
 - c. Microinfarction (smaller than lacunes)
 - d. Dilatation of perivascular spaces
 - e. Microbleeds

2. Small Vessel disease often occurs in association with atherosclerosis and affects large and medium-sized arteries
 - a. By intimal proliferation and accumulation of lipids and cholesterol within the vessel wall
 - b. Plaques form at bifurcations of arteries and in areas of blood flow derived shear stress (stenosis of the lumen)
 - c. Plaques rupture occurs from:
 - i. Local thrombosis (primarily due to endothelial dysfunction)
 - ii. Emboli from both cholesterol plaque material and fibrin-platelet clots
3. Vessel wall changes of small artery arteriosclerosis occur in 200–800 μm sized blood vessels
 - a. Similar to atherosclerosis but the vessels do not calcify
4. Lipohyalinosis:
 - a. Occurs in arteries of 30–300 μm size
 - b. Asymmetric fibrosis and hyalinosis associated with foam cells and accumulation of blood derived lipids and proteins within the vessel wall
5. Arteriolosclerosis
 - a. Occurs in arterioles between 50–150 μm in diameter
 - b. A concentric hyaline thickening of the vessel wall with stenosis
6. White matter hyperintensities (most easily seen on MRI) and associated with sporadic and familial SVD:
 - a. Most common in the elderly and may be seen frequently in normal subjects
 - b. White matter changes are characterized by:
 - i. Demyelination axonal loss
 - ii. Astroglisis
 - iii. Often severe in the deep white matter
 - iv. Spares U-fibers
 - v. Associated with microglial activation
 - c. White matter lesion progression:
 - i. Growth of existing lesions
 - ii. WMH are surrounded by regions of milder injury ('penumbra')
 - iii. Gradual spatial spreading
 - iv. New lesions accrue in approximately 20% of patients in addition to growth of prior lesions
 - d. Study of CADASIL patients (pure SVD) reveals that:
 - i. Lacunes develop at the edge of white matter hyperintensities along the course of perforating vessels
7. Leukoaraiosis
 - a. Age related (as well as disease caused) white matter hyperintensities
 - i. Major risk factors are age and hypertension
 - b. Pathology:
 - i. Demyelination/axonal loss/gliosis/infarcts
 - ii. Fibrohyalinosis of small vessels (30–150 μm) in size
 - iii. Venous collagenosis
8. Microinfarcts
 - a. Smaller than lacunar infarcts (1 mm or less)

- b. In SVD occurs in the white matter
- c. In CAA they occur in the cortex
- d. Watershed microinfarcts:
 - i. Occur in hyper perfused areas between two vascular territories

Lacunar Stroke

Overview

Lacunes are small ovoid lesions 1–2 mm in size noted in deep nuclear gray matter of the basal ganglia and thalamus as well as the internal capsules, centrum semiovale and pons. They are found in the setting of poorly controlled diabetes and hypertension. They are caused by fibrinoid necrosis of the endothelium and adventitia of the single perforating arterioles. The infarct is limited to the territory of deep perforators and is caused by in situ infarction. The process may also be caused by atheromatous occlusion of the mouth of these blood vessels. If a series or a group of perforators are involved simultaneously emboli are suspected as causal (this most often occurs in the lenticulostriate territory).

Discrete clinical syndromes are noted with infarctions of these perforators which outline their territory and allow anatomic localization.

Involvement of arm, face, and leg suggests lacunar infarction of the middle 1/3 of the posterior limb of the internal capsule. Genu involvement is suggested by more face than arm involvement and severe dysarthria. The posterior 1/3 of the capsule may be selectively involved with hemisensory numbness. Occasionally, a single extremity may become weak from involvement of the medullary stria arteries that perfuse the centrum semiovale. The motor and sensory fibers are separated in the deep fibers of the centrum semiovale. The dysarthria clumsy hand syndrome occurs from posterior ventral 1/3 pontine infarction in which the corticobulbar fibers, speech and arm fibers are closely opposed. Ataxic hemiparesis suggests pontine lacunar involvement at the midpontine level.

Lacunar infarctions rarely ever are associated with headache, visual field cut or aphasia. Pure motor, pure sensory and mixed deficits are common. There are no cortical sensory or behavioral manifestations which differentiates these from pial artery strokes. Pure motor hemiparesis with a IIIrd nerve pattern (Weber, Benedict; Claude's and Nothnagel's) places the lesion in the midbrain. Rarely hemiballisms occurs from lacunar infarction of the subthalamic nucleus due to paramedian thalamic involvement. Lacunes of basilar artery territories are suggested by dizziness, diplopia, and intranuclear ophthalmoplegic without weakness.

Arterial Territories Involved with Lacunar Stroke

1. Involvement of the territory of one single perforating arteriole

2. <1.5 cm lesion on CT or MRI; (ovoid in shape)
3. Infarct is limited to the territory of the deep perforators
4. Caused by in situ small vessel disease
5. Infarcts limited to the territory of deep perforators may occur with:
 - a. Cardiac emboli
 - b. Ipsilateral internal carotid artery stenosis or occlusion
6. Diabetes is a major risk factor for lacunes
7. The most suggestive clinical syndrome for lacunar infarction:
 - a. Pure motor hemiparesis with face, arm and leg involvement
8. Arterial networks that supply subcortical territories:
 - a. Deep perforating branches form the ACA
 - i. Recurrent artery of Heubner (A2)
 - ii. Direct anterior lenticulostriate branches
 - b. Deep perforating branches from the anterior choroidal artery
 - c. Thalamic arteries from P1 and P2 segments
 - i. Interpeduncular (top of the basilar)
 - ii. Thalamoperforate
 - iii. Thalamogeniculate
 - iv. Posterior choroidal artery
 - v. Tuberothalamic artery (from the posterior communicating artery) These arteries are perforators, but have collateral branches and are not terminal branches
 - d. White matter medullary arteries
 - i. Originate from the superficial (pial) branches of the MCA > ACA > PCA
 - ii. 2–5 cm long
 - iii. Selective territories
 - iv. No collaterals
 - v. Subserve the centrum semiovale
 - vi. Do not anastomose with the deep perforators (lenticulostriate arteries)
 - e. Cortical arteries with subcortical territories that supply:
 - i. U-fibers
 - ii. Extreme capsule
 - iii. External capsule
 - iv. Claustrum
 - f. Most commonly found lacunar strokes occur in the:
 - i. Centrum semiovale
 - ii. Basal ganglia
 - iii. Thalamus
 - iv. Midbrain
 - v. Pons
 - vi. Medulla
 - g. Lenticulostriate territories (M1 and M2)
9. Infarction in these territories are often not lacunar (i.e., from one perforator) but may be secondary to distal field ischemia (carotid stenosis) or cardiac thromboembolism

Epidemiology of Lacunar Stroke

1. Lacunes – 20–30% of ischemic strokes
2. Blacks and Hispanics have twice the incidence of whites
3. No increase in HCVD, DM, cigarette smoking, hypercholesterolemia or TIA compared to other ischemic strokes
4. Some series a 40–50% incidence of ischemic heart disease
5. If a specific lacunar syndrome is present: there is an 87% chance the patient has suffered a lacunar stroke
6. Predictive value for lacunar stroke:
 - a. Pure sensory stroke 100%
 - b. Highly correlated
 - i. Ataxia, hemiparesis
 - ii. Sensorimotor stroke
7. Ataxic hemiparesis can occur from: corona radiata, pons, basal ganglia or thalamus infarction
 - a. Pontine site is the most frequent
8. 25% of lacunes are due to a non-lacunar mechanism
 - a. Atherosclerosis
 - b. Cardiac source of emboli
 - i. 10–15 perforators are affected simultaneously
 - ii. Larger size

General Characteristics

1. Lacunes are the result of small vessel disease and are usually ovoid lesions
 - a. Minimal cerebral cortex involvement (occurs with sensorimotor lesions)
 - b. Imaging evidence of a lesion less than 15 mm
 - c. Often concomitant hypertensive cardiovascular disease or diabetes mellitus
 - d. Overlap both in risk factor profile and clinical symptoms with large artery disease
 - e. Lacunes are defined as occlusions of a single perforating artery:
 - i. Large lacunae are 15–20 mm in diameter
 - ii. Small lacunae are 3–4 mm
 - f. Generally, large lacunes have more symptoms; small lacunes are symptomatic if in a critical location of a sensory or motor tract
2. If a specific clinical syndrome is present there is an 87% chance the patient has suffered a lacunar stroke
3. Some series a 40–50% incidence of concomitant ischemic heart disease
4. Predictive value for lacunar stroke:
 - a. Pure sensory stroke 100%
 - b. Highly correlated:
 - i. Ataxic hemiparesis
 - ii. Sensorimotor stroke
5. 25% of lacunes are due to a non-lacunar mechanism
 - a. Atherosclerosis
 - b. Cardiac source of emboli
 - i. 10–15 perforators are occluded
 - ii. Larger size than those from small vessel disease
6. May have stuttering course over 2–3 days

7. No cortical sensory loss
8. May have behavioral changes; minimal cognitive deficits
9. No visual field deficit

Clinical Syndromes*Pure Sensory Stroke***General Characteristics**

1. Smallest of the symptomatic deep infarcts
2. Approximately 6% of lacunar strokes
 - a. The most common lacunar syndrome
 - i. 45–57% in 3 major stroke registries
 - ii. Approximately 9.5% of pure sensory strokes are not due to lacunar infarction

Clinical Manifestations

1. Numbness of a single extremity
2. Rarely, if larger in the thalamus, numbness of a portion of the hemibody (VLP nucleus) or rarely the face (VPM)
3. Nociceptive deficits
4. Proprioceptive deficits
5. Face, arm and leg (83% of pure sensory stroke)
6. Cheiro-oral-pedal syndrome
 - a. 80% are caused by lacunar stroke
7. Face and arm (7%)
 - a. 35% of this pattern are caused by lacunar stroke
8. Arm and leg (8%)
9. Partial pure sensory deficits
 - a. Isolated oral sensory loss with restricted acral sensory loss

Pathology

1. Territories involved:
 - a. Internal capsule (posterior one third of the posterior limb)
 - b. Ventral posterolateral nucleus (VPL) and ventral posteromedial nucleus (VPM) thalamic nuclei
 - c. Rostral pontine tegmentum that involves:
 - i. Medial lemniscus
 - ii. Lateral spinothalamic tracts
 - d. Anterior thalamic radiations
 - e. Anterior limb of the internal capsule
 - i. Facial brachial pattern of weakness
 - f. Leg weakness – the lesion is more posterior in the internal capsule
 - g. Distal upper limb – pontine infarction
 - h. Medullary pyramid – flaccid hemiparesis that spares the face
2. Pathologic mechanisms
 - a. Occlusion (atheroma at ostium) of deep perforating end artery
 - b. Lipohyalinosis of perforator
 - i. Fibrinoid necrosis of media of the perforating arteriole
 - c. Embolus to a group of perforators
 - d. Basilar artery branch disease in pontine infarction due to atherosclerosis of the basilar artery

Neuroimaging

1. Small ovoid lesions 1 to 3 mm in size in the expected clinical territory
2. Large (>15 mm lesion) more likely embolic

*Ataxic Hemiparesis***General Characteristics**

1. Ataxic hemiparesis accounts for 9 to 18% of lacunar strokes

Clinical Manifestations

1. Hemiparesis or cortical spinal signs associated with ipsilesional cerebellar signs
 - a. Lesion topology
 - i. Lesions in the white matter of the corticospinal tract (motor cortex to pontine nuclei)
 - ii. Afferents to the middle cerebellar peduncle or cerebellar afferent zone for proprioception
 - iii. Thalamic cerebellar nuclei (proprioceptive receiving area)
 - iv. 3a of SI in the sensory cortex that projects back to MI. There are subtle differences with lesions at each level of this pathway
2. Partial hemiparesis, nystagmus, dysarthria suggests an infratentorial lesion
3. No facial involvement, dysarthria or sensory loss suggests a cortical lesion
4. Painful ataxic hemiparesis
 - a. Edema or ischemia of the internal capsule
 - b. Pain and ataxia greater than weakness
 - i. Lesion in VPL of the thalamus
 - ii. Cerebellar nuclei: a zone that receives proprioceptive afferent fibers (VL, area X near the centralis lateralis intralaminar nucleus)
 - c. Frontal infarction associated with cerebellar diaschisis (opposite side of the infarction and demonstrated by SPECT scan)

Pathology

1. Lipohyalinosis or fibrinoid necrosis of arterioles
2. Lesion topology
 - a. Internal capsule – 39%
 - b. Thalamus – 13%
 - c. Corona radiata – 13%
 - d. Lentiform nucleus – 8%
 - e. Cerebellum – 4%
 - f. Frontal cortex – 4%

Neuroimaging*MRI*

1. Ovoid lesions with low signal intensity on T2-weighted images and high signal intensity on T2-weighted sequences in clinically relevant areas

*Sensorimotor Stroke Syndrome***General Characteristics**

1. This subtype may be classified by the associated sensory deficits in addition to the motor deficits
 - a. All sensory modalities affected
 - b. Solely nociceptive deficits
 - c. Only proprioceptive deficits
 - d. Involvement of only one limb

Pathology

1. Fibrinoid necrosis (hypertension)
2. Lipohyalinosis (lipid dysregulation)
3. Atherosclerosis (atheroma at the origin of the perforating vessel)
4. Territories involved:
 - a. Thalamic capsule component of the corona radiata and putamen
 - b. Ventral posterior lateral thalamus and internal capsule
 - c. Cortical infarction anterior to the Rolandic fissure
 - d. In the Stroke Data Bank Study, lesions were seen in:
 - i. Posterior limb of the internal capsule – 30%
 - ii. Corona radiata – 22%
 - iii. Genu of the internal capsule – 7%
 - iv. Thalamus – 9%
 - v. Anterior limb of the internal capsule – 6%

Neuroimaging

1. MRI/FLAIR
2. DWI
3. Tractography and magnetic transfer imaging
4. Define
 - a. Small strategic infarction
 - b. Degree of lacunar involvement

*Pure Motor Stroke***General Characteristics**

1. The most frequent lacunar syndrome
2. 85% of pure motor strokes are caused by a lacunar infarct
3. 28% have an associated dysarthria

Clinical Manifestations

1. Contralateral hemiparesis
2. Brachiorural distribution
3. Facial weakness with dysarthria
4. Dysarthria – lingual weakness
5. Isolated limb paresis
6. Bilateral
7. No associated cognitive, sensory or visual symptoms

Pathology

1. Stroke topology
 - a. Anterior and mid internal capsule
 - b. Pons
 - c. Cerebral peduncle
 - d. Corona radiata

- e. Centrum semiovale
- f. Medulla
- g. Bilateral capsule
- h. Medullary pyramids
- i. Motor knuckle of the cortex
- 2. Fibrinoid necrosis, lipohyalinosis and atheroma. Embolus (rare)

Neuroimaging

- 1. MRI/FLAIR
- 2. DWI
- 3. Tractography

Dysarthria Clumsy Hand Syndrome

General Characteristics

- 1. Isolated acute-onset dysarthria is an uncommon presentation of transient ischemic attack or stroke
 - a. Occurs in less than 1.3% of confirmed strokes

Clinical Manifestations

- 1. Dysarthria and clumsiness of one hand with or without central facial paralysis
- 2. Dysphagia
- 3. Tongue deviation

Pathology

- 1. Stroke topology
 - a. Upper basis pontis
 - b. Corona radiata
 - c. Genu of the internal capsule
- 2. Fibrinoid necrosis, lipohyalinosis and atheroma at the origin of perforating small vessels

Neuroimaging

- 1. MRI/FLAIR sequences
- 2. DWI
- 3. Tractography

Clinical Summary of Described Lacunar Syndromes

- 1. Pure sensory stroke (PSS) (primarily thalamus)
- 2. Pure motor hemiparesis
 - a. Corona radiata
 - b. Middle internal capsule
 - c. Cerebral peduncle (medial 3/5)
 - d. Ventral pons
 - e. Medullary pyramidal
 - i. At decussation with cruciate pattern (ipsilateral arm; contralateral leg)
- 3. Ataxic hemiparesis (AH) (pontine gray – MCP and descending CST)
- 4. Dysarthria clumsy hand syndrome (pons)
- 5. Pure motor hemiparesis sparing the face (farther posterior in the middle 1/3 of the posterior limb of the internal capsule)

- 6. Mesencephalic; decreased upgaze (Nothnagel's syndrome)
 - a. Rostral interstitial nucleus of the medial longitudinal fasciculus
 - b. Posterior commissure
- 7. Thalamic dementia (DM, AV nuclei)
- 8. PMH with horizontal gaze palsy – lower 1/3 of pons, PPRF (para pontine reticular formation)
- 9. PMH with IIIrd nerve (Weber's syndrome): midbrain
- 10. PMH with IIIrd nerve and ataxia (Claude's syndrome): midbrain
- 11. PMH with IIIrd and movement disorder (Benedict's syndrome): midbrain
- 12. PMH with VIth nerve palsy (Ramon's syndrome): pons
- 13. PMH with confusion (brainstem RF; thalamic AV/DM nuclei)
- 14. Sensorimotor stroke (thalamic capsular)
- 15. Hemiballism – (STN; paramedian mesencephalic vessels)
- 16. Lacunes of the basilar territory (dizzy, diplopia, gaze dysfunction)
- 17. Lateral medullary partial infarction (penetrators from the vertebral artery)
- 18. Lateral pontomedullary territory (partial AICA)
- 19. Loss of memory (DM nuclei of thalamus); paramedian perforator)
- 20. Locked in syndrome (infarction of ventral pons; bilateral cerebral peduncles)
- 21. Unusual lacunar syndromes:
 - a. Weakness in one leg with falling (corona radiata; ventral portion of ventral pons)
 - b. Pure dysarthria – posterior 1/3 of ventral pons and cerebral cortex
 - c. Acute dystonia (thalamoperforate artery to basal ganglia)
 - d. Lacunar strokes and cognitive deficits:
 - i. Silent lacunar infarct with:
 - 1. Brain atrophy
 - 2. Multiple subcortical sites
 - 3. Enlarged ventricles
 - ii. Decreased executive function
 - iii. Decreased visuospatial ability

Differential Diagnosis by Arterial Territory and Anatomical Structure of Pontine Stroke with Lacunar Infarction

- 1. Paramedian arteries from the basilar artery (BA)
 - a. Medial basis pontis
 - b. Ventral tegmentum:
 - i. Corticospinal tract
 - ii. VIth cranial nerve fibers as they exit
 - iii. Facial nerve fibers as they exit
 - iv. Rare PPRF (para pontine reticular formation by extension)
- 2. Short circumferential arteries (BA)
 - a. Lateral 3/5 of the pons involved

3. Long circumferential arteries (BA)
 - a. Lateral tegmentum
 - b. Tectum
 - i. Cerebellar projections
 - ii. Vth and VIIIth cranial nerves
 - iii. Part of sensory lemniscus infarcted
4. Large bilateral pontine infarcts:
 - a. Basilar artery lesions
 - i. PPRF, one-and-a-half syndrome
 - ii. Ocular bobbing and dipping
 - iii. <0.5 mm pupils
 - iv. Decreased consciousness
 - v. Decerebration
 - vi. Hyperactive reflexes
 - vii. Babinski signs

Differential Diagnosis Between Pontine Hemorrhages vs. Lacunar Infarction

1. Ischemic:
 - a. Prior TIA
 - b. Stuttering clinical course
2. Hemorrhage:
 - a. Abrupt headache
 - b. Nausea and vomiting
 - c. Meningeal irritation
 - d. Rapid decrease of consciousness
3. Lacunar syndrome may be due to hemorrhage or infarction; isolated small hemorrhage may be associated with:
 - a. Dysarthria clumsy hand syndrome
 - b. Pure sensory stroke
 - c. Ataxic hemiparesis

Differential Clinical Features in the Patterns of Pure Motor Hemiparesis (PMH) and Sensory Stroke

1. Motor Cortex Weakness
 - a. Hand and arm representation is in the precentral gyrus "motor knuckle"
 - i. C5–C6 roots are represented medially
 - ii. C8–T1 are more lateral
 - b. Infarction frequently appears as a pseudo radial palsy (wrist drop)
 - c. Embolic pathogenesis from the internal carotid artery
 - d. Midbrain infarction:
 - i. Rare that face is involved in isolation
 - ii. Cranial Nerve III or VI involved with pure hemiparesis, ataxia or movement disorder
 - e. Medullary pyramid infarction:
 - i. Flaccid hemiparesis that spares the face
2. Ataxic Hemiparesis or Corticobulbar Dysfunction
 - a. Ataxic hemiparesis:
 - i. Infarction of the descending corticospinal tracts and pontine crossing fibers (comprises the middle cerebellar peduncle)
 - ii. Leg more severely affected than the arm
 - b. Dysarthria – clumsy hand syndrome:

- i. Corticobulbar fibers to the Xth and XIIth nerve with contralateral ataxia of the hand and arm
3. Pure Sensory Stroke:
 - a. Lacune in the centrum semiovale (deep penetrating medullary arteries)
 - i. Usually a feeling of numbness or heaviness
 - b. Infarction of the ventrobasilar thalamic complex (VPM or VPL):
 - i. Patients may describe numbness, paraesthesias, formication or pain
 - ii. Bilateral intraoral loss of sensation (VPM). This is to be differentiated from a vascular brainstem stroke in which patients may feel numbness on one side of the tongue. VPL involvement may present as numbness of the trunk and extremities in 20% of patients. Dysesthetic, paraesthesia and burning occurs more often in the involved territory. Later this territory may be associated with the hyperpathia of Dejerine-Roussy syndrome (thalamic pain). Associated thermal and mechanical allodynia and hyperalgesia are frequently present concomitantly with this syndrome. Thalamic lesions respect the midline and may involve vibration sensibility. Exception is bilateral decreased periumbilical sensation
 - c. Thalamic-capsular lacunar infarction most often causes sensorimotor stroke. Feeling loss is perceived as numbness and heaviness
 - d. Involvement of the ventral medial spinothalamic tract (quintothalamic tract) by lacunar infarction at medullary levels causes unilateral or bilateral facial pain or numbness (onion skin distribution)
4. Hemiballism – infarction of at least 2/3 of the corpus Luysi (subthalamic nucleus. Usually thalamoperforate or paramedian thalamic penetrating artery is occluded)
5. Tetraplegia (locked in syndrome):
 - a. Overwhelmingly a large pontine or midbrain stroke
 - b. Patients are fully awake
 - c. Quadriplegic
 - d. Able to blink and look up and down on command
 - e. Unable to perform lateral eye movements
 - f. Involvement of the basis pontis (basilar artery) or the cerebral peduncles (bilaterally)
 - i. P1 segment of the PCA's (infarcts the cerebral peduncle)
6. Patterns of lacunar weakness with gait abnormality:
 - a. Weakness in one leg with falling
 - i. Basis pontis (ventral portion of medial pons)
 - ii. Posterior corona radiata fibers
 - b. Pure dysarthria: corona radiata, internal capsule, cerebral peduncle; basis pontis
 - i. No difference in dysarthria from any lesion
 - ii. Imprecise articulation of labials and glottals
 - iii. Monotonous voice
 - iv. Slowed rate

- v. Pontine or medullary areas have more severe dysarthria
- vi. Left paravermian cerebellar lesions pivotal in dysarthria
 - 1. Coordination of articulation and respiration is disrupted
- c. Acute dystonia:
 - i. Thalamus (VA, VL or VIM)
 - ii. 2) Putamen

Rarer Lacunar States

1. Loss of memory:
 - a. Anterior thalamic nuclei
 - b. Anterior limb of internal capsule that involves anterior thalamic efferent fibers
2. Thalamic dementia (dorsal medial nucleus from paramedian infarction)
3. Pure motor hemiparesis sparing the face
4. Multiple lacunar infarctions:
 - a. Primarily in the basal ganglia
 - b. "État" Lacunaire
5. Dysarthria, facial, lingual paresis
 - a. Genu capsular syndrome
6. Cerebellar lacunes:
 - a. Unusual small round lesions in the watershed between SCA, PICA, AICA
 - b. One case of giant lacune in the cerebellum
 - c. SCA greater deep territory supply from AICA or PICA
 - d. Large artery occlusion, cardiac embolic, end artery lesion

Overview of Cerebral Microbleeds (CMB)

General Characteristics

1. Blood extravasation into the perivascular or Virchow-Robin space without further parenchymal damage
2. Less than 10 mm in size
3. Hemosiderin engulfed by perivascular macrophages
4. CMBs are noted in 4.7–24.4% of normal elderly individuals
5. Risk factors for CMB:
 - a. Age
 - b. HCVD
 - c. Diabetes mellitus
 - d. Cow serum cholesterol
 - e. ApoE- ϵ 4 and 2 status
 - f. Smoking
 - g. CAA
6. Deep CMB mainly associated with HCVD; cortical microbleeds most often linked to CAA
7. CMBs are noted in 50% of patients with intracerebral hemorrhage
8. ApoE- ϵ 4 and ApoE- ϵ 2 are associated with increased burden of CMBs on MRI evaluation for both ischemic and hemorrhagic lesions

9. ApoE- ϵ 4 and ApoE- ϵ 2
 - a. Increase cortical cerebral blood vessel fragility (BBB dysfunction and leakage of blood proteins and lipids into the vessel wall)
 - b. APOE- ϵ 4 glycoprotein:
 - i. Enhances the disposition of amyloid peptide into the vessel wall
 - ii. Associated with blood vessel smooth muscle loss and blood vessel thickening
 - c. APOE- ϵ 2 allele
 - i. Increased fibrinoid necrosis of amyloid laden vessels
 - ii. Increased incidence of newly developed microbleeds and intracranial hemorrhage
 - d. APOE- ϵ 4 and APOE- ϵ 2 are associated with an increased burden on MRI for both hemorrhagic and ischemic cerebral vascular disease

Progression of Small Vessel Disease with Severe Uncontrolled Hypertensive Cardiovascular Disease

1. Effects the deep gray of the basal ganglia and contiguous white matter
 - a. Spreads to more peripheral white matter and leptomeningeal arteries
 - b. Spread to thalamic and cerebellar white matter vessels and then to the brainstem vessels
 - c. Cortical vessels are not involved

Binswanger's Disease

1. Noted in severe poorly controlled hypertensive patients
2. A subcortical vascular encephalopathy with widespread demyelination, axon loss which spares U-fibers (connect adjacent cortical convolutions)
 - a. A severe SVD of arteriosclerosis and lipohyalinosis
 - b. CADASIL has similar pattern of cerebral involvement

Microhemorrhages

General Characteristics

1. Small foci of hemorrhage that increase with age; less than 10 mm
2. Cortical microbleeds are primarily associated with CAA while hypertension is the primary cause of those seen subcortically and in the basal ganglia
3. Cortical microbleeds are more prevalent in the ApoE- ϵ 4 and ApoE- ϵ 3/ApoE- ϵ 3 genotype
4. Correlated with:
 - a. Leukoaraiosis (white matter disease of aging)
 - b. Ischemic and hemorrhagic stroke
 - c. Alzheimer's disease
5. Are present in about 36% of patients over the age of 80 years
6. May be associated with a disseminated process

Clinical Manifestations

1. Intracerebral hemorrhage
 - a. Increased risk in patients taking anticoagulant therapy
2. Lobar hemorrhage (occipital predominant) in association with CAA; deeper hemorrhages associated with HCVD
3. Possible relationship with convolutional cortical subarachnoid hemorrhage
4. TIA episodes in CAA may represent the clinical equivalent of cerebral microbleeds
5. Vascular cognitive dysfunction
 - a. Released heme activates microglia that induce inflammatory pathology by releasing inflammatory cytokines

Pathology

1. Cerebral microbleeds are related to microvascular dysfunction
 - a. Age dependent capillary hemorrhage
2. The primary mechanism for cerebral microbleeds is a focal tear in a small artery or arteriole:
 - a. Amplified by CAA and HCVD

Neuroimaging

1. MRI has well demarcated focal lesions
2. Gradient ECHO and susceptibility weighted MRI sequences are the preferred imaging techniques
3. The presence of cerebral microbleeds is correlated with:
 - a. Lower fractional anisotropy and higher mean diffusion tensor imaging in ApoE ϵ 4 patients
 - b. Suggestion that cerebral microbleeds that present focally are associated with diffuse microstructural white matter damage

Retinal, Vestibular Small Vessel Diseases of the Brain***Eales Disease****General Characteristics*

1. Disease of young men
2. Occurs in the second to fourth decades of life
3. Prevalent in the Middle East and India
 - a. In India it has been associated with tuberculosis
4. No systemic symptoms
5. Eye symptomatology is dominant
6. Systemic illnesses that can present with retinopathy and stroke include:
 - a. SLE
 - b. Sarcoidosis
 - c. Ulcerative colitis
7. A syndrome of retinal neovascularization
8. Human leukocyte antigen (HLA)
 - a. Higher phenotype frequency of human leukocyte antigen
 - b. HLAB5, DR1 and DR4 individuals may be susceptible to retinal vasculitis

9. Association with tuberculosis has been suggested
 - a. Patients may be hypersensitive to tuberculo-protein
 - b. Epiretinal membrane samples have been reported as positive for mycobacterium species
 - c. Some patients have been described with meningitis

Clinical Manifestations

1. Ophthalmological features are dominant:
 - a. May be asymptomatic
 - b. Retinal periphlebitis
 - c. Retinal revascularization that may cause vitreous hemorrhage
 - d. Retinal capillary ischemia
 - e. Perivenous and periarterial sheathing
 - f. Macular arteries are less severely affected:
 - i. Relative sparing of central vision
 - g. Uveitis
 - h. Signs and symptoms predominant and present in three stages
 - i. Venous inflammation (vasculitis)
 - ii. Occlusion
 - iii. Retinal neovascularization
2. Cerebrovascular Manifestations
 - a. Focal ischemic infarcts
 - b. Large vessel thrombosis
3. Patients may suffer focal small vessel infarcts or occasional large vessel stroke
4. Retinal vasculitis associated with CNS vasculitis
 - a. Retinal hemorrhages associated with epistaxis
 - b. Young men
 - c. Recurrent monocular vitreous hemorrhage; may involve the second eye
 - d. May be associated with:
 - i. Subacute myelopathy
 - ii. Chronic lymphocytic meningitis
 - iii. Middle cerebral artery stroke

Pathology

1. Retinal ischemia
 - a. Retinal and/or optic nerve revascularization that causes
 - i. Vitreous hemorrhage
 - ii. Retinal detachment
 - b. Cerebral vasculitis
 - c. Large vessel stroke

Neuroimaging

1. Cerebral vasculitis
2. Large vessel infarction
3. Intracranial hemorrhage

Laboratory Evaluation

1. Arterial fundoscopic evaluation (fluorescein)

Differential Diagnosis of Eales Retinopathy

1. Sickle cell disease
2. Diabetic retinopathy
3. Retinopathy of prematurity
4. Familial exudative vitreoretinopathy
5. Hyperviscosity syndromes
6. Idiopathic retinal vasculitis
7. Neuroretinitis (IRVAN syndrome)
8. Systemic illnesses that can present with retinopathy and stroke include:
 - a. SLE
 - b. Sarcoidosis
 - c. Ulcerative colitis
9. There is discussion that the neurologic features associated with the retinopathy may be due to the underlying condition and may not be specific to Eales disease

Susac's Syndrome (Retinocochleocerebral Syndrome)*Overview*

An autoimmune disease that is characterized by encephalopathy, branch retinal artery occlusion and sensorineural hearing loss.

General Characteristics

1. Clinical triad of encephalopathy, deafness, retinal artery branch occlusion
 - a. Microangiopathy: affects the precapillary arteriole of the brain, retina and inner ear
2. Age varies between 8–58; predominantly females between the age of 20–40
3. Fluctuating course

Clinical Manifestations

1. Headache and behavioral change may be premonitory
2. Diffuse encephalopathy in which decreased auditory and visual perception is common
3. Psychiatric and behavioral alterations can progress to dementia
4. Focal neurologic involvement
 - a. Cranial Nerves III, VI and VIII
 - b. Hemihypesthesia
 - c. Hemiparesis
 - d. Generalized seizures and myoclonus
5. Retinal involvement
 - a. Branch retinal artery occlusion (BRAO)
 - i. Fluorescein angiography demonstrates multifocal fluorescence
 - b. Amputated retinal arteries (branch occlusion)
 - c. Thickened arterial walls with “light streaking”
 - d. Edema; cherry red macula
6. Auditory and visual loss may be simultaneous
7. Auditory loss:
 - a. Unilateral or bilateral hearing loss
 - b. Cochlear hearing loss

- i. Loss of low and intermediate frequencies (microinfarction of the apical cochlea)
8. Vertigo and tinnitus may occur from infarction of the vestibular labyrinth
9. Cause of multiple bursts of activity over 3 years; final stage is 1 to 8 years in a self-limited disease
10. Encephalopathy
 - a. In approximately 25% of patients the process may be preceded by slowly progressive altered mentation

*Pathology***Cerebrovascular Manifestations**

1. Small vessel disease (arteriolar)
2. Obliteration of small intracranial arteries
3. Ischemic and hemorrhagic infarction
4. Thrombotic mechanisms are more common than embolic
5. Microinfarcts in end arterioles distribution (white and gray matter) as well as the retina and cochlea
6. Hypertrophic astrocytes in white matter surrounding arterioles
7. Non-specific periarteriolar cell infiltrate
8. Disease of the vascular wall with thrombosis
9. Anti-endothelial cell injury

*Neuroimaging***MRI**

1. Multiple small hyperintense T2-weighted lesions in supratentorial gray and white matter
2. Lesions may be round or linear
3. Lesions occur in the central corpus callosum
4. Infratentorial lesions of the middle cerebellar peduncle, cerebellum and brainstem
5. Leptomeningeal involvement is seen in 30% of patients
6. Fluctuation of lesions overtime

Fluorescein Retinal Angiography

1. Distal branch retinal occlusions
2. Pathognomonic multifocal fluorescence
3. Plaques (endothelial damage)
 - a. Mid arteriolar segment involvement

Laboratory Evaluation

1. CSF protein may be elevated
2. Factor VIII and vWF antigen is increased in some patients

Differential Diagnosis

1. Cogan's syndrome (interstitial keratitis prominent)
2. Brown-Vialetto-Van Laere syndrome
 - a. Pontobulbar palsy (lower cranial nerves)
 - b. Familial and sporadic forms have been identified
3. MS (hearing loss and arteriolar occlusive retinal disease don't occur)
 - a. Generalized corpus callosum demyelination
 - b. Callosal lesions are Dawson's fingers (rare)
4. Acute disseminated encephalomyelitis (ADEM)

- a. Monophasic; lesions are the same age
- b. Unusual for retinal and VIIIth nerve involvement
- 5. SLE
 - a. Psychosis, seizures and proximal myopathy are characteristic
- 6. Polyarteritis
 - a. Ocular and auditory involvement is rare
 - b. Systemic involvement (kidney is the most prominent)
 - c. Usual CNS presentation is encephalopathy
- 7. Wegener's granulomatosis
 - a. Sinus and respiratory tract involvement
 - b. Systemic necrotizing vasculitis
 - c. May have glomerulonephritis
- 8. Hypersensitivity vasculitis (Henoch-Schönlein purpura)
 - a. Neurologic, retinal, auditory involvement is rare
 - b. Skin and vein involvement is most prominent
- 9. CADASIL
 - a. Notch 3 gene
 - b. Foveal telangiectasia changes in the retina
 - c. Migraine, small vessel disease, dementia

Rare Diseases in the Differential Diagnosis

1. Usher's syndrome (autosomal recessive)
 - a. Retinitis pigmentosa
 - b. Labyrinthitis
2. Vogt-Koyanagi-Harada syndrome
 - a. Uveo-meningeal syndrome (recurrent meningitis)
 - b. Dementia
 - c. White forelock
 - d. Harada (prominent VIIIth nerve involvement)
 - e. Blindness from diffuse exudative choroiditis and retinal detachment
3. Rocky Mountain Spotted Fever (retinal arterioles)
4. Takayasu's syndrome
 - a. Aortic arch derived vessel involvement
 - b. Ischemia of the retina (positional blindness); claudication of vision (with walking); early cataracts
5. Mitochondrial encephalomyopathies
 - a. Kearns-Sayre syndrome
 - i. Ophthalmoplegia
 - ii. Heart block
 - b. MELAS
 - i. Stroke-like episodes that do not respect a vascular territory
 - ii. Manifestations of most mitochondrial diseases include:
 1. Short stature
 2. Diabetes
 3. Ophthalmoplegia
 4. Cardiomyopathy
 5. Fatigue
 6. Weakness
 7. Sensorineural hearing loss
 8. Migraines

Acute Posterior Multifocal Placoid Pigment Epitheliopathy (APMPPE)

Overview

APMPPE is a self-limiting chorioretinal inflammatory disease that affects healthy young adults with rapid loss of central vision.

General Characteristics

1. Primarily an ophthalmologic syndrome best evaluated with fluorescein angiography (indocyanine green angiopathy)
2. Associated with:
 - a. Infectious/post-infectious disorders (bacterial and viral)
 - i. Tuberculosis
 - ii. Streptococcus
 - iii. Syphilis
 - iv. Lyme's disease
 - v. Schistosoma mansoni
 - vi. Epstein-Barr Virus (EBV)
 - vii. Adenovirus
 - b. Vaccination
 - i. Swine flu
 - ii. Hepatitis B
 - iii. Meningococcal
3. Inflammatory conditions:
 - a. Lymphadenopathy
 - b. Nephritis
 - c. Wegener's granulomatosis
 - d. Crohn's disease
 - e. Ulcerative colitis
 - f. Thyroiditis
4. Autoimmune disorders
 - a. Post-streptococcal syndrome
 - b. Anticardiolipin antibodies
 - c. Juvenile rheumatoid arthritis
 - d. Grave's disease
5. Paraneoplastic syndrome
 - a. Renal cell cancer

Clinical Manifestations

1. Ophthalmologic syndrome characterized by:
 - a. Multiple cream-colored placoid lesions
 - b. At the posterior pole in the level of the pigment epithelium and choroid
 - i. Demonstrated by indocyanine green fluorescein angiography
 - c. Occlusive choroidal vasculitis
 - d. Papillitis
 - e. Optic neuritis
 - f. Entity may be a continuum of Harada's disease; a possible autoimmune cause of uveo-meningeal syndrome
 - g. Inflammatory yellow-white lesions at the level of the retinal pigment epithelium (probable choroidal hypoperfusion)

2. Both eyes are affected simultaneously; ocular involvement may occur seriatim
3. Visual blurring; scotoma and distortion of vision
4. Vision usually recovers after several weeks but deficits may be permanent
5. Fundoscopic examination
 - a. Pathology is in the retinal pigment epithelium
 - b. Well circumscribed gray-white flat lesions
6. Stroke
 - a. Arteritis pattern

Neurologic Features

1. Neurological complications (mean age 26.5)
2. VIIIth nerve involvement
3. CNS vasculitis
4. Optic neuritis
5. Neuro-otological signs (tinnitus, hearing loss, vertigo)
6. Headache
7. Aseptic meningitis
8. Pseudo tumor cerebri
9. Meningoencephalitis (associated with vasculitis of CNS)
10. MS like episodes

Cerebrovascular Disease Associated with APMPE

1. Similar to primary angiitis of CNS
2. Cerebral vein thrombosis
3. Cortical and tentorial strokes in 70% of patients
 - a. Posterior cerebral and MCA territories
 - b. 40% of patients with deep white matter infarcts
 - c. Striatocapsular infarcts
4. Ischemic and hemorrhagic stroke (rare)
5. Lobar hemorrhage from cortical venous thrombosis (rare)

Pathology

1. Vasculitis of the CNS
2. Primary involvement of:
 - a. Retinal pigment epithelium
 - b. Choriocapillary vasculitis
 - c. Partial occlusive vasculitis
 - d. May be a continuum between APMPE and Harada's disease
 - e. Possible uveo-meningeal syndrome similar to:
 - i. Vogt-Koyanagi-Harada disease
 - ii. Behcet's syndrome
 - iii. Sarcoid
 - iv. Wegener's granulomatosis
3. Granulomatous involvement of medium-sized blood vessels
4. Some autopsies have demonstrated granulomas with Langhans cells

Neuroimaging

1. Arteriographic evidence of vasculitis (approximately one third of cases)
2. Ocular computed tomography:

- a. The outer nuclear layer, external limiting membrane and the inner and outer segment (IS/OS) line are disrupted

Laboratory Evaluation

1. Elevated CSF leukocytes and protein

Differential Points Between APMPE, Eales and Susac's Disease

1. Eales primarily affects retinal arteries (neovascular proliferation and vitreous hemorrhage)
 - a. Young men (20 to 40)
 - b. Stroke is rare
2. Susac's (young women approximately age 30)
 - a. Microangiopathy of the retina, cochlea and brain
 - b. Lesions in the corpus callosum (middle area)
3. APMPE
 - a. Rapid decrease in central vision
 - b. Yellow-white multiple placoid lesions of the retina
 - c. Acute/chronic visual blurring, scotoma or metamorphopsia
 - d. Both eyes are involved simultaneously or less commonly sequentially within a few days
4. Inflammatory conditions that are associated with retinal edema
 - a. Vogt-Koyanagi-Harada disease
 - b. Ocular Toxoplasmosis

Hereditary Endotheliopathy with Retinopathy, Nephropathy and Stroke (HERNS)

General Features

1. Chromosome 3p21; mutation of the TREX1 gene
 - a. Codes for a 3'-5' DNA exonuclease
2. Progressive visual loss in the 3rd to 4th decade
3. Neurologic deficits begin 4 to 10 years after initiation of the disease

Clinical Manifestations (Clinical Features)

1. Central vision loss with decreased visual acuity
2. Premonitory behavioral and psychiatric symptoms (early as the second decade)
3. Stroke-like episodes may be presenting symptom; may progress over several days
4. Later in the course there are multifocal cortical and sub-cortical signs of small vessel stroke
 - a. Migraine is common
 - b. 50% of patients have renal dysfunction

Ophthalmologic Signs

1. Retinal vasculopathy
 - a. Loss of macular capillaries
 - b. Dilated tortuous telangiectatic vessels; capillary shunts
 - c. Fluorescein angiography
 - i. Juxtafoveolar capillary obliteration with microaneurysm
 - d. Peripheral retina is involved late in the disease's course

Pathology

1. Small blood vessels occluded by fibrin thrombi
2. Electron microscopy:
 - a. Multilaminated vascular basement membranes
 - b. Kidney, stomach, omentum and skin are concomitantly involved
 - c. Generalized vasculopathy with disruption of capillaries and arterioles
 - d. Breakdown of the blood-brain barrier
 - e. A primary endothelial injury

*Neuroimaging***MRI**

1. Reveals T2 sequence high intensity lesions in deep white matter (contrast enhancing)
 - a. Overtime, contrasting lesions in the deep frontoparietal area
2. May have space occupying mass lesions

Laboratory Evaluation

1. Fluorescein angiogram of the retina
 - a. Macular capillary dropout
2. Dilated tortuous telangiectasia vessels and capillaries

Cogan's Syndrome (Typical or Classic)*Overview*

A chronic inflammatory disorder, affecting multiple systems, characterized by interstitial keratitis and sensorineural hearing loss; may also be associated with systemic vasculitis (rare).

General Characteristics

1. Occurs in young adults (25 years mean age)
2. Men and women affected equally
3. Autoantigens: There is evidence of inner ear autoimmunity possibly triggered by a viral infection. Putative autoantigens are CD148 and Connexin 26
4. Cerebrovascular complications are large vessel stroke and cavernous sinus thrombosis

Clinical Features

1. Systemic features:
 - a. Headache, fever, weight loss, fatigue
 - i. Arthralgias and myalgias (30%)
 - b. 10% have systemic vasculitis
 - a. Aortic insufficiency (10%)
 - b. Distal coronary arteries may be affected
 - c. Skin
 - d. Viscera
 - e. Kidneys
 - f. CNS
 - g. Muscles
2. Neurological manifestations
 - a. Blindness (corneal opacification)

- b. Vertigo
- c. Ataxia
- d. Hearing loss
 - i. Vestibular auditory dysfunction from inflammation of the labyrinth
3. Ophthalmologic features
 - a. Acute interstitial keratitis
 - b. Bilateral interstitial keratitis (nonsuppurative cellular infiltrate of the corneal stroma)
 - c. Keratitis fluctuates
 - d. Patchy corneal involvement and absence of intraocular inflammation
 - e. Retinal hemorrhage and papilledema
 - f. Orbital pseudotumor
 - g. Central artery or vein occlusion
 - h. Presents with:
 - i. Red eyes
 - ii. Photophobia
 - iii. Reduced vision
 - iv. Interstitial keratitis
 - v. Uveitis (rare)
4. Vestibulocochlear manifestations:
 - a. Severe hearing loss in all cases
 - i. Asymmetric and sudden
 - b. Vertigo, tinnitus and ataxia
 - c. Inflammation of the labyrinths
 - d. Acute and often bilateral
 - e. Decreased caloric response
 - f. May be coincidental with visual loss
5. Stroke (pial arteries)

Typical Cogan's Signs and Symptoms

1. Photophobia, lachrymation, eye pain
2. Blurred vision
3. Intermittent symptoms for years
4. Ménière's-like attacks may precede eye pain
5. Total deafness and absence of vestibular function

Atypical Cogan's Syndrome*General Characteristics*

1. Vasculitis and systemic manifestations
2. Inflammatory ocular disease exemplified by
 - a. Uveitis
 - b. Scleritis
 - c. Episcleritis
 - d. Retinal vasculitis
 - e. Optic nerve edema without interstitial keratitis
3. There may be vestibular auditory dysfunction that occurs at more than 2 years after onset of eye symptoms

Clinical Manifestations

1. Involvement of the CNS or PNS varies from 5 to 50%
2. Vasculitis
 - a. Occurs in atypical disease

- b. Aortitis and aortic insufficiency in the classic syndrome
- c. Neurologic symptoms
 - i. Stroke
 - 1. Cerebrovascular disease
 - a. Cerebral venous sinus thrombosis
 - b. PICA thrombosis
 - c. Ischemic brain (cerebellar) lesions
 - d. Frequency of neurologic involvement about 13%
 - e. Emboli to large arteries from valvular disease (rare)
 - ii. Encephalopathy
 - ii. Seizure
 - iii. Myelopathy
 - iv. Mononeuritis multiplex
 - v. Cavernous sinus thrombosis
 - d. Differential diagnosis includes syphilis
- 3. Cerebrovascular disease
 - a. Cerebral venous sinus thrombosis
 - b. PICA thrombosis
 - c. Ischemic brain (cerebellar) lesions
 - d. Frequency of neurologic involvement about 13%
 - e. Emboli to large arteries from valvular disease (rare)

Neuroimaging for Typical and Atypical Cogan's Syndrome

MRI

1. Multiple ischemic brain lesions
2. Soft tissue obliteration of the membranous labyrinth

Angiography

1. Cerebral venous thrombosis
2. PICA thrombosis
3. Signs of suggestive of vasculitis

CT

1. Intralabyrinthine calcifications (rare)

Pathology

Typical Cogan's Syndrome

1. Vasculitic process affecting vessels of all sizes
2. Microscopic evaluation of the aorta
 - a. Inflammatory changes
 - b. Destruction of the internal elastic membrane
3. Autoantibodies against corneal, inner ear and endothelial antigens may be present

Atypical Cogan's Syndrome

1. Eye pathology includes:
 - a. Retinal hemorrhage
 - b. Papilledema
 - c. Orbital pseudotumor
 - d. Central artery or vein occlusion

Laboratory Evaluation for Typical and Atypical Cogan's Syndrome

1. Elevated erythrocyte sedimentation rate (ESR), anemia, leukocytosis and thrombocytosis
2. Lumbar puncture (LP) may demonstrate pleocytosis and elevated protein
3. Negative tests for syphilis and autoantibodies that include rheumatoid factor, anti-nuclear antibodies and ds DNA
4. Audiometry, electronystagmography and vestibular function deficits are positive

Retinal Vasculopathy with Cerebral Leukodystrophy (RVCL)

Overview

The RVCL spectrum presents primarily as small vessel disease. Three variants that have been mapped to chromosome 3p21 are: Hereditary Retinal Vasculopathy (HRV), Cerebroretinal Vasculopathy (CRV) and Hereditary Endotheliopathy, Retinopathy and Nephropathy (HERNS).

An infantile syndrome that is similar but does not map to 3p21 is: Hereditary Infantile Hemiparesis with Arteriolar Retinopathy and Leukoencephalopathy (HIHARL).

Cerebroretinal Vasculopathy (CRV), HERNS and Hereditary Retinal Vasculopathy (HRV)

General Characteristics

1. Genetics
 - a. All three diseases are linked to a locus on chromosome 3p21
 - b. Autosomal Dominant
2. Causative gene mutations of TREX 1
 - a. Encodes a 3'-5' DNA repair exonuclease
 - b. Frame shift mutation
3. Other diseases with TREX-1 mutations that have clinical similarity but distinct clinical features:
 - a. Aicardi-Goutières syndrome (AGS)
 - b. Familial Chilblain Lupus (FCL)
 - c. Systemic Lupus Erythematosus (SLE)
4. The truncated protein from the mutation retains exonuclease activity but loses perinuclear localization
5. Hereditary systemic angiopathy (HSA) has recently been described and is also suggested to be on the retinal vasculopathy with cerebral leukodystrophy spectrum

Clinical Manifestations

1. Middle age at onset (4th–5th decade)
2. Predominant CNS involvement
3. TIA, stroke, focal motor and sensory deficits
4. Depression
5. Headaches
6. Cognitive dysfunctions
7. Decreased renal function
8. G.I. bleeding
9. Increased alkaline phosphatase
10. Migraine
11. Raynaud's Phenomena
12. 100% mortality in 5–10 years due to neurologic deficits

Neuropathology

1. Coagulative necrosis secondary to obliterative vasculopathy
2. Minimal inflammatory infiltrate
3. Fronto-parietal cortex motor involvement; lesions also occur in the basal ganglia, cerebellum and pons
4. One third of patients have hepatic and renal involvement
5. Thickening and reduplication of the retinal capillary basal lamina

Neuroimaging

1. Retinal fluorescein angiography:
 - a. Capillary drop-out (macular region; decreased central vision)
 - b. Prominent juxtafoveolar capillary obliteration and telangiectasia
2. Lesions are most prominent in the fronto-parietal lobes
 - a. Lesions enhance

Differential Diagnosis of RVCL

1. Variants of RVCL with linkage to 3p21 (3p21 mutations)
 - a. CRV (Cerebral Retinal Vasculopathy)
 - b. HVR (Hereditary Vascular Retinopathy)

HERNS (Hereditary Endotheliopathy Retinopathy with Nephropathy)

1. Brain, kidney, GI tract and skin are involved
2. Pathology (by electron microscopy) reveals multilaminated vascular basement membrane
 - a. Hereditary Infantile Hemiparesis with Arteriolar Retinopathy and Leukoencephalopathy (HIHARL)
 - i. Not linked to 3p21
 - ii. Vascular endothelial dysfunction
 - iii. Possible increased susceptibility to decreased cerebral blood flow from cortical spreading depression
 - iv. Migraine with aura, retinal hemorrhage and tortuosity
 - v. Dilatation of perivascular spaces and microbleeds

Cerebroretinal Vasculopathy (CRV)**General Features**

1. Genetics
 - a. Autosomal dominant
 - b. 100% penetrance
 - c. Chromosome 3p21 mutation

Clinical Manifestations

1. Onset is middle age (4th to 5th decade)
2. Primarily retinal involvement
3. 100% mortality over a 5 to 10 year period
4. Macular edema, capillary obliteration, microaneurysms and telangiectasia
5. Strokes, visual loss, dementia
6. Neurologic manifestations
 - a. TIA and ischemic stroke

Pathology

1. Coagulative necrosis secondary to an obliterative vasculopathy
2. Minimal inflammatory infiltrate
3. Pons, cerebellum and basal ganglia also involved
4. One third of patients with concomitant hepatic and renal involvement
5. Fibrinoid necrosis without inflammation

Neuroimaging**CT/MRI**

1. Topographic stroke

Laboratory Evaluation

1. Ophthalmologic evaluation by retinal fluorescein angiography
 - a. Macular capillary dropouts with loss of central vision
 - b. Juxtafoveolar capillary obliteration and telangiectasia

Hereditary Vascular Retinopathy (HVR)**General Features**

1. Retinal vasculopathy
2. Migraines
3. Raynaud's phenomena
4. Visual acuity preserved
 - a. Primarily peripheral retinal involvement
5. Similar course to cerebroretinal vasculopathy (CVR) and Hereditary Endotheliopathy with Retinopathy, Nephropathy and Stroke (HERNS)

Venous Stroke**Venous Strokes Overview**

Venous strokes should be suspected in the setting of the last trimester of pregnancy and the first month of the perineurium, any prothrombotic state and dehydration. Clinically, there is a depressed mental status early in the course of the process as well as a step wise and progressive onset rather than an apoplectic initial event, which characterizes embolus, hemorrhage and ischemic stroke. Repeated seizures and vomiting are common associated with severe headache. Papilledema is more common than with ischemic or hemorrhagic events. The sinuses are commonly occluded. Lateral sinus involvement should be suspected with mastoid pain that may radiate to the sternocleidomastoid muscle associated with Vth and VIth nerve involvement. The temporal lobe and cerebellum may be involved concomitantly. Sagittal sinus thrombosis frequently presents with focal seizures of the leg or bilateral signs and symptoms. Severe headache, papilledema and rapid loss of consciousness strengthen the diagnosis. Cavernous sinus involvement is frequently heralded by periorbital headache, fever, stiff neck. There is progressive orbital and retinal congestion culminating in paresis of III, IV and VI.

Often there is complete ophthalmoplegia and frequent spread to the contralateral eye.

Occlusion of the internal cerebral veins, the vein of Galen and straight sinus present with stupor or coma. They often have had a severe headache and hemiparesis prior to depression of mental status.

Cortical cerebral venous occlusion presents with focal neurological signs, seizures at presentation, headache but minimal depression of consciousness.

Cerebellar venous occlusions often pursue a pseudotumoral course with brainstem compression.

MRI evaluation that demonstrates a delta sign at the confluences of sinuses, bilateral thalamic and basal ganglia hemorrhage, small compressed ventricles and vascular lesions out of a typical arterial distribution suggest venous stroke and sinus occlusion.

Specific Territories of Venous Drainage

1. Superior sagittal sinus (SSS) and its veins
 - a. Drain a major part of the cerebral hemispheres
2. Inferior sagittal sinus, straight sinus and tributaries drain:
 - a. Deep white matter of the cerebral hemispheres
 - b. Basal ganglia
3. At the torcular of Herophilus (confluens of sinuses):
 - a. SSS is continuous with the right lateral sinus
 - b. Straight sinus is continuous with the left lateral sinus
4. Lateral sinus has two segments:
 - a. Transverse (attached to the border of the tentorium)
 - b. Sigmoid (attached to the inner aspect of the mastoid bone)
5. Cavernous sinus:
 - a. Drains the periorbital and facial territories
 - b. Joins the internal jugular vein and transverse sinus through the petrosal sinus
 - c. Drains Sylvian the fissure through the sphenoparietal sinus

General Characteristics

1. Accounts for approximately .5% of all strokes
2. Approximately 5–7 cases per million children and 3–4 patient per million adults
3. Most cases are associated with sinus thrombosis
4. Women account for 75% of the cases

Clinical Manifestations

1. Headache is the most common symptom of sinus thrombosis
 - a. Usually it presents over several days but can occur acutely; a higher incidence in women than men and also carries a higher chance of hemorrhage
2. Patients with a chronic cause may have papilledema
3. Severe symptoms occur with:
 - a. Occlusion of the deep venous system
 - i. Coma

- ii. Bilateral motor deficits
- b. Parenchymal lesions
4. Focal or generalized seizures are common:
 - a. Focal neurological signs in the absence of increased intracranial pressure suggests isolated cortical vein thrombosis
 - b. Seizures occur more often with:
 - i. Parenchymal lesions
 - ii. Sagittal sinus thrombosis
 - iii. Cortical venous thrombosis
5. Coma occurs with large hemispheric infarcts or hemorrhage
 - a. Compression of the thalamus or mid-brain
6. Predictors of mortality and morbidity following venous infarction:
 - a. Coma
 - b. Seizures (more common with hemorrhage)
 - c. Depressed consciousness
 - d. Deep cerebral vein thrombosis
 - e. Right intracranial hemorrhage
 - f. Posterior fossa lesions
 - g. Worsening of previous deficits
7. Intracranial hemorrhage occurs in approximately 40% of patients with venous ischemia

Neuropathology

1. Superior sagittal sinus thrombosis with cortical vein thrombosis
 - a. Involves the superficial cerebral hemispheres
2. Thrombosis of the straight sinus involves the basal ganglia
3. Isolated cortical vein thrombosis is rare
4. Usual pathology: venous thrombosis with or without cerebral infarction; basal ganglia or thalamic hemorrhage
5. Venous obstruction causes:
 - a. Cerebral edema
 - b. Infarction or hemorrhagic infarction of the cortex
 - c. Petechial hemorrhage
 - d. Superior sagittal sinus thrombosis may cause:
 - i. Bilateral basal ganglia hemorrhage
 - ii. Unilateral or bilateral thalamic hemorrhage
 - e. Hemorrhagic infarction may be circumscribed or widespread that may involve cortical and deep structures
 - f. Multiple or single intracerebral hemorrhage

Neuroimaging

1. Most sensitive technique is a combination of MRI to visualize thrombosis vessel with consequent catheter angiography which detects the non-visualization of the same vessel
2. The delta sign (at the confluence of sinuses or the “cord” sign) is detected in approximately 30% of patients
3. Approximately 30% of scans may be negative
4. MRI alone or with DWI shows mixed patterns of edema, infarction and hemorrhage

Venous Sinus Thrombosis

General Characteristics

1. The Superior Sagittal Sinus (SSS) is the most commonly involved
 - i. Solely involved approximately 30 to 40% of the time
2. In 10 to 15% of patients with venous sinus thrombosis, the lateral sinus is unilaterally involved
3. Rarer sinus involvement includes:
 - a. Deep venous system
 - b. Isolated cortical veins

Clinical Manifestations

1. A stepwise and progressive onset
2. Headaches in 75 to 90% of patients
3. Vomiting is common
4. There is a depression of mental status early in the course of the illness
5. Recurrent seizures with severe headaches
6. Hemiparesis commonest focal deficit
7. Hemisensory deficit is seen in approximately 10% of patients
8. Neurologic signs are cumulative
9. Alternating or ascending hemiparesis is rare
10. Papilledema occurs in chronic conditions

Neuropathology

1. Clotting disorders:
 - a. Antithrombin III
 - b. Protein C and S deficiency
 - c. Factor V Leiden mutation
 - d. Prothrombin gene mutation
 - e. SLE anticoagulant
 - f. Activated Protein C resistance
 - g. Methylene tetrahydrofolate reductase deficiency
 - h. Anticardiolipin antibody
 - i. Increased factor VIII
 - j. Oral contraceptives
 - k. Ulcerative colitis
 - l. Regional enteritis
 - m. Polycythemia vera
 - n. Hemolytic anemia
 - o. Pregnancy and the puerperium
 - p. Leukemia
 - q. Paroxysmal nocturnal hemoglobinuria (decreased membrane glycoprotein)
 - r. Carcinoma (thrombin like material)
 - s. Idiopathic thrombocytosis
 - t. Nephrotic syndrome
 - u. Ménériér's syndrome (protein losing enteropathy)
 - v. Androgen therapy
 - w. Asparaginase therapy (blocks antithrombin III)
 - x. Cryofibrinogenemia
 - y. Disseminated intravascular dissemination
 - z. Behçet's disease

2. Structural changes in the venous sinus wall:
 - a. Metastatic disease (invasion)
 - b. Lung; breast, choriocarcinoma, prostate cancers
 - c. Lymphoma (invasion)
 - d. Non-Hodgkin's lymphoma
 - e. Behçet's disease
 - f. Arteriovenous malformations
 - g. Sarcoidosis
 - h. Leukemia (invasion of wall)
 - i. Meningitis
 - j. Chronic otitis media
 - k. Wegener's granulomatosis
 - l. Aspergillosis
 - m. Mastoiditis (lateral sinus)

3. Blood flow, rheology, systemic causes of venous occlusion:
 - a. Congestive heart failure
 - b. Cachexia and marasmus
 - c. Trauma
 - d. Cerebral artery thrombosis
 - e. Chronic obstructive airway disease
 - f. Trichinosis
 - g. Transvenous pacemaker placement
 - h. Dehydration
 - i. Hyperpyrexia (release of thromboplastin from platelets)
 - j. Congenital heart disease
 - k. Budd–Chiari syndrome
 - l. Diabetes mellitus
 - m. Vasculitis
 - n. Homocystinuria
 - o. Sickle cell (SS) disease
4. Cerebral edema
5. Ischemic or hemorrhagic infarction of the involved obstructed venous drainage territories
6. Basal ganglia or thalamic hemorrhage

Neuroimaging

1. Demonstration of thrombi in the sinuses and cerebral veins by MRI, MR venography or CT venography

Lateral Sinus Thrombosis

General Characteristics

1. Both otic and non-otic etiologies

Clinical Manifestations

1. Pain occurs:
 - a. Mastoid area
 - b. Sternocleidomastoid muscle
 - c. Headaches in frontotemporal and occipital areas
 - d. Vertigo, nausea and vomiting
 - e. Diplopia from involvement of the VIth nerve (Dorello's canal at the petrous apex under the petroclinoid ligament)
 - f. Paresthesias or pain in the face (involvement of the Vth nerve in Meckel's cave)

- g. Vth and VIth nerve concomitant involvement (Gradenigo's syndrome)
 - i. Nerves are affected at the petrous apex
 - ii. Requires pneumatized temporal bone
 - iii. Unilateral deafness
- h. Lethargy (increased ICP)
- i. Otic hydrocephalus
- j. Temporal lobe and cerebellum involved concomitantly
- k. Temporal lobe involvement
 - i. Posterior aphasia
 - ii. Superior quadrantanopia
 - iii. Agitation
- l. Cerebellar involvement
 - i. Gait ataxia
 - ii. Ipsilateral rotary nystagmus
- m. Spread of the thrombus
 - i. Into the jugular veins (if an axillary or jugular line is infected the spread is to the lateral sinus)
 - ii. Adjacent sinuses
 - iii. Rare concomitant pulmonary emboli

Neuropathology

1. Coagulopathy and systemic illness (inflammatory bowel disease)
2. Spread of infection from middle ear and mastoid
 - a. Draining ears and perforated ear drums
3. Spread of infection from the lateral sinus through jugular veins

Neuroimaging

1. Lytic lesions and opacification of the mastoid air cells
2. Eburnation and bone sclerosis
3. Concomitant secondary cholesteatoma
4. Demonstration of thrombi in the sinus by MRI, MR venography or CT venography

Superior Sagittal Sinus Thrombosis

General Characteristics

1. The superior sagittal sinus (SSS) is most commonly involved in venous sinus thrombosis
2. It is involved solely among the sinuses 30–40% of the time

Clinical Manifestations

1. Depends on concomitant involvement of cortical veins
 - a. Focal motor or sensory deficits
 - b. Seizures (leg more often than arm)
 - c. Often bilateral signs and symptoms
 - d. Signs and symptoms may be transient
2. Pseudotumor cerebri may occur if SSS is solely involved:
 - a. Severe headache
 - b. Papilledema
 - c. VIth nerve palsy
 - d. Decreased level of consciousness
 - e. Edema and hemorrhage of the medial dorsal cerebral hemisphere

Neuropathology

1. Associated with:
 - a. Puerperium
 - b. Parasagittal meningioma
 - c. Carcinomatosis of the meninges
 - i. Breast, lung and rarely prostate carcinoma
 - d. Head trauma
 - e. Behçet's disease
 - f. Prothrombotic states

Neuroimaging

1. Demonstrated by MRV
2. Parasagittal T2-weighted sequence hyperintensities
3. Bilateral basal ganglia on thalamic hemorrhages
4. Delta sign at confluences of sinuses (clot visualized)

Cavernous Sinus Thrombosis (CST)

General Characteristics

1. The primary source of CST may be a distant inflammatory focus in immune-compromised patients
2. May cause ischemic stroke (rare) by septic arteritis

Clinical Manifestations

1. Fever often with stiff neck
2. Headache (if early, it is often periorbital)
3. Facial pain (VIth nerve distribution)
4. Conjunctival edema and erythema
5. Orbital and retinal congestion
6. Involvement of IIIrd, IVth, VIth cranial nerves
7. V1 and occasionally V2 (usually slightly posterior to the sinus)
8. May cause complete ophthalmoplegia
9. Occlusion of ophthalmic artery (blindness)
10. Bilateral eye findings
11. Involvement of ICA with hemiparesis (rare)
12. Cavernous sinus thrombosis with spread to superior petrosal sinus
 - a. Causes Vth nerve involvement
13. Noninfectious clinical manifestations:
 - a. Indolent course
 - b. Proptosis
 - c. Conjunctival edema
 - d. Blood vessels do not reach the iris in infective or non-infective CST. Blood vessels do in cavernous arterial venous fistulae
 - e. No or minimal oculomotor involvement

Neuropathology

1. Infection of veins draining the medial face, orbit, nose and nasal sinuses
2. Infectious etiologies include:
 - a. Staphylococcus aureus
 - b. Pneumococci

- c. Streptococci
- d. Gram negative bacteria
- e. Mucormycosis
- f. Aspergillus
- 3. Noninfectious etiologies:
 - a. Surgery of sinuses/facial structures
 - b. Prothrombotic states
 - c. Thrombosis of dural A-V fistula

Neuroimaging

- 1. Ophthalmic veins (the superficial middle and inferior cerebral veins) connect with the sphenoparietal and sphenoid sinuses
- 2. Cavernous sinus drains into the pterygoid venous plexus via emissary veins and into the jugular vein and sigmoid sinus via the inferior and superior petrosal sinuses
- 3. Absence of valves in the cavernous sinuses underlie the spread of infection
- 4. MRV and catheter angiography if MRA does not adequately demonstrate thrombi in this system

Internal Cerebral Veins, Vein of Galen and Straight Sinus

General Characteristics

- 1. The deep venous system drains:
 - a. Thalamus
 - b. Basal ganglia
 - c. Midbrain
 - d. Geniculate bodies
 - e. Cerebellum

Clinical Manifestations

- 1. Occlusion of the internal cerebral vein and vein of Galen:
 - a. Clinical features:
 - i. Patients present stuporous or in coma
 - ii. Severe headache may precede decreased level of consciousness
 - iii. Hemiparesis
 - b. If thalamic and basal ganglionic hemorrhage supervene
 - i. Coma
 - ii. Decerebrate posture
 - iii. Vertical gaze palsy
 - iv. Apathy and abulia in some patients as a presenting sign

Neuropathology

- 1. Hemorrhagic infarction
- 2. Etiologies include:
 - a. Dehydration
 - b. Sickle cell disease
 - c. Infection
 - d. Ulcerative colitis
 - e. Oral contraceptives

Neuroimaging

- 1. Combination of MRI to visualize the thrombosed vessel and MRV to detect non-visualization of the identical vessel
- 2. Bilateral thalamic and basal ganglia lesions
- 3. DWI heterogeneous signal intensity in affected areas
 - a. Apparent diffusion coefficient map (ADC) may be close to normal

Jugular Vein Thrombosis

General Characteristics

- 1. The major cause of Lemierre's syndrome that is caused by infection in the oropharyngeal region with subsequent involvement (thrombophlebitis) of the internal jugular vein (IJV)
- 2. Involvement of the contiguous carotid sheath may occur which contains:
 - i. Internal jugular vein
 - ii. Carotid artery
 - iii. Vagus nerve
 - iv. Lymph nodes
 - v. Cranial nerves IX, XI XII that are in the upper sheath

Clinical Manifestations

- 1. Headache, fever and vomiting
- 2. Carotid artery occlusion (arteritis)
 - a. Cranial nerve IX–XII palsies
 - b. Horner's syndrome
 - c. Trismus if infection involves the pterygomandibular area

Neuropathology

- 1. Thrombus in the internal jugular vein can spread to the liver and lungs
- 2. Often internal jugular vein infection occurs from a palatine tonsil infection with the bacterium *Fusobacterium necrophorum*
- 3. Drug abuse (injection into jugular vein)
- 4. Other causes of internal jugular vein infection:
 - a. Dental procedures
 - b. Parotitis (HIV patients)
 - c. Mastoiditis
 - d. Otitis media

Neuroimaging

MRI/MRV

- 1. Identifies possible source of the infection (MRI) and extent of the thrombus (MRV)

Cortical Cerebral Venous Thrombosis

General Characteristics

- 1. In association with occlusion of the superior sagittal sinus
- 2. Pattern of neurological involvement is not in an arterial distribution

Clinical Manifestations

1. Seizures at presentation
 - a. Spread of affected body area (worsening) with each seizure
2. Focal neurological signs:
 - a. Aphasia
 - b. Hemiparesis
3. Headache
4. Less commonly a decreased level of consciousness

Neuropathology

1. Prothrombotic states
2. Puerperium
3. Associated superior sagittal sinus or other sinus involvement

*Neuroimaging***MRI**

1. Brain edema with hemorrhage (out of an arterial distribution)
2. Pial surface of the hemisphere is involved

MRV

1. Evaluates other sinuses and demonstrates the thrombotic veins

Cerebellar Venous Occlusion*General Characteristics*

1. Usually associated with lateral sinus disease
2. Prothrombotic states

Clinical Manifestations

1. Severe headache
2. Incoordination of the affected side
3. Lower cranial nerve palsies
4. Pseudotumoral course with brainstem compression

Neuropathology

1. Hemorrhagic infarction out of an arterial distribution
2. Tonsillar herniation

*Neuroimaging***MRI/MRV**

1. MRI/MRV to evaluate the cerebellar veins and the extent of edema

Differential Diagnosis of Tumors that Cause Venous Sinus Compression

1. Ewing's sarcoma (extension from occipital region of skull)
2. Plasmacytoma
3. Metastasis most commonly from breast and lung cancer
4. Neuroblastoma
5. Choriocarcinoma
6. Prostate cancer

Differential Diagnosis Between a Mass beneath the Inner Table of Skull vs Tumor Invasion of the Dura and Sinus

1. Diagnostic Features of Venous Occlusive disease:
 - a. Specific circumstances as noted
 - b. Headaches is often the presenting symptom
 - c. Seizure and lethargy more common than in arterial disease
 - d. Increased intracranial pressure in the absence of focal deficits
 - e. Slower and more indolent progression than arterial disease

*Imaging Evaluation***CT**

1. Evidence of sinus and middle ear disease
2. Cord sign
 - a. Cerebral vein imaged as high density linear, thin tubular structure
3. Delta sign at the confluens of sinuses
 - a. Hyperdense triangular mass within the sinus on contrast CT; which does not enhance
4. Bilateral thalamic and basal ganglia hemorrhage
5. Small compressed ventricles
6. Lesions out of a typical arterial distribution
7. Deep Venous Occlusion demonstration by CT
 - a. Bilateral hypodensity of thalamus and basal ganglia
 - b. Edema and compression of the IIIrd ventricle
 - c. Retention of contrast in thalamostriate veins, basilar vein of Rosenthal, non-opacification of vein of Galen

Contrast Enhanced CT

1. Dilated cortical and medullary veins
2. Gyral enhancement

MRI/MRV

1. May directly image the occluded venous sinus
2. Demonstrates collaterals
3. MRI may be negative in 30% of patients

Arteriography

1. Delineates all venous and arterial structures
 - a. Now necessary as angioplasty and intravenous thrombotics may be options
 - b. Better visualization of congenital variants
2. Multifocal and bilateral
3. Seizures and increased intracranial pressure
4. Cortical surface causes focal leg seizure (superior sagittal sinus) or arm (cortical vein)

Medical Causes of Stroke**Overview**

The medical causes of stroke occur in younger patients and are associated with cardiac disease, autoimmune vasculitis,

infection, mitochondrial deficits or clotting factor dysfunction. Dissection from trauma or in association with collagen vascular disease and migraine is also common. Specific diseases such as cerebral autosomal dominant arteriopathy with subcortical infarction and leukoencephalopathy (CADASIL), hereditary endotheliopathy, neuropathy, renal disease and stroke (HERNS) as well as mitochondrial disease and named diseases such as Susac, Eales, Sneddon's, Cogan's and Grönblad–Strandberg disease, all test the diagnostic acumen of the examiner. Clotting disorders of deficiency, inhibition of activated coagulation factors or hereditary fibrinolytic defects are AD, AR or acquired. The examiner needs to elicit the seminal characteristic of each entity to diagnose the category of medical illness and then the specific disease.

Genetic causes of embolic stroke are:

1. Mitral valve prolapse – autosomal dominant
2. Tuberous sclerosis – autosomal dominant
3. Familial atrial myxoma (autosomal dominant and recessive)
4. Hereditary cardiac conduction defects (long QT) – autosomal dominant
5. Hereditary cardiomyopathies (autosomal dominant and recessive, X-linked)
6. Mitochondrial disease (maternal inheritance)

Mitral valve prolapse has a prevalence rate of 5–21% in the population. It occurs occasionally in an AD form and rarely causes a cerebral embolus. Auscultation reveals a mid-systolic murmur and 2D-ECHO cardiography determines greater than 2 mm or more abnormal movement of the anterior or posterior leaflets.

Tuberous sclerosis patients are easily diagnosed by their characteristic skin manifestations, seizures and mental retardation. Rhabdomyosarcoma may be the cause of cerebral emboli and is autosomal dominant.

Hereditary long QT syndrome most frequently presents with syncope especially provoked by drugs that decrease cardiac conduction or with rare sudden death during strenuous athletics.

Hereditary cardiomyopathies with a dilated myocardium occur in mitochondrial disease, limb-girdle muscular dystrophy, congenital myopathies, Duchenne's MD, Becker's MD, and myotonic dystrophy. All of these entities have characteristic physical findings such as proximal weakness, calf hypertrophy, contracture of elbows, arms and ankles (Emery-Dreifuss muscular dystrophy) and rigid spine syndrome.

Mitochondrial disease should be suspected in short patients who suffer undue fatigue with exercise, sensorineural hearing loss, diabetes and dilated cardiomyopathy.

Atrial myxomas with emboli may present with fevers of unknown origin, petechiae across the chest wall, pial vessel emboli and peripheral cerebral aneurysms that bleed (myxomatous material grows through the walls of the affected arteries).

Genetic causes of thrombotic stroke are:

1. CADASIL

2. CARASIL
3. Fabry's
4. HANAC
5. HERNS
6. PADMAL
7. Hereditary infantile stroke
8. Ehlers-Danlos disease type IV
9. Marfan's disease
10. PXE (Pseudoxanthoma elasticum)
11. Mitochondrial diseases
12. Homocysteinemia
13. Neurofibromatosis
14. Menke's disease
15. Retinal diseases (HERNS, HANAC, Susac's disease, CRV)
16. Moyamoya
17. Progeria
18. Dyslipoproteinemias such as Tangier disease (orange tonsils, alpha hypolipoproteinemia and intermittent neuropathy)
19. Hemoglobinopathies particularly sickle cell disease which has conjunctival telangiectasis and arachnodactyl. Neurofibromatosis type I has characteristic coast of Maine hyperpigmented lesions and abnormalities of the renal vasculature

Clotting disorders secondary to polycythemia vera cause strokes primarily in the posterior circulation and tend to thrombose large cerebral vessels. Retinal venous occlusion in coagulopathies from clotting factor inhibitor deficiency is characteristically seen in young patients whose parents have had fetal wastage. Protein losing enteropathy, nephrotic syndrome and migraine with aura are all associated with stroke. Protein S deficiency and stroke occurs in middle aged women. Protein C deficiency often occurs concomitantly with the Factor V Leiden mutation. Antithrombin III deficiency should be suspected in the setting of severe resistance to heparin anticoagulation. Anticardiolipin antigen and lupus anticoagulant often are associated with migraine with visual aura. Cerebral sinus thrombosis is common in all defects of inhibitors of clotting.

Platelet abnormalities and stroke should be suspected in a setting of petechiae particularly of the lower extremities. The primary antiphospholipid antibody syndrome is associated with spontaneous abortion and fetal wastage. Valve cusps are affected and the syndrome may be associated with cerebral emboli. The lupus anticoagulant is an antibody to phospholipids (on platelets) which blocks the formation of the prothrombin activator and is most often associated with clotting and not hemorrhage (depends on titer). There is usually evidence of systemic venous clotting.

In general, platelet counts of greater than one million/mm³ are associated with hypercoagulability. Functional platelet abnormalities rather than absolute number may be the important parameter. This may occur in a small group of migraine patients and in essential thrombocythemia.

Heparin induced thrombocytopenia and thrombosis occurs as a transitory and asymptomatic reduction in platelet count or as an immunopathologic condition. The later (Type II) usually occurs after the 5th day of treatment and causes both arterial and venous thrombosis. Gangrene of a limb, thrombosis and stroke is the usual triad. White clots are noted in blood vessels (particularly visible in the retina).

Disseminated intravascular coagulation occurs in a setting of gram negative sepsis, cancer and obstetrical emergency. It is announced by oozing from all venipuncture sites and acrocyanosis. Arterial and venous clotting as well as hemorrhage dominates the clinical profile.

The following discussion highlights the major characteristics and differential features of the genetic causes of embolic and thrombotic stroke, coagulopathies and rheological abnormalities that are seen in clinical practice.

Genetic Causes of Embolic Stroke

General Characteristics

1. Mitral valve prolapse (MVP) – AD
 - a. Associated with:
 - i. Osteogenesis imperfecta
 - ii. Ehlers-Danlos syndrome
 - iii. Marfan's disease
 - iv. Duchenne's muscular dystrophy
 - v. Becker's muscular dystrophy
 - vi. von Willebrand's disease
 - vii. Fragile X syndrome
2. Tuberous sclerosis – AD
 - a. Cardiac rhabdomyomas that cause emboli
 - b. 80% are new mutations
 - c. Abnormalities of cerebral arteries and aorta also occur
3. Familial atrial myxoma (AD, AR)
 - a. AD/AR forms; most atrial myxomas are sporadic
 - b. 20% of familial atrial myxomas are associated with an AD heredity
 - c. Also associated with:
 - i. Myxoid fibroadenoma
 - ii. Lentiginous blue nevi
 - iii. Large cell calcifying Sertoli cell tumors
 - iv. Primary adrenocortical nodular dysplasia
4. Pituitary growth hormone tumors
5. Hereditary cardiac conduction defects (long QT) AD
6. Hereditary cardiomyopathy AD, AR, X-linked
7. Mitochondrial disease (maternal inheritance)

Hypertrophic Cardiomyopathy (HCM)

General Characteristics

1. Most common genetic cardiovascular disease affects 1 in 500 in the general population
2. Autosomal dominant; 24 genes identified (encode sarcomeric proteins)
 - a. Myocyte disarray which leads to premature death and remodeling

- b. Pathologies include hypertrophy, fibrosis, myocardial ischemia and coronary artery disease
- c. Dispersion of repolarization due to gap junction dysfunction that leads to:
 - i. Supraventricular arrhythmias (10–40% in hypertrophic cardiomyopathy)
 - ii. Atrial fibrillation is most common
3. Can occur at any age: annual mortality rate of 1%

Clinical Manifestations

1. Many patients are asymptomatic
2. Dyspnea in 90%
3. Exercise intolerance
4. Presyncope/syncope (often associated with arrhythmia)
5. Atrial fibrillation and ventricular tachycardia presentations
6. Sudden death

Cardiac Dysrhythmia with Emboli

Idiopathic Hypertrophic Subaortic Stenosis (IHSS)

General Characteristics

1. Syncope after exercise
 - a. Norepinephrine constricts the subaortic outlet; epinephrine dilates blood vessels in skeletal muscle. Severe hypotension results after strenuous exercise due to dilation of blood vessels from release of epinephrine in skeletal muscle
2. Atrial fibrillation occurs late in the course of the illness
 - a. Emboli during the arrhythmia
3. Females at greater risk than males for stroke
4. Hypertension a cause of stroke
5. Other stroke mechanisms:
 - a. Associated mitral annulus calcification
 - b. AV conduction defect

Dilated cardiomyopathy (DCM) with Arrhythmias

General Characteristics

1. DCM with and without conduction-system disease
2. Familial DCM with CSD (conduction syndrome) chromosome 1 p1-q21
3. X-linked dystrophinopathy (Becker's; Duchenne)
4. Female carrier of Becker's MD and Duchenne's MD
5. Sporadic and AR limb-girdle muscular dystrophy (2C–2F)
6. Emery-Dreifuss Muscular Dystrophy (severe arrhythmias that requires pacing)
7. Myotonia type I, LGMD 1b
8. Adhalinopathies
9. Barth syndrome
10. Rigid Spine syndrome
11. Welander's distal myopathy
12. Distal vacuolar myopathy
13. Systemic carnitine deficiency

Genetic Enzymatic Causes of Thrombotic Stroke

Hyperhomocysteinemia

General Characteristics

1. Enzymatic deficiencies of methionine metabolism that produce homocysteine. Its intracellular metabolism is complex and sequential:
 - a. Transsulfuration to cysteine
 - b. Remethylation to methionine
 - c. Homocysteine is catabolized to cystathionine by:
 - i. Pyridoxine dependent condensation with serine
 - ii. Cystathionine β -synthase catalyzes the first step in transsulfuration
 1. Deficient in classic homocystinuria
 - d. Mechanisms of hyperhomocystinuria:
 - i. Hereditary defects in enzymatic pathways
 - ii. Deficiencies of vitamin cofactors
 - e. Major enzyme deficits are:
 - i. Cystathionine β -synthase (pyridoxine dependent)
 - ii. Methylene tetrahydrofolate reductase
 - iii. Methionine synthase (MTHFR and cobalamin needed as cofactors)
 - f. Homocysteine elevation also occurs with:
 - i. Age
 - ii. Smoking
 - iii. Deficiency of B12, B6 or folic acid
 - iv. Specific drugs (statins, niacin, metformin, levodopa, antihypertensives, some oncologic agents and theophylline)
 - g. Incidence is 1:83,000 in the general population
 - h. Most common enzyme deficiency is:
 - i. Cystathionine β -synthase (24 mutations identified)
 1. Chromosome 21
 2. Homozygosity for homocystinuria is between 1.5%–3% in the general population

Clinical Manifestations

1. Presentation:
 - a. Peripheral venous thrombosis (most common)
 - b. Myocardial infarction
 - c. Cerebrovascular disease
2. Marfanoid habitus
3. Cognitive impairment
4. Livedo reticularis
5. Malar flush
6. Dislocated lenses in one or both eyes
7. Myopia
8. Glaucoma
9. Optic atrophy (rare)

Neuropathology

Stroke Mechanisms

1. Artery-to-artery embolism
2. Arterial dissection
3. Carotid artery disease
 - a. Dilation and medial wall damage rather than atherosclerosis

Putative Pathogenesis of Stroke Due to Elevated Homocysteine

1. Accelerated atherosclerosis
2. Arterial dilation
3. Increased:
 - a. Tissue factor expression
 - b. Platelet reactivity
 - c. Thrombin generation
 - d. Factor V activity
 - e. Monocyte chemotactic protein-I (MCP-1)
 - f. IL-8 (expression in vascular smooth muscle)
4. Decreased:
 - a. Fibrinolysis
 - b. Endothelial function
 - c. Thrombomodulin
 - d. Heparin sulfate
5. Homocystinuria may lead to a prothrombotic state

Recent Concepts

1. Lowering homocysteine by B group vitamin supplementation does not reduce cardiovascular risk; suggested that homocysteine levels are a “concomitant” marker rather than pathogenic
2. Elevated plasma homocysteine causes:
 - a. Reduced methylation potential
 - i. Due to decreased S-adenosyl-methionine (Adn Met)/S-adenosyl homocysteine (Ado Hcy) ratio
 - ii. Mechanism for CVD:
 1. Dependent on DNA methylation (epigenetic regulation) that induces inhibition of cyclin A transcription
 2. Leads to decreased endothelial cell growth

Neuroimaging

1. Small vessel disease of the brain
2. Large vessel disease of the cerebral arteries
3. Angiography

Methylenetetrahydrofolate Reductase (MTHFR)

General Characteristics

1. Autosomal recessive: located on chromosome 1P
2. Critical for the metabolism of folic acid and methionine
3. Prevalent in North Americans:
 - a. 50% are heterozygous for a thermolabile mutation
 - b. MTHFR mutation C6771 homozygous polymorphism:
 - i. Causes hyperhomocysteinemia and increases stroke risk

Clinical Manifestations

1. Congenital form:
 - a. Global developmental delay: failure to thrive
 - b. Seizures
 - c. Cardiovascular manifestations occur with age
2. Adult form
 - a. Possible increase in ischemic stroke

Neuropathology

1. Accelerated atherosclerosis
2. Small vessel disease

Neuroimaging

1. Small vessel disease
2. Topographic pial vessel stroke

Laboratory Evaluation

1. Low CSF folate and plasma methionine levels
2. No megaloblastic anemia

Organic Acidemias*Propionic Acidemia***General Characteristics**

1. An organic acidemia
2. Deficit of the enzyme propionyl-coenzyme A carboxylase (a mitochondrial enzyme)

Clinical Manifestations*Childhood Form*

1. Developmental delay
2. Episodic severe acidosis/encephalopathy triggered by infection or metabolic decompensation
3. Hyperammonemia
4. Visual hallucination
5. Movement disorder
6. Seizures
7. Central nervous and optic nerve involvement
8. Cognitive deficits
9. Metabolic stroke-like episodes

Adult Form

1. Progressive cognitive decline
2. Cardiac and G.I. dysfunction
3. Stroke-like episodes

Neuroimaging*MRI Evaluation*

1. Basal ganglia infarction (caudate, G.P., putamen)
2. Subcortical white matter demyelination
 - a. Often periventricular
3. Metabolic pattern dysfunction not in a vascular territory

MRS (Spectroscopy)

1. Decreased basal ganglia glutamate and glutamine
2. Decreased N-acetyl-aspartate (neuronal death)
3. Increased lactate
4. Indicative of switch to anaerobic metabolism

Neuropathology

1. Bio-energetic stroke
 - a. Deficits in Krebs cycle and respiratory chain function

*Methyl Malonic Aciduria (MMA)***General Characteristics**

1. Incidence is about 1:250,000 newborns

2. Inborn error of metabolism

3. May be seen in adults and is associated with B12 metabolism deficits

Clinical Manifestations*Neonates*

1. Retinopathy
2. Hydrocephalus
3. Microcephaly
4. Metabolic stroke
5. Seizures (children)

Adult Presentation

1. Subacute bilateral visual loss
2. Basal ganglia involvement

Neuropathology

1. Megamitochondria demonstrated in the kidney
2. Deficiency of methylmalonyl CoA mutase
3. Metabolic stroke

Neuroimaging*MRI Evaluation*

1. Bilateral globus pallidus (acute infarction) in all patients
2. Lacunar infarcts in pars reticulata of the substantia nigra

Laboratory Evaluation

1. Gas chromatograph-mass spectroscopy (GC-MS)
 - a. Methylmalonic acid demonstrated

*Glutaric Aciduria (Acidemia) Type I***General Characteristics**

1. Glutaryl-CoA dehydrogenase is the deficient enzyme; on the short arm of chromosome 19; Autosomal recessive
2. Mitochondrial nuclear enzyme defect
3. Incidence of 1:30,000 people

Clinical Manifestations*Presentation in Infancy*

1. Macrocephaly
2. Hypotonia/jitteriness/tremor
3. Fever of unknown origin; hyperhidrosis
4. Seizures
5. Coma
6. Metabolic crisis:
 - a. Precipitated by fever and dehydration
 - b. Leads to striatal necrosis

Adult Clinical Presentation

1. Majority of patients present as dystonic cerebral palsy with basal ganglia involvement; baseline axial hypotonia occurs with time
2. May evolve to rigid – Parkinsonian syndrome
 - a. Oral-facial involvement is prominent

Neuroimaging*MRI Evaluation*

1. Frontal temporal atrophy

2. Delayed myelination pattern
3. Increased T2-weighted sequence hyperintensities in the periventricular white matter and U-fibers
4. Ventriculomegaly
5. Subdural hygromas
6. Putamen may be involved solely or with:
 - a. Caudate and globus pallidus
 - b. Thalamus and dentate

Laboratory Evaluation

1. Accumulation of glutamic acid (GA) and 3-hydroxy glutamic acid (3-OHGA)

Neuropathology

1. Metabolic-mediated neuronal damage:
 - a. Excitotoxicity
 - b. Failure of energy production
 - c. Oxidative stress
2. Glutaric acid and 3-hydroxyglutaric acid (3-OHGA) accumulate:
3. During a metabolic crisis
4. Failure of BBB transport mechanism
5. Excretion of glutaryl carnitine may lead to secondary carnitine deficiency

Glutaric Aciduria (Acidemia) Type II

General Characteristics

1. Multiple acyl-CoA dehydrogenase deficiencies that cause electron transfer flavoprotein deficiencies
2. Neonatal, infantile, childhood and later onset forms

Clinical Manifestations

1. Vomiting
2. Hypoglycemia
3. Metabolic acidosis
4. "Sweaty feet" odor
5. Seizures
6. Aphasia
7. Myoclonus
8. Stroke-like episodes
9. Cyclic vomiting
10. Facial dysmorphism

Late Onset Phenotype

1. May present as proximal myopathy (increased fat in muscle)
2. Cyclic vomiting

Neuroimaging

MRI Evaluation

1. Increased T2-weighted signals in the putamen, middle cerebellar peduncle and splenium of the corpus callosum
2. Periventricular white matter hyperintensities in T2-weighted sequences

Pathology

1. Gliosis and heterotopias in the brain
2. Associated polycystic kidney
3. Genital defects

Laboratory Evaluation

1. Urinary excretion of organic acids

Ornithine Transcarbamylase Deficiency

General Characteristics

1. X-linked recessive; Xp21.1
2. The most common inherited cause of hyperammonemia secondary to ammonia cycle dysfunction

Clinical Manifestations

1. Severe neonatal form in males
2. Partial form in males and females
3. Late onset form

Neonatal and Infantile Forms

1. Developmental delay
2. Recurrent hyperammonemia
3. Encephalopathy
4. Coma
5. Female patients are often asymptomatic

Late Onset

1. Reported in patients taking valproic acid
2. In women heterozygous for the mutations during the postpartum period

Neurologic Features

1. Developmental delay
2. Seizures
3. Autistic signs
4. Hyperactivity (ADHD)
5. Ataxia
6. Dysarthria
7. Hyperammonemic crisis with stress

Cerebrovascular Signs and Symptoms

1. Recurrent stroke-like episodes
2. Cerebral ischemic infarction (rare)
3. Intracranial hemorrhage (rare)
4. Cerebral edema

Neuropathology

1. Similar to the changes of hepatic encephalopathy
2. Affects predominately white matter and astrocytes

Laboratory Evaluation

1. Unexplained hyperammonemia in an adult
2. Allopurinol challenge that induces an increase of orotate in the urine
3. Gene identification

*Neuroimaging***MRI**

1. As the severity of the illness increased:
 - a. Peri-insular white matter involvement progresses to the frontal, parietal, temporal and occipital lobes
 - b. Stroke-like episodes compatible with “bio-energetic failure”

MRS

1. Increased gln levels in frontal white matter
2. Decreased myoinositol in frontal white matter

Fabry's Disease*General Characteristics*

1. X-linked disorder of glycosphingolipid metabolism
 - a. A deficiency of lysosomal alpha-galactosidase A that leads to:
 - i. An accumulation of neutral glycosphingolipids – predominantly globotriaosylceramide in the lysosomes of endothelial and smooth muscle cells in blood vessels
 - ii. Common polymorphisms in the genes for angiotensinogen (AGT), AGT promoter and angiotensinogen II receptor type I (AGTRI)
 1. AGT promoter and AGTRI genotypes are noted in Fabry's phenotypes in .6% of high risk populations
2. Prevalence 1:40,000 males
3. Heterozygous patients present with no symptoms or a milder disease
4. Heterozygous females:
 - a. Asymptomatic or a milder disease phenotype
 - b. Occasionally they are as symptomatic as males
5. Cerebrovascular manifestations are common in both hemizygote and symptomatic heterozygote groups
 - a. 4% of cryptogenic strokes may have mutations in the α -galactosidase gene

*Clinical Manifestations***General Neurologic Features**

1. Early in the disease course:
 - a. Episodic crises of severe neuropathic pain
 - i. Precipitated by exercise and often associated with fever
2. Minute to hour duration
3. Primarily acroparesthesias
4. Heat intolerance
 - a. Autonomic dysfunction with anhidrosis (infiltration of ceramide trihexoside in the autonomic ganglia and the autonomic fibers to sweat glands)

General Signs and Symptoms

1. Heterozygous males

- a. Angiokeratomas (cherry red papules); periumbilical area, extensor surfaces of elbows and knees and genitals (bathing suit distributions)
- b. Corneal and lenticular opacities
- c. Dilatation and tortuosity of conjunctival vessels
- d. Retinal vessel abnormalities
- e. Hypohidrosis (with heat intolerance)
- f. Cardiac dysfunction
- g. Renal failure
2. Heterozygote females
 - a. Lumbosacral degeneration
 - b. Asymptomatic
 - c. Some signs/symptoms similar to male patients
3. Cerebrovascular disease
 - a. Male hemizygotes
 - i. Ischemic strokes in the fourth decade
 - ii. Anterior and posterior circulation involvement; posterior circulation more frequently involved than anterior
 - iii. Small vessel disease
 - iv. Cause of vascular dementia for patients less than 65 years old
 - b. Heterozygote women
 - i. Cerebrovascular symptoms a decade later than males
 - ii. 50% involvement in vb system; 10% certain carotid involvement
 - iii. Headaches greater than seen in males
 - iv. Central retinal vein occlusion
 - c. Greater involvement of posterior circulation whose putative mechanisms are:
 - i. VB dolichoectasia
 - ii. Thickening and luminal compromise of medium and small arteries
 - iii. Deep small cerebral infarcts
 - d. Cardiogenic embolism
 - i. Coronary artery disease (left ventricular wall dysfunction)
 - ii. Valvular heart disease (mitral valve)
 - iii. Mitral valve prolapse
 - iv. Hypertrophic cardiomyopathy (especially in heterozygote women)
 1. Often associated with AF
 2. Occurrence in women greater than men
 - e. Carotid artery atherosclerotic plaque
 - i. Less than controls
 - ii. Greater intima to media thickness
 - f. Orthostatic hypotension due to ANS dysfunction
 - g. Prothrombotic state:
 - i. Activation of platelets by endothelial dysfunction due to deposition of glycosphingolipids
 - ii. Endothelial cell dysfunction with increased
 1. Soluble intercellular adhesion factors-1
 2. Vascular cell adhesion molecule-1
 - iii. P-selection (increased)

- iv. Plasminogen activator inhibitor (increased)
- v. Integrin CD11b increased
- vi. Decreased thrombomodulin
- vii. Approximately 35% of patients have factor V Leiden mutations
- h. Intrinsic vascular abnormalities:
 - i. Down-regulation of nitric oxide pathway
 - ii. Increase oxidative stress which leads to:
 - 1. Accelerated atherosclerosis
 - 2. Vasodilatation
 - i. Intracranial arterial dolichoectasia causes:
 - i. Neurovascular compression syndromes
 - ii. Triventricular hydrocephalus
 - iii. Isolated III, V, VIII, XIIth nerve palsy by compression from basilar of vertebral arteries
 - iv. IIInd cranial nerve compression from dolichoectatic supraclinoid carotid arteries
 - v. Putative mechanism:
 - 1. Deposition of glycosphingolipids in the lysosomes of the smooth muscle of arterial walls
 - 2. Possible cause of ICH (loss of structural integrity of vessel walls)
 - a. Hypertension from concurrent renal vessel disease
 - b. Both hemi- and heterozygotes

Neuropathology

Cerebrovascular Pathology

1. Infarcts of:
 - a. Superficial hemispheric pial arteries
 - b. Small deep perforating vessels
 - c. Brainstem and cerebellum
2. Rare intracerebral hemorrhage
3. Narrowing of lumen secondary to glycosphingolipid deposits in lysosomes of both endothelial cells and smooth muscle of the arterial wall

Neuroimaging

MRI

1. Superficial territorial and deep perforating artery infarction of the hemispheres and brainstem and cerebellar blood vessels
2. Dolichoectasia of the basilar and vertebral arteries
3. Small vessel disease pattern in patients older than 54 years
4. Approximately one third of younger patients may have no lesions

MRS (Magnetic Resonance Spectroscopy)

1. NAA/creatine and phosphocreatine and are decreased
 - a. Suggestive of neuronal loss

Dyslipoproteinemias – Tangier Disease

General Characteristics

1. Familial hypoalphalipoproteinemia

- a. Autosomal recessive
- b. Due to mutations in both alleles of the ABCA1 gene
 - i. ABCA1 protein transports cellular cholesterol and phospholipids to the extracellular acceptor free apoA-1 to form high density lipoprotein (HDL)

Clinical Manifestations

1. Peripheral neuropathy occurs in approximately 50% of patients
 - a. Remitting relapsing multifocal neuropathy with sensory abnormalities
 - b. Sphingomyelia like neuropathy
 - i. Muscle wasting and anesthesia involve the face and upper extremities prior to spread to the lower extremities
 - 1. Putative neuropathy of the dorsal roots
 - c. Enlarged orange tonsils
 - d. Hepatosplenomegaly
 - e. Premature atherosclerosis with topographical stroke

Neuropathology

1. Hyperplastic foam cells
 - a. Inability to efflux cholesterol by the ABCA1 transporter
2. Lipid-laden cells to the reticuloendothelial system cause both the tonsillar enlargement on the hepatosplenomegaly
3. Premature atherosclerosis
 - a. Early coronary heart disease
 - b. Topographical stroke
4. Recurrent lobar intracerebral hemorrhage
5. Accumulation of cholesterol esters in many tissues

Neuroimaging

1. Recurrent lobar intracerebral hemorrhage
 - a. Demonstrated cerebral microbleeds
2. Large vessel stroke

Laboratory Evaluation

1. HDL less than 5mg/dL
2. Low plasma cholesterol – less than 150mg/dL
3. High plasma triglycerides

Genetic Cause of Thrombotic Stroke Overview

The genetic causes of stroke overlap with diseases of the vessel wall, coagulopathies, autoimmune, infectious diseases, enzyme deficiencies, mitochondrial disease, hemoglobinopathies and specific small vessel diseases.

Homocysteinemia, the glutaric acidurias, MMA, MTHFR and ornithine transcarbamoylase deficiency have been discussed primarily as enzymatic causes of thrombotic stroke. CADASIL, CARASIL and Fabry's are discussed primarily as causes of small vessel disease. Mitochondrial diseases fit many categories but are best classified as due to "bioenergetic failure".

This chapter will concentrate on those genetic causes of stroke with many systemic features. It will focus on Marfan's disease, pseudoxanthoma elasticum (PXE), Ehlers-Danlos, neurofibromatosis, progeria, Menkes disease and Moyamoya syndrome.

Marfan's Syndrome

General Characteristics

1. Connective tissue disorder that is system wide:
 - a. Skeleton and skin abnormalities
 - b. Cardiovascular system (aortic root dilation)
 - c. Lens dislocation and myopia
 - d. Lung involvement (emphysema)
 - e. MASS – myopia, mitral valve prolapse, aortic dilatation, skin and skeletal abnormalities

Genetics

1. Autosomal dominant; sporadic in about 25% of patients
 - a. Chromosome 15: mutation in the FBN1 gene that encodes fibrillin-1
 - b. Possible second locus:
 - i. 3p24-25
 - ii. Possible mutations in genes coding for TGF- α (important for angiogenesis)
 - c. Fibrillin-1
 - i. Major component of the extracellular matrix; the fibrillary structure for elastin deposition
 - d. Diagnosis requires a major criteria in two organ systems and involvement in a third

Clinical Manifestations

1. Dissection of the ascending aorta, the carotid and vertebral arteries
 - a. Arch dissection: pain in the face and carotid artery stroke
 - b. Dissection below the subclavian artery – pain straight through to the back with paraplegia
 - c. An excess of cerebral aneurysm but not subarachnoid hemorrhage
2. Emboli:
 - a. Cardiac arrhythmia
3. Spinal defects:
 - a. Craniospinal junction
 - i. Greater than 50% of patients have increased atlantoaxial translation (greater than 5 mm with neck flexion) causes odontoid compression of the spinal cord
 - ii. 36% have basilar impression (greater than 135° angle between the planum sphenoidale and the clivus)
4. Ectasia of the dural sac with irritation of lumbosacral nerve roots and back pain
5. Laryngeal nerve paralysis from aortic compression of the recurrent laryngeal nerve
6. Severe scoliosis
7. Multiple facial anomalies with retrognathia
8. Congenital ectopia lentis (may be the most specific finding)

Neuropathology

1. Defect is primarily in the vessel media with profound diminution of elastic fibers

Neuroimaging

1. Embolic stroke of cerebral vessels
2. Intracranial artery dissection
3. Arterial (cerebral) tortuosity and aneurysm
4. Dilatation of the aortic root

Differential Diagnosis

1. Homocystinuria
 - a. Mental retardation
 - b. Autosomal recessive
2. Congenital contractural arachnodactyly (Beals syndrome)
 - a. Marfanoid features; Autosomal dominant
 - b. Heart defects
 - c. Ocular defects
3. Loeys-Dietz syndrome
 - a. Transforming growth factor β receptor
 - i. 11(TGBRA) gene mutation
 - ii. Arterial tortuosity and aneurysms
 - iii. Hypertelorism
 - iv. Bifid (bifurcated) uvula/cleft palate

Pseudoxanthoma Elasticum (PXE) (Grönblad–Strandberg Syndrome)

General Characteristics

1. Female predominance (2:1)
2. Mutations in the ABCC6 gene on the short arm of chromosome 16 (16p13.1); Autosomal dominant and recessive forms; Autosomal dominant form possibly has more severe vascular disease
3. ABCC6 gene encodes:
 - a. Multi-drug resistance associated protein 6 a trans membrane transporter protein of the ABC (ATP binding cassette) family
 - b. β – Thalassemia patients have high prevalence of PXE

Clinical Manifestations

1. Systemic Signs
 - a. Additional eye signs
 - i. Choroid retinal atrophy
 - ii. Subretinal edema
 - iii. Pattern dystrophy-like changes
 - iv. Retinal drusen
2. Heart
 - a. Premature coronary artery disease
 - i. Sudden death
 - ii. Cardiomyopathy
 - b. Endocardial changes (elastic fiber changes)
 - i. Thickened mitral valves
 - ii. Mitral stenosis; MVP
 - iii. Restrictive cardiomyopathy (calcification of the endocardium)

3. GI tract
 - a. Gastrointestinal hemorrhage
 - i. Often the presenting symptom
 - ii. Degeneration of small-sized arteries
 - iii. Microaneurysms and angiomatous malformations
4. Skin: linear, round or oval yellow orange elevated lesions (resemble xanthomas)
 - a. Face, neck, axilla, inguinal, umbilical topography
 - b. Late stage – lax and redundant skin
 - c. Involvement of skin and mucosa in:
 - i. Lips
 - ii. Mouth
 - iii. Vagina
 - iv. Rectum
 - d. Gastric mucosa
 - e. Endocardium and heart valves
5. Eye involvement
 - a. Classic
 - i. Angioid streaks
 1. Red, brown or gray
 2. Wider than veins
 3. Radiate from the disc
 - ii. Rupture of Bruch's membrane (a thin membrane separating the blood vessel-rich layer from the pigmented layer of the retina)
 - b. "Peau d'orange" (a French term meaning that the retina resembles the skin of an orange)
 - c. Chorioretinal scarring and hemorrhage
 - d. Optic nerve infarction
 - i. Involvement of the posterior ciliary arteries
 - ii. Comet bodies

Cerebrovascular Disease in PXE

1. Hypertension
2. Aneurysmal dilation of the aorta
3. Calcification of peripheral arteries with intermittent claudication
4. Occlusive cervicocranial arterial disease; intra- and extracranial
5. Subarachnoid hemorrhage
6. Carotid artery
 - a. Increased thickness; more elastic with increased intimal-medial thickness
 - b. Tortuosity and ectasia
7. Ischemic symptoms develop in the 5th and 6th decades
8. Concomitant pathology of hypertensive cardiovascular disease
 - a. ICH
 - b. Lacunar infarction
 - c. Microvascular disease (Binswanger)
9. Aneurysm formation and SAH
 - a. Cavernous sinus
 - i. May present with cranial nerve palsy rather than SAH
10. Possibly increased incidence of dissection

Neuroimaging

1. Occlusive cervicocranial disease that is intra- or extracranial
2. Tortuosity and ectasia of cervical arteries
3. Lacunar infarction
4. Microvascular disease
5. Hyperintensive changes

Neuropathology

1. Decreased calcium extracellular homeostasis
2. Loss of elastic tissue, fragmentation of the internal elastic membrane; calcifications between the intima and media

Differential Diagnosis of Identified Genes for Arterial Calcification

1. ENPPI
2. ABCC6 (PXE)
3. NTSE
4. SLC20A2
5. CD73 deficiency

Differential Diagnosis of Angioid Streaks

1. Sickle cell anemia
2. Paget's disease
3. Hypophosphatemia
4. Ehlers-Danlos syndrome
5. Lead poisoning
6. PXE
7. ITP
8. Trauma
9. Pituitary disease

Differential Diagnosis of Arterial Calcification

1. Aging
2. Diabetes mellitus
3. Chronic kidney disease
4. Generalized arterial calcification of infancy
5. PXE
6. Familial idiopathic basal ganglia calcification

Moyamoya Syndrome

General Characteristics

1. Prevalence in asymptomatic Japanese population is 50.7/100,000 people
 - a. Patients in Northeast Asia have genetic disease and not syndrome
 - b. Two peak ages:
 - i. Children younger than 14 years
 - ii. Young adults between 25–49 years
 - iii. Japanese female to male ratio is 1.6- to 1.8: 1
 - c. Genetics
 - i. AD with incomplete penetrance
 - ii. Complex chromosome rearrangements at 6p25.3; variant RNF 213c14576G7A
 - iii. Genetic form is more common in children

*Clinical Manifestations**Cerebrovascular Disease in Adults*

1. Recurrent stroke or TIA is a common presentation
 - a. Border zone territorial stroke between MCA/ACA and MCA/PCA
2. Infarctions in the cortex, deep hemispheric white matter or basal ganglia
3. Progressive ischemic frontal lobe syndrome occurs with behavioral changes
4. Brainstem strokes are rare
5. Less frequent: headache and seizures than in children
6. May present with ICH
 - a. Asymptomatic microhemorrhages
 - b. Recurrent hemorrhages are frequent
 - c. Pathogenesis of hemorrhages can be rupture of collateral blood vessel, small false aneurysm or vascular malformation
 - d. Hemorrhages
 - i. More frequent in 46–55 year old patients
 - ii. Intracerebral in 60% (BG and thalamus)
 - iii. Intraventricular in 30%
 1. Extension from the thalamus
 2. Direct from the caudate
 - iv. Deep penetrating arteries
 1. Degenerative changes; hypertrophied
 2. Develop microaneurysms
 3. Small asymptomatic hemorrhages in the paraventricular white matter, subcortex
 - v. Rare: SAH; high incidence of posterior circulation aneurysm
 1. Small false aneurysms along the ventricular surface and Moyamoya collaterals are a source of SAH
 - vi. A unilateral process is against Moyamoya disease

Neuroimaging

1. There are six angiographic stages from narrowing of the distal ICA (stage I to the cerebral circulation supply from meningeal pial collaterals of the external carotid)
2. Collaterals from the ethmoidal arteries
3. Intracranial saccular aneurysms: posterior > anterior circulation
 - a. Arise at arterial bifurcations

MRI

1. Infarctions are primarily in deep hemispheric nuclei and hemispheric white matter
2. Border zone topography infarction primarily between ACA/MCA
3. Dilated leptomeningeal and transdural collateral arteries

Neuropathology

1. Bilateral severe stenosis or occlusion of the terminal ICA and proximal ACA and MCA; can affect the PCA; superficial temporal artery and the middle meningeal artery

Microscopic Evaluation of Large Intracranial Arteries

1. Thickening of the intimal and medial layers
2. Proliferation and degeneration of smooth muscle cells
3. Fragmentation of the internal elastic membrane
4. No inflammatory, calcification or lipid droplets
5. Ethmoidal collaterals involve the frontal basal areas, vault and Moyamoya vessels are collaterals (a generalized vascular network)
6. Collaterals develop from external carotid artery as well as the thalamoperforators, the dorsal branches of the PCA, tectal plexus and posterior choroidal vessels
7. Associated with a greater number of illnesses

Menkes Disease*General Characteristics*

1. Mutations in the ATP7A gene on the long arm of the X chromosome (xq12-q13)
2. P-type ATP protein that is encoded functions to translocate metal cations across cellular membranes; transports copper to those enzymes that require it
3. ATP7A mutations also cause:
 - a. Occipital horn disease
 - b. Distal hereditary motor neuropathy
4. Patients have low copper levels in the brain
5. Signs and symptoms are due to deficiencies of Cu^{2+} dependent enzymes such as ceruloplasmin; superoxide dismutase; dopamine β -hydroxylase (DBH)

*Clinical Manifestations**Neurologic Signs and Symptoms*

1. Classic presentation:
 - a. Neonatal
 - i. Hypothermia
 - ii. Poor feeding
 - iii. Failure to thrive
 - iv. Seizures
 - b. Scalp hair
 - i. Twisted, colorless, friable
 - ii. Fractures of the hair shaft at regular intervals
2. Severe tortuosity of blood vessels
3. Long bone-metaphyseal spurring and a diaphyseal periosteal reaction
4. Hydronephrosis; bladder diverticula

*Neuroimaging***MRI**

1. Vascular tortuosity
2. Cerebral atrophy
3. Infarcts of deep gray matter and the cortex
4. Asymptomatic subdural hematoma

Pathology

1. Tortuous arteries
 - a. Irregular lumen

- b. Split intimal lining
- c. Non sulfate and sulfate chondroitin are deposited within elastin fibers
 - i. Poor elastin formation and cross linking
 - ii. Dysfunction of copper dependent lysyl hydroxylase
 - iii. Focal degeneration of gray matter with gliosis
 - iv. EM demonstrates increased mitochondria in Purkinje cells and cortical neurons

Progeria

General Characteristics

1. Characterized by premature aging
2. Childhood form: Hutchinson-Gilford progeria syndrome (HGPS)
3. Adult Progeria: Werner's syndrome
4. Several progeria-like syndromes have been defined genetically and clinically

Genetics

1. Genetics of progeria and progeroid syndromes
 - a. Progeria is caused by mutation of the LMNA gene that encodes lamins A and C
 - i. Lamins are nuclear intermediate filaments; their basic nuclear functions are:
 1. Chromatin organization
 2. DNA replication
 3. Transcription
 4. Cell cycle progression
 - ii. Cell lines from HGPS demonstrated lack of transcriptional deregulation due to:
 1. Lack of functional lamin A
 2. Progerin acceleration
 3. Lamin β 1 silencing
 - iii. Progerin is a truncated version of the lamin A protein that has a deletion of 50 amino acids near the C-terminus. This mutated lamin A does not properly integrate into the lamina, which disrupts the scaffold protein structure and leads to significant disfigurement of the nucleus
 - iv. The autosomal recessive form is due to a germ line mosaicism. This mutation causes a phenotypic spectrum of disease
2. Progeroid Disorders
 - a. Two major groups
 - i. Disorders of LMNA gene that codes for lamin A
 1. Progeria
 2. Mandibuloacral dysplasia (MAD); mutation of lamin A/C gene
 - ii. Disorders of abnormal DNA repair
 1. Werner's syndrome
 - a. Short arm of chromosome 8
 - b. Causes genomic instability

Clinical Manifestations

1. Scleroderma-like skin at birth (over the abdomen) in some children

2. Head and facial dysmorphism
 - a. Head to face ratio is increased
 - b. Dilated scalp veins
 - c. Alopecia is present by adolescence
 - d. Spares eye brows and lashes
 - e. Narrow beak nose
 - f. Ears and mandible are small
 - g. High pitched voice
3. Bones are thin; clavicles are thin
4. Loss of bone from distal phalanges
5. Severe premature cardiovascular disease
 - a. Myocardial infarction is the major cause of death (mean age is 13 years)

Cerebrovascular Disease

1. Clinical occlusive infarctions
 - a. Affects the cervical carotid and vertebral arteries
 - b. Intracranial large artery disease
 - c. Perforating artery disease of the basal ganglia and white matter

Imaging Evaluation

MRI

1. MRI demonstrates infarctions of:
 - a. Pial vessels
 - b. Watershed territories
 - c. White matter
 - d. Lacunar
 - e. Arterioles
 - f. Large arteries
 - g. Silent infarcts in 60% of patients

Angiography

1. Distal stenosis of vertebral arteries
2. Calcified cervical and internal carotid arteries
3. Stenosis of intra/extracranial vessels

Neuropathology

1. Dramatically accelerated cardiovascular disease similar to CVD of aging (atherosclerotic disease)
2. Vessels exhibit prominent adventitial fibrosis
3. Progerin found in blood vessels at higher rate than controls
4. Down regulation of mitochondrial oxidative phosphorylation

Werner's Syndrome

General Characteristics

1. Autosomal recessive with genetic instability
2. Werner's syndrome gene (WRN)
 - a. Encodes a member of the human RecQ helicase protein family; chromosome 8p12
 - b. WRN deficient cells:
 - i. Reduced cell division
 - ii. Chromosomal instability (variegated translocation mosaicism)
 - iii. Sensitive to DNA damaging agents

Clinical Manifestations

1. Short stature
2. Cataracts (posterior, cortical, subcapsular)
3. Scleroderma-like skin
4. Hyperkeratotic ulcerated skin (hands/feet)
5. Premature hair graying and hair loss
6. Increased:
 - a. Osteoporosis
 - b. Diabetes mellitus, Type II
 - c. Atherosclerosis (cardiovascular disease)
 - d. Cancer
 - e. Severe macular degeneration
7. Dysmorphic features
8. Retinitis pigmentosa
9. Hypogonadism
10. Atrophy of skeletal muscle

Neurologic Features

1. Development of meningiomas and neural sheath tumors

*Neuropathology**Cardiovascular Pathology*

1. Increased arterial wall density as measured by carotid duplex in the intima-media and adventia
2. Generalized atherosclerotic lesions with stenosis and plaque formation in coronary and cerebral arteries
3. Accelerated atherosclerosis
 - a. Calcification of aortic and great vessels
 - b. Calcification of mitral and aortic valves
4. Pulmonary arterial lesions
5. Strokes in all topographical distributions; silent infarcts
6. Cardiac death more common than stroke related death

Cerebrovascular Pathology

1. Intracranial steno occlusive arterial lesions
2. Basal cistern collateral vessels
3. Infarction by MRI in 60% of patients (approximately 50% were silent)

Related Syndromes

1. Mandibuloacral dysplasia
2. Wiedemann-Rautenstrauch syndrome

Neurofibromatosis, Type I*General Characteristics*

1. Mutation of gene on chromosome 17
 - a. Protein encoded is neurofibromin; a GTPase-activating enzyme
2. Incidence ranges from 1:2500 to 1:3000 live births

Clinical Manifestations

1. Café-au-lait spots (greater than 6) Lisch nodules (iris) neurofibromas
2. Increased incidence of glial malignant tumors: myelogenous leukemia, pheochromocytoma (benign)

3. Peripheral nerve sheath tumors, malignant peripheral nerve sheath tumors
4. Vasculopathy
5. Optic nerve glioma
6. Learning disabilities
7. Attention deficit disorder
8. Sphenoid wing dysplasia
9. Pseudoarthrosis of the tibia

Neuropathology

1. NF1 vasculopathy affects arterial and venous blood vessels of all sizes
2. Two major vascular pathologies in NF1
 - a. Occlusive intimal form that affects small arteries
 - b. Aneurysmal form with replacement of the muscular wall with fibrohyaline thickening in arterioles of .1–1 mm
3. Arterial lesions caused by:
 - a. Proliferation of Schwann cells within arteries and proliferation of smooth muscle
 - b. Secondary fibrosis
 - c. Other arteries affected include:
 - i. The abdominal aorta
 - ii. The mesenteric arteries
 - iii. Visceral arteries
 - iv. Muscular arteries
 - d. May also present with multiple arterial aneurysms and venous thrombosis
4. Vascular anomalies:
 - a. Intra and extracranial arterial connections
 - b. Often present with concomitant intravascular occlusive disease
 - c. Large and medium-sized arteries are affected in any territory
 - d. Possible dysfunction of neurofibromin in blood vessel endothelial and smooth muscle cells
 - e. Recurrent strokes occur in the same or different territories
 - i. Internal carotid artery > MCA > PCA are affected
 - f. Both intra and extracranial vessels can accrue stenotic lesions
 - g. Hemispheric territorial infarction is most common
 - h. Lacunar infarction and ocular ischemia (retinal) and global occur
5. Aneurysm:
 - a. Occurs in the vertebral or other large neck arteries that can present as:
 - i. Large neck mass
 - ii. Brachial plexus lesion
 - iii. Medullary compression syndrome
 - b. Intracranial saccular and fusiform aneurysms occur at:
 - i. Circle of Willis
 - ii. Distally (posterior choroidal artery)
 - iii. Fusiform aneurysm of the intrapetrosal carotid artery cause:

1. Spheroid wing dysplasia or VIth nerve palsy
- c. The form of the disease associated with cerebral aneurysms is the intimal aneurysmal form
- d. Moyamoya disease
 - i. Slowly progressive distal carotid stenosis
- e. Arteriovenous malformations
- f. Renal artery stenosis with hypertension

Neuroimaging

Angiography

1. Occlusive arterial disease
 - a. Focal concentric stenosis
 - b. Long segment irregular narrowing
 - c. Hypoplasia without luminal narrowing
 - d. Does not occur at bifurcations (as opposed to atherosclerosis)
2. Arteriovenous fistula particularly of the vertebral arteries is associated with:
 - a. Stenosis and pseudo-aneurysmal dilatation of the feeding vessel
3. Moyamoya changes (lenticulostriate collaterals) from gradual bilateral carotid occlusion
 - a. Extensive leptomeningeal collaterals from the external carotid to the Circle of Willis due to proximal occlusions of major intracranial vessels

Ehlers–Danlos Syndrome

General Characteristics

1. Ehlers–Danlos syndrome is a group of connective tissue diseases (approximately 10 subtypes) with overlapping clinical features
 - a. Major types are I, II, or III (approximately 80% of patients)
 - b. Subtype IV most important for cerebrovascular complications; incidence is 1 in 50,000–500,000 persons
 - c. Decreased synthesis of type III collagen
 - i. All of these patients demonstrate autosomal dominant inheritance
 - ii. COL 3A1 gene (mutations) on chromosome 2
 1. Exon skipping and multi-exon deletions of COL 3A1 gene chromosome 2
 2. Encodes for alpha-1 chain of type III collagen; produces a pro-collagen that causes it to be thin and friable

Clinical Manifestations

1. Hyperelastic skin
2. Hyperextensible joints
3. Increased scarring after injury
4. Platelet dysfunction
5. Cardiac defects
6. Type IV EDS may have dysmorphic facial features and easy bruising but no hyperextensibility of joints or hyperelastic skin

Cerebral and Vascular Complications

1. Aneurysms (type IV; type I rare)
 - a. Intra and extracranial aneurysms
 - b. Multiple aneurysms
 - c. Most common aneurysm is of the internal carotid artery
 - i. In the cavernous sinus
 - ii. At the site of emergence from the sinus
2. Presentation
 - a. Rupture in the cavernous sinus cavity
 - b. SAH
 - c. Carotid cavernous fistula
 - i. Spontaneous rupture or following minor head trauma
 - ii. Symptoms include:
 1. Periorbital swelling
 2. Conjunctival erythema with arterioles reaching the iris
 3. Pulsatile tinnitus
 4. Retinal engorgement
 5. Increased ocular pressure
 6. Proptosis occurrence
3. Arterial dissection
 - a. Documented in both intra and extracranial vessels
 - b. Dissection of intrathoracic artery can secondarily occlude cervical vessels
 - c. Dissection occurs in intra-abdominal, pelvic, and intrathoracic vessels
 - d. Complications during arteriography are common due to friability of the tissue
 - e. Spontaneous dissections
 - f. During surgery and procedures

Neuroimaging

1. Carotid cavernous fistula
2. Intra and extracranial aneurysms. Rarely in both carotid and vertebral arteries concomitantly
3. Arterial dissection of cerebral as well as thoracic, abdominal, and pelvic vessels
4. Intracranial carotid artery is the most common site of aneurysm

Neuropathology

1. Fragmentation of intimal elastic membrane
2. Fibrosis of the arterial wall
3. Microscopic rupture between media and adventia
4. Abnormal Type III collagen in blood vessels

Differential Diagnosis Between Marfan's Syndrome and Ehlers-Danlos Disease

1. Marfan's syndrome has fewer cerebrovascular aneurysms
2. Aortic arch and pulmonary arteries affected more in Marfan's syndrome
3. Carotid-cavernous fistula (both)
 - a. May follow minor head trauma

- b. Spontaneous occurrence
- c. May occur concomitantly with intracranial aneurysms
- 4. Arterial Dissections (both)
 - a. Arteries fail to hold sutures (EDS)
 - b. Dissection of both intra and external arteries (EDS)
 - c. Carotid and basilar arteries are thin walled, enlarged and tortuous (EDS > Marfan's)
 - d. Arteriograms are dangerous (EDS)
 - e. More friable tissue (EDS)

Hemoglobinopathies – Sickle Cell Disease

General Characteristics

1. Autosomal inheritance
 - a. β globulin gene substitution in codon 6 that forms abnormal hemoglobin (HbSS) disease
 - b. HbSS constitutes 60–70% of the hemoglobinopathies
 - c. Hemoglobin is a heterotetramer with 2α and 2β chains
2. Risk factors for ischemic stroke in children
 - a. Overt or silent stroke (MRI)
 - b. Increased cerebral blood flow
 - c. Aplastic crises
 - d. Nocturnal hypoxemia
 - e. Acute chest syndrome
 - f. Seizures
 - g. SEM globin gene haplotype
3. Risk factors for ischemic stroke in adults
 - a. Increased homocysteine
 - b. Prior TIA
 - c. Atrial fibrillation
 - d. Hyperlipidemia
 - e. Diabetes mellitus
4. HbS > HbC for risk of ischemic stroke; HbA has little or no risk of ischemic stroke

Clinical Manifestations

1. HbS disease
 - a. Scleral telangiectasia
 - b. Arachnodactyly
 - c. Auto-splenectomy
 - d. Pneumococcal peritonitis
 - e. Meningitis
 - f. Bone marrow infarction
 - g. Severe joint and abdominal pain
 - h. Acute chest syndrome
 - i. Numb chin syndrome

Neurological Complications

1. Occlusive disease of large intracranial arteries and small penetrating vessels
2. Silent infarcts
 - a. About 20% in children
 - b. Cognitive impairment without overt ischemic stroke in children
3. Dilated and ectatic arteries
4. Moyamoya collateral patterns (MCA or terminal carotid occlusion)
5. SAH (rare)

SSA Disease

1. Stroke propensity

SC Disease

1. “Sea fan” macular sign (abnormal collection of blood vessels)
2. Propensity of strokes during pregnancy
3. Aseptic necrosis of the hip

Neuropathology

1. Thickened arterial walls from intimal and subintimal proliferation
2. Rare thrombosis of veins and cerebral sinuses
3. Deoxygenated HbS interaction with other HbS molecules leads to RBC polymerization
 - a. Decreased RBC deformability
 - b. Vaso-occlusion of vessels and the vaso-vasorum
4. Sickled cells
 - a. Adhere to the endothelium
 - b. Activate inflammatory cells and clotting factors that form the nidus for thrombosis
 - c. Initiate small vessel sludging
 - d. Deficiency of endothelial nitric oxide which decreases compensatory vaso dilation

Neuroimaging

1. MRI/MRA
 - a. Silent infarction
 - b. Cortical and subcortical infarction
 - c. Border zone infarction
 - d. Moyamoya syndrome

Laboratory Evaluation

1. Trans Cranial Doppler (TCD)
 - a. Velocities above 200 cm/second may occur in large vessels

Mitochondrial Disease and Stroke

Overview

1. Mitochondrial DNA mutation in 75% of affected patients
2. Affects 9.2/100,000 adults less than 65 years; disease occurs in about 1 in 5000 individuals
3. Cardiac involvement is progressive
 - a. Sudden death
 - b. Cardiomyopathy
 - c. Ventricular pre-excitation
 - d. Conduction system disease

Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-Like Episodes (MELAS)

General Characteristics

1. Multisystem disease affecting organs with high energy demands (heart, CNS, skeletal muscle)
2. Mitochondrial genome:
 - a. Circular DNA within the mitochondrion

- b. Tissue dependent copy number (heteroplasmy: ratio of mutated vs wild type mitochondria in each cell)
- c. Maternal transmission
- d. Encodes:
 - i. Mitochondrial transfer RNA (tRNA)
 - ii. Ribosomal RNA
 - iii. 13/80 proteins in the respiratory chain
- e. Mitochondria are exposed to free radicals generated by the respiratory chain and have poor repair mechanisms
- f. Mitochondrial dysfunction causes ATP depletion due to failure of the respiratory chain
- g. Mutations identified in both tRNA, rRNA and protein encoding genes
- h. MELAS most often is caused by point mutation in mtDNA m3243 within the tRNA encoding gene tRNA^{Leu(UUR)}

Clinical Manifestations

- 1. Fever and infection possible triggers
- 2. Episodic vomiting, migraine headaches and seizures
- 3. May occur in adolescence
- 4. Siblings of MELAS patients with the 3243 mutation may present with different phenotype:
 - a. Diabetes and deafness
 - b. Myopathy
- 5. Clinical associations of MELAS:
 - a. Diabetes
 - b. Short stature
 - c. Hearing loss
 - d. Ophthalmoplegia
 - e. Ataxia
 - f. Pigmentary retinopathy
 - g. MERRF (Myoclonic Epilepsy with Ragged Red Fibers)
 - h. Ischemic colitis
 - i. Hypertrophic cardiomyopathy
 - j. Fatigue
 - k. Cognitive impairment
 - l. Nephropathy
 - m. Hypothyroidism
 - n. Hypogonadism
- 6. Most common presentation of MELAS is migraine headache and seizures with recurrent stroke-like episodes
- 7. Stroke-like episodes:
 - a. In general do not follow a vascular distribution
 - b. Involve the posterior parietal and occipital lobes
 - c. Rare brain embolization from cardiac involvement (CHF; arrhythmia)
 - d. Episodes most consistent with mitochondrial dysfunction and alterations in calcium homeostasis

Neuropathology

- 1. Mutations in subunits of components of the respiratory chain
 - a. Oxidative stress
 - b. Energy failure in the affected tissues
 - c. Ragged red fibers on muscle biopsy

Neuroimaging

MRI Findings and Differential Diagnosis from Other Mitochondrial Diseases

- 1. MELAS and Alpers' disease
 - a. Primarily cerebrocortical lesions
- 2. Leigh's syndrome
 - a. Basal ganglia involvement
- 3. Congenital lactic acidosis with or without pyruvate dehydrogenase deficiency
 - a. Cerebrocortical atrophy
 - b. Agenesis or atrophy of the corpus callosum
- 4. Associated other mitochondrial syndromes from the A32437G mutation
 - a. Maternal inherited deafness with diabetes
 - b. Progressive external ophthalmoplegia

Laboratory Evaluation

- 1. Elevated resting lactate and pyruvate levels (blood and CSF)
- 2. Muscle biopsy:
 - a. Ragged red fibers (abnormal collection of mitochondria on Gomori trichrome stain)
- 3. Genetic mutation analysis of peripheral blood leukocytes

Myoclonic Epilepsy with Ragged Red Fibers (MERRF)

General Characteristics

- 1. Double point mutations causing MELAS-like presentation
 - a. m.8356T>C (MERRF)
 - b. m.3243A>G (MELAS)
- 2. Heteroplasmy in the blood of 4 described patients

Clinical Manifestations

- 1. MERRF followed by a MELAS presentation occurs in the double mutation
- 2. Migraine with stroke-like episodes associated with lactic acidosis and dementia
 - a. Ataxia and myoclonic epilepsy

Neuropathology

- 1. Mutations in the MT-TK gene are the most common cause of MERRF; contained in mitochondrial DNA
 - a. The most prominent deficiencies involve the NADH-CoQ reductase of C complex I and in cytochrome C oxidase (COX, complex IV)
- 2. Ragged red fibers in muscle biopsy

Neuroimaging

- 1. May demonstrate calcification of the basal ganglia
- 2. Occipital lobe atrophy

Kearns-Sayre Syndrome

General Characteristics

- 1. Large mitochondrial deletions

2. Red ragged fibers rarely seen in children
3. Mitochondrial electron microscope defects noted in children
4. May involve intramuscular capillaries

Clinical Manifestations

1. Cardiac complications
 - a. Early right bundle branch block
 - b. May progress rapidly to AV block
 - c. First or second degree AV block
 - d. QT prolongation
 - e. Torsades de Pointes ventricular tachycardia
 - f. Late dilated cardiomyopathy
2. Syncope or sudden death may be presenting feature
3. Proximal myopathy
4. Slowly progressive external ophthalmoplegia
5. Short stature; growth hormone failure
6. Cardioembolic stroke

Leigh's Syndrome (Subacute Necrotizing Encephalomyelopathy)

General Characteristics

1. Genetically heterogeneous
 - a. Affects nuclear or mitochondrial DNA
2. Most common biochemical deficits
 - a. COX complex and pyruvate dehydrogenase complex
3. Infantile form diagnosed by developmental delay and elevated serum and CSF lactate
4. Late onset cases occur

Clinical Manifestations

Juvenile Form

1. Spastic paraparesis
2. Visual disorder
3. Acute sensorimotor neuropathy, ataxia, deafness and retinitis pigmentosa (NARP)
4. Myopathy and cardiomyopathy
 - a. Respiratory depression and coma
5. Emboli from cardiomyopathy

Imaging Evaluation

MRI

1. Symmetric hypointense T1/hyperintense on T2-weighted sequences; lesions in the basal ganglia
 - a. Putamen and brainstem
 - b. Sparing of red nuclei and mammillary bodies (occasionally the mammillary bodies are hemorrhagic)

Neuropathology

1. Gray matter degeneration
2. Brainstem and spinal cord necrosis
 - a. Spongiosis, endothelial proliferation and demyelination

Saguenay-Lac Saint Jean (Cox Deficiency)

General Characteristics

1. Autosomal recessive; the largest known cohort of patients with a genetically homogeneous nuclear encoded congenital lactic acidosis
 - a. A354V mutation in LRPPRC (leucine-rich pentatricopeptide repeat containing)

Clinical Manifestations

1. Developmental delay
2. Facial dysmorphism
3. Fulminant lactic acidotic crises
4. Leigh's syndrome like
5. Stroke-like episodes

Neuropathology

1. Cytochrome oxidase deficiency in the brain and liver
2. Necrotizing encephalopathy involving the thalamus, brainstem and spinal cord
3. Vascular proliferation and gliosis

Neuroimaging

MRI

1. Hypointense signal on T1-weighted sequences with hyperintense signal with T2-weighted sequences

Laboratory Evaluation

1. High CSF lactate

Disorders of Cerebral Thrombosis and Hemostasis

Overview

1. Physiology
 - a. The brain has an intrinsic capacity to regulate thrombosis and hemostasis
 - b. Hemostasis is defined as the arrest of bleeding and the maintenance of blood flow within a vessel
 - c. Thrombosis is the formation of clot within a blood vessel
 - d. Coagulation refers to the transformation of liquid into a semisolid mass
 - e. The classic Virchow triad model of thrombosis and hemostasis illustrates the complex interplay between blood flow, clotting factors and the endothelium of the vessel wall. It explains features of both thrombosis and maintenance of hemostasis
2. Circulating cells are the components of primary hemostasis and coagulation factors comprise secondary hemostasis
3. Four component model of coagulation comprise:
 - a. Hepatic factors
 - b. Bone marrow derived hematopoietic cells (platelets and monocytes)
 - c. The vascular endothelium
4. Blood Vessel Injury

- a. Platelets initiate the process of primary hemostasis at the site of injury (burst plaque, trauma, dissection by forming a plug)
 - i. Platelets adhere to subendothelial von Willebrand factor (vWF) and exposed collagen through glycoprotein1b/IX/V and glycoprotein1a/IIa receptor complexes
 1. Platelet endothelial complex adherence initiates platelet intracellular signaling cascades that induce their activation
 2. Activated platelets:
 - a. Undergo structural change
 - b. Secrete their granules
 - c. Produce thromboxane A2 (TXA2)
 - d. Aggregate
 3. Platelet plug forms by:
 - a. Recruitment of additional platelets by secreted TXA2
 - b. Secreted adenosine diphosphate (ADP)
 - c. Thrombin
 4. Activated platelet surface phospholipids:
 - a. Serve as a platform for the enzyme complexes of the clotting cascade
 - b. Coagulation
 - i. Tissue factor is the primary initiator of coagulation (extrinsic cascade)
 1. Tissue factor (TF) binds factor VII. The TF-VIIa complex activates factor IX and X
 2. Activated IXa binds to VIIIa on membrane surfaces that activate factor X that then forms the prothrombinase complex. Factor Xa converts prothrombin to thrombin
 - c. Generated thrombin
 - i. Converts fibrinogen to fibrin
 - ii. Activates coagulation factors V and VIII that amplify its own generation
 - iii. Activates factor XIII that stabilizes the fibrin clot
 - iv. Activates factor XI (intrinsic pathway) to maintain Xa generation
 - d. The extrinsic pathway activation is amplified by the intrinsic pathway
 - e. Regulation of fibrin clot generation:
 - i. The generation and removal of the fibrin pathways, three of which are endothelial based. The coagulation system is regulated by the fibrinolytic system and natural coagulation inhibitors
 - ii. Regulatory pathways for fibrin generation
 - iii. Tissue factor inhibiting pathway (TFIP)
 1. Blocks the reaction between tissue factor and VIIa
2. Circulating thrombin III and its cofactor heparin sulfate proteoglycan (HSPS):
 - a. Inhibit all coagulation proteases involved in the coagulation cascade
 - b. Limits coagulation to the site of injury
 - c. Protects the circulation from liberated proteases
3. Thrombomodulin/Protein C pathway
 - a. Thrombin binding to the endothelial cell receptor Thrombomodulin activates circulating protein C (APC)
 - b. Activated protein C:
 - i. Degrades factor Va and VIIIa
 - ii. Protein S is a cofactor of protein C
 - iii. Binding of thrombin to the thrombomodulin
 1. Inhibits cleavage of fibrinogen
 2. Decreases activation of platelets
 3. Inhibits thrombin
4. Fibrinolytic pathway
 - a. Vascular endothelial cells modulate blood fluidity through secretion of membrane associated thrombo-resistance molecules (as noted above)
 - b. Fluid phase proteins:
 - i. Endothelin
 - ii. Nitric oxide
 - iii. Tissue plasminogen activator
 - iv. Prostacyclin
 - c. Cell surface protein regulators
 - i. TFPI (tissue factor pathway inhibitor I)
 - ii. Antithrombin III-HSPG (also circulates)
 - iii. Thrombomodulin-protein C pathway
 - d. Endothelial cells assemble fibrinolytic proteins and express urokinase receptor and annexin A2
 - e. Annexin A2
 - i. Multifunctional calcium regulated membrane binding protein
 - ii. It forms a heterotetramer with protein P11 (also known as S100A) which chaperones A2 to the plasma membrane

- iii. The A2-P11 complex:
 1. Binds tissue plasminogen activator (tPA) as well as plasminogen which accelerates the catalytic generation of plasmin
 2. Plasmin limits fibrin accumulation

Organ-Specific Thrombosis and Hemostasis

1. Local organ expression of endothelial factors and receptors determine thrombosis and hemostasis in the face of systemic changes in coagulation parameters
 - a. Differential expression of coagulant and anticoagulant factors in different locations within the vascular tree
 - b. Endothelial Protein C receptor
 - i. Predominately expressed in large arteries and veins
 - ii. Tissue factor pathway inhibitor
 1. Expressed in capillaries
 - iii. Nitric oxide
 1. Expressed in arteries
 - iv. vWF expressed in veins
 - c. Protein C, Protein S or antithrombin III deficiency
 - i. Predispose to venous thrombosis of the lower extremity at valve pockets due to concomitant stagnant blood flow and hypoxia
 - d. Polycythemia vera, paroxysmal nocturnal hemoglobinuria and essential thrombocythemia
 - i. Preferentially effect intra-abdominal veins (Budd-Chiari syndrome)
 - e. Erythromelalgia
 - i. Thrombotic occlusion of arterioles (not the painful Nav1.7 neuropathy) primarily localizes to the toes, fingers and is caused by myeloproliferative disease, polycythemia vera and essential thrombocythemia
 - f. Warfarin induced skin necrosis
 - i. Effects buttocks, thighs and the breast
 - ii. Caused by the thrombotic occlusion of venules
 - iii. Deficiency of protein C

Organ Specific Hemorrhage

1. Possibly dependent on deficiencies within the intrinsic or extrinsic pathways
 - a. Murine model: decreased expression of VII and tissue factor cause hemorrhage in heart, lung testes, uterus and placenta
 - i. Low factor VIII and IX lead to hemorrhages in joint muscles and joints (tissue factor expression is low)
 - b. Subdural hematoma (often with minimal trauma)
 - c. Experimental evidence supports low levels of tissue factor and hemorrhage in:
 - i. Heart
 - ii. Lung
 - iii. Testis
 - iv. Uterus
 - v. Placenta

Brain-Specific Regulation of Thrombosis and Hemostasis

1. Blood-Brain Barrier:
 - a. Tight junction proteins (transmembrane)
 - i. Occludins and claudins that interact with the actin cytoskeleton and zonula occludin (ZO) proteins
 - ii. Limits molecular transport into the brain
 - iii. Protects against hemorrhage
 - b. The brain has increased ladder-like adherens junctions formed by:
 - i. Cadherin and catenin proteins
 - ii. At endothelial junctions
 - c. The blood-brain barrier (BBB) pericyte junctions
 - i. Paracrine production of trophic factors that enhance the BBB as do adjacent astrocytes
 - ii. Forms another structural support for tight junctions
 - iii. Phagocytic function that blocks egress of erythrocytes from capillaries
 - iv. Protection against capillary brain hemorrhage

Specific Functional Characteristics of the Vascular Endothelium

1. Thrombomodulin
 - a. Enhanced expression in small arteries concomitant with small vessel pathology
 - b. Endothelial protein C receptor
 - i. Located adjacent to thrombomodulin in the endothelial membrane enhances its expression
 - ii. Preferentially located in the endothelium of arteries and veins and has minimal expression in the brain and other organ capillaries
2. Fibrinolytic pathway: tPA and plasminogen activator inhibitors – 1:
 - a. tPA
 - i. Pivotal endothelial-dependent serine protease
 - ii. Binds to fibrin
 - iii. Activates the fibrinolytic pathway
 - iv. Almost no capillary expression
 - v. Systemic endothelial cells release tPA after stimulation by factorX-thrombin
 - b. Plasminogen activator inhibitor-1
 - i. The major fibrinolytic inhibitor
 - ii. Enhanced expression of PAI-1 In brain microvascular endothelium (BBB models) support:
 - a. Restricted tPA and increased expressions of PAI-1 in the microvascular endothelium
 - b. Regulation of brain microvascular fibrin types may be regulated by the BBB
3. Tissue Factor
 - a. The principal inducer of the coagulation cascades
 - b. Surrounds blood vessels and encases organs
 - c. The brain has a high concentration of tissue factor
 - d. The CNS sources of tissue factor are:
 - i. Astrocytes
 - ii. BBB associated astorcytes
 - iii. Brain surface pericytes

4. Tissue Factor Pathway Inhibitor (TFPI)
 - a. Protease inhibitor and synthesized by endothelial cells
 - b. Action mediated by Xa inhibition of the TF-VIIa complex
 - c. Low brain expression
5. Antithrombin III-HSPG
 - a. Protease inhibitor synthesized by the liver
 - b. Actions amplified when bound to its cofactor HSPG (absent in brain capillaries)
 - c. Covalent inhibitory complex is associated with coagulation factor
6. Protease Nexin I
 - a. A serine protease inhibitor
 - b. Synthesized by smooth muscle cells and platelets
 - c. Inhibits thrombin and plasminogen activation
 - d. Localized to pericytes and astrocytes
 - e. Function is uncertain
7. Prostacyclin and endothelial nitric oxide
 - a. Pivotal endogenous platelet aggregate inhibitors
 - b. Prostacyclin synthesized by prostacyclin synthetase from prostaglandin H₂ primarily from endothelial cells
 - i. Experimental studies suggest less brain expression than in other organs
 - c. Endothelial NOS (eNOS), also known as nitric oxide synthase 3 (NOS3)
 - i. The primary nitric oxide synthase
 - ii. Experimental support for equal brain and organ expression
 - iii. Endothelial derived NO a major regulator of platelet function and aggregation

Clinical Conditions from Factor and Inhibitor Dysfunction

Antithrombin III

General Characteristics

1. 58-kDa serpin (serine protease inhibitor)
2. Inhibits thrombin, factor Xa and factor IXa
3. Activity amplified by heparin
4. Defect may be quantitative or qualitative
5. Acquired loss from protein losing enteropathy and the nephrotic syndrome
6. Genetics:
 - a. Most often AD
 - b. Type I antithrombin deficiency:
 - i. Reduction in both activity and antigen concentration
 - c. Type II antithrombin deficiency:
 - i. Decreased activity but normal antigen concentration

Clinical Manifestations

1. Strong family history of venous thrombosis
2. Approximately 50% of patients suffer:
 - a. Venous thrombo-embolism (VTE)
 - i. Less than 60% activity carries a 10 fold risk of thrombo-embolism
 - ii. Homozygous defect associated with in utero or perinatal death

3. Pulmonary embolism
4. Rare myocardial infarction
5. Rare peripheral arterial disease
6. Occasional stroke

Laboratory Evaluation

1. Antithrombin activity (heparin cofactor) assay
2. Immuno assay for antithrombin antigen
3. Test confounders
 - a. Liver failure
 - b. Unfractionated or low molecular weight heparin

Protein C

General Characteristics

1. Serine protease zymogen of the vitamin K dependent family
2. In the presence of thrombomodulin, thrombin converts it to the active form which then inhibits factors Va and VIIIa
3. Usually autosomal dominant
 - a. Heterozygotes suggested by protein C level of less than 70%; increased venous thromboembolism approximately 4 fold higher
 - b. Homozygote presentation:
 - i. Life threatening thrombosis at birth
 - ii. Neonatal puerpera fulminans with extremity necrosis and gangrene
 - c. Protein C to S ratio a determinant of protein C gene mutation or carrier status

Clinical Manifestations

1. Lower extremity venous thrombosis
2. Cerebral venous thrombosis
3. Occasional arterial thrombosis
4. Rare cerebral embolus from the heart

Laboratory Evaluation

1. Protein C activity (clotting assay)
2. Protein C amidolytic and immune assays
3. Test confounders
 - a. Vitamin K antagonist
 - b. Liver failure
 - c. Vitamin K deficiency

Protein S

General Characteristics

1. Is the cofactor for activated protein C (APC)
 - a. True plasma protein S (about 40%) has APC cofactor activity
 - b. 60% of plasma protein S is bound to C4b binding protein which increases during infection
2. Levels of Protein S are decreased with:
 - a. Nephrotic syndrome
 - b. Protein losing enteropathy
 - c. Liver disease
 - d. Antibodies to protein S occur with post-viral purpura fulminans

Clinical Manifestations

1. Risk factor for stroke in middle aged women (arterial stroke)
2. Dural venous thrombosis
3. Stroke in young patients with the concomitant risk factor of smoking
4. 4–5 fold risk of venous thromboembolism

Laboratory Evaluation

1. True protein S antigen evaluation by immune assay
2. Total protein S antigen and APC cofactor activity (clotting assay)
3. Test confounders
 - a. Vitamin K antagonists and deficiency
 - b. Liver failure
 - c. Pregnancy
 - d. Oral contraceptive
 - e. Hormone replacement therapy

*Factor V Leiden Mutation***General Characteristics**

1. Most common cause of decreased Protein C function
 - a. Activated Protein C (APC)
 - i. Inactivates Factors V and VIII_a
 - ii. Proteins that APC inactivates, Factor V_a and Factor VIII_a, are highly procoagulant cofactors and therefore promotes thrombosis
2. Mutation of the gene that codes for factor V (factor V G1691A)
3. Factor V Leiden prevalence in the general population:
 - a. Heterozygote 7.7%
 - b. Homozygote .2%

Clinical Manifestations

1. Thromboembolism in pregnancy
2. Venous thromboembolism of the lower extremities
3. Cerebral venous and dural sinus thrombosis
4. Increased risk of arterial stroke in young patients

Laboratory Evaluation

1. APC resistance (APTT-based assay)
2. Factor V Leiden genotyping (PCR)

*Prothrombin Gene Mutation***General Characteristics**

1. Second most common gene mutation causing a prothrombic state
2. AR, mutation in the gene (G20210A)
3. Two phenotypes:
 - a. Hypo-prothrombinemia
 - i. Can increase levels of coagulant activity
 - ii. Antigen type
 - b. Dysprothrombinemia
 - i. Low coagulant activity
 - ii. Borderline or normal antigen levels

Clinical Manifestations

1. Cerebral venous thrombosis
2. Rare arterial clotting
3. Recurrent peripheral venous thrombosis embolism

Laboratory Evaluation

1. Prothrombin genotyping by PCR

*Coagulation Factor Deficiency***General Characteristics**

1. Hemophilia A (factor VIII) and B (factor IX) with von Willebrand disease account for more than 95% of inherited coagulation deficiencies
2. Hemophilia A is five times more prevalence than hemophilia B
3. Genetics:
 - a. X-linked
 - b. F8 and F9 are the genes encoding factor VIII and IX respectively
 - c. Sporadic mutations in 30% of patients
4. Severity depends on the level of clotting factors VIII or IX
 - a. Severe disease <1%
 - b. Moderate 1–5%
 - c. Mild 5–40%
5. Approximately 1/3 of patients develop inhibitory antibodies to the replacement factor
 - a. Inhibitory antibodies directed against factor VIII is a CD4+ dependent process

Clinical Manifestations

1. Bleeding into the joints, skin, abdomen and cranium
2. Intracranial bleeding occurs in 2–14% of severe hemophilia
 - a. Following mild head trauma
 - b. Neonatal hemorrhage (approximately 3%)
 - c. Associated with acute and chronic subdural hematoma

*von Willebrand Factor Deficiency***General Characteristics**

1. The most common inherited bleeding disorder
2. Severity depends on degree of the defect
3. Von Willebrand factor is a glycoprotein that:
 - a. Induces platelet adhesion to exposed subendothelium at the site of injury
 - b. Causes platelet aggregation
4. Genetics
 - a. Both AD or AR inheritance

Clinical Manifestations

1. Mucocutaneous bleeding
2. Too much bleeding in the setting of mild trauma (tooth extraction)
3. Rare spontaneous intracranial bleeding

Laboratory Evaluation

1. Bleeding time and PFA-100 closure time may be prolonged
2. Abnormal ristocetin induced platelet aggregation

*Acquired Low Levels of Coagulation Factors***General Characteristics**

1. Most of the Factor VIII and IX deficits are due to autoantibodies in treated patients
2. Acquired hemophilia:
 - a. Rare autoimmune disease
 - b. Caused by antibodies against factor viii and ix
 - c. In patients older than 65 years:
 - i. Solid tumors
 - ii. Lymphoproliferative diseases
 - iii. Autoimmune diseases
 - iv. Pregnancy
 - v. Intolerance to drug therapy

Clinical Manifestations

1. Severe bleeding episodes occur in 80–90% of patients
2. Mortality rate of 10–25%

Laboratory Evaluation

1. Prolonged a PTT
2. Low Factor VIII or IX activity
3. Detectable inhibitor (Bethesda assay)

*Multiple Coagulation Deficiencies***General Characteristics**

1. Most common causes
 - a. Vitamin K deficiency
 - b. Liver disease
 - c. Disseminated intravascular coagulation
2. Vitamin K
 - a. Pivotal for post-translation (gamma) – carboxylation of factors II, VII, IX, X, protein C and S
 - b. Deficiencies of Vitamin K in adults occur most often from:
 - i. Malabsorption
 - ii. Vitamin K antagonists
 - iii. Antibiotics
 - iv. Rodenticides
3. Liver disease
 - a. Synthesizes most coagulation factors except factor VIII, vWF and coagulation regulatory proteins
 - b. Gamma – carboxylation of vitamin K dependent proteins is impaired in liver failure and cholestasis
 - c. Severe hepatic failure is associated with:
 - i. Decreased factor V
 - ii. Hypo and dysfibrinogenemia
 - iii. Impaired syntheses of antithrombin, plasminogen, α -2, antiplasmin and plasminogen activator inhibitor type I (tPAI-1)

- iv. Causes fibrin deposition and activation of the coagulation cascades
- v. A consumptive coagulation may occur when:
 1. Decreased clearance of activated factors and t-PA
 2. Impaired syntheses of PAI-1 and α -2 antiplasmin

Clinical Manifestations

1. Coagulation deficits: vitamin K antagonists
 - a. Intracranial hemorrhage
 - i. International normalized ratio (INR) greater than 5 often seen in a hemorrhage
 - ii. 70% of bleeds are intracranial and 80% are subdural
 - iii. Vitamin K antagonists account for about 10% of ICH (2–9/100,000 population/year)
 - iv. May unmask brain bleeding in otherwise asymptomatic patients particularly those with CVD, hypertension or vascular malformations
 - v. Intracranial risk of hemorrhage is increased with vitamin K antagonists and the use of antiplatelet agents
 - vi. Drugs that interfere with Vitamin K antagonists include:
 1. Amiodarone
 2. Miconazole
 3. Phenylbutazone
 4. Quinidine
 5. Cimetidine
 6. Thyroid hormones
 7. Antibiotics

*Post Thrombolysis***General Characteristics**

1. Use of streptokinase, urokinase or primarily intravenous or intra-arterial t-PA for ischemic stroke

Clinical Manifestations

1. Intracranial hemorrhage occurs
 - a. In infarctions that occur in greater than 2/3 of the territory of the affected vessel
 - b. Setting of hypertension
 - c. Longer the time window from ictus (thrombolytic therapy)
 - d. In the setting of MCA occlusion by CT
 - i. Loss of the insular stripe
 - ii. Indistinct caudate head
 - iii. Corical effacement

*Acquired Deficiency of Coagulation Inhibitor***General Characteristics**

1. Accelerated consumption of antithrombin III, protein C and protein S occurs with:
 - a. An ischemic or thromboembolic incident

- b. Disseminated intravascular coagulation
- c. Surgery
- d. Sepsis and DIC
- 2. Antithrombin deficiency occurs with:
 - a. Decreased hepatic syntheses
 - b. Disseminated intravascular coagulation
 - c. Loss in ascites and inflammatory bowel disease
 - d. Nephrotic syndrome
 - e. Heparin
- 3. Protein S deficiency may occur with kidney disease
- 4. Protein C and S deficiency occur with vitamin K antagonists
- 5. L-asparaginase
 - a. Utilized for acute lymphoblastic leukemia
 - b. Decreases antithrombin, protein C and S (inhibits synthesis)
- 6. Oral contraceptives
 - a. Combination of estrogen and progesterone
 - b. Increase VII, IX, and X
 - c. Decrease antithrombin and protein S
 - d. Induce a mild prothrombotic state
 - e. Cerebral vein and sinus thrombosis are increased particularly in patients with the G120A prothrombotic mutation
- 7. Tamoxifen
 - f. Estrogen receptor modulator
 - g. Decreased antithrombin, protein C and S, increased free protein S and factors VIII, IX, and vWF

Thrombocytopenia

General Characteristics

1. Differential diagnostic points for inherited thrombocytopenia
 - a. Family history of low platelets
 - b. Lack of platelet increase following anti-immune modulations
 - c. Abnormal size of platelets
 - d. Increased bleeding in proportion to platelet number
 - e. Birth onset
 - f. Absent radii
 - g. Stable platelet levels for a prolonged period

Acquired Thrombocytopenia in Adults

General Characteristics

1. Most common cause of thrombocytopenia but rarely causes intracranial hemorrhage
2. Bleeding occurs with levels less than 10,000–20,000/mm³ (in absence of platelet functional deficit)
3. Major causes of acquired thrombocytopenia
 - a. Bone marrow failure
 - i. Myeloproliferative disease
 - ii. Metastatic infiltration
 - b. Vitamin B12 deficiency
 - c. Acute alcohol toxicity
 - d. Drug interference (quinine, quinidine, sulfonamides)

4. HIV induced thrombocytopenia
5. Hepatitis C infection
 - a. Autoimmune thrombocytopenia develops in about 3% of patients
6. Sepsis
7. Abciximab treatment
 - a. Anticoagulants during endovascular procedures can cause acute thrombocytopenia (within hours) or can be delayed (5–8 days)

Platelet Dysfunction

Overview

Inherited platelet disorders are rare and can compromise adhesion, aggregation or storage pool release.

Glanzmann's Thrombasthenia

General Characteristics

1. Autosomal recessive
2. Defect in GPIIb/IIIa which causes failure of platelet aggregation

Clinical Manifestations

1. Childhood onset
2. Lifelong mucosal bleeding
3. Intracranial hemorrhage may occur

Laboratory Evaluation

1. Platelet count, size and morphology are normal
2. Bleeding time and PFA-100 closure time are prolonged
3. Platelet aggregometry demonstrate no platelet aggregation with all platelet tests except collagen and ristocetin

Bernard-Soulier Syndrome

General Characteristics

1. Lack of the glycoprotein GPIIb-IX-X complex (receptor for vWF)
2. Macrothrombocytopenia

Clinical Manifestations

1. Disproportionate bleeding for platelet numbers
2. Acquired platelet dysfunction occurs with:
 - a. Aspirin
 - b. NSAIDs
 - c. GPIIb/III inhibitors
 - d. Myeloproliferative disease

Inherited Cause of Thrombophilia and Stroke

General Characteristics

1. Children may be at risk for ischemic stroke if they have inherited thrombophilia which includes deficient:
 - a. Antithrombin III
 - b. Low levels of protein C and S
 - c. APC resistance
 - d. Factor V Leiden

- e. Prothrombin G20210A mutation
- f. Methylenetetrahydrofolate reductase (MTHFR) C6 77T mutation
- g. Plasma hematocrit greater than 95th percentile
- 2. Adults
 - a. Association of thrombophilia and ischemic stroke occurs with:
 - i. Factor V Leiden mutation
 - ii. MTHFR C 677T mutation
 - iii. Prothrombin 20210A mutation
- 3. Thrombophilia causes about 1–4% of ischemic strokes in young adults

Clinical Manifestations

- 1. Thrombophilia increases the risk of stroke during:
 - a. Pregnancy and puerperium along with comorbid conditions that include:
 - i. Pregnancy associated with hypertension
 - ii. Caesarean section
 - iii. Non-white ethnicity
 - iv. Cardiomyopathy
 - v. Congestive heart failure
 - b. Hormone replacement therapy
 - c. A possible association with PFO

Increased Factor VIII

General Characteristics

- 1. Associated with:
 - a. Spontaneous abortion
 - b. Thrombophlebitis
 - c. Preceding infection
 - d. Crohn's disease
 - e. Ulcerative colitis
- 2. Coagulopathy of inflammatory bowel disease caused by:
 - a. Increased Factor VIII
 - b. Elevated Factor V
 - c. Decreased antithrombin III
 - d. Platelet dysfunction

Clinical Feature

- 1. Ischemic stroke

Autoimmune Induced Coagulopathy

Heparin Induced Thrombocytopenia (HIT)

Type I HIT

General Characteristics

- 1. Non-immune-mediated
- 2. Occurs in 10–20% of patients utilizing heparin
- 3. Causes slight non-progressive thrombocytopenia ($>100,000/\text{mm}^3$)
- 4. Platelet count returns to baseline within a few days even with continued heparin

Clinical Manifestations

- 1. No bleeding or thrombosis

Type II HIT

General Characteristics

- 1. Immune-mediated associated with IgG antibodies
- 2. There are three subtypes:
 - a. IgG antibodies without thrombocytopenia
 - b. HIT subtypes
 - i. Thrombocytopenia
 - ii. No clinical symptomatology
 - iii. Thrombocytopenia with clinically relevant thrombosis

HIT with Thrombosis

General Characteristics

- 1. Exposure to heparin induces platelet factor-4 (PF-4) release which binds to heparin
- 2. The PF-4 heparin complex activates platelets which induces the clotting cascade
- 3. HIT 3 occurs in 3–5% of patients who have utilized unfractionated heparin for 5 days or longer
- HIT 3 occurs in approximately 1% of patients who have utilized low molecular weight heparin

Clinical Manifestations

- 1. No other explanation for thrombocytopenia
- 2. Diagnostic points:
 - a. Greater than 50% fall in platelets
 - b. Occurs between 5–10 days, may be seen on the first day if the patient has had heparin within prior 30 days
 - c. Thrombosis with skin necrosis or acute systemic reaction after intravenous unfractionated heparin
- 3. Patient at higher risk:
 - a. Elderly patients
 - b. Post-surgical prophylaxis for deep vein thrombosis (orthopedic and cardiovascular surgery)
 - c. Prothrombotic concomitant risks associated with 60% of patients
- 4. Associated cutaneous allergic reactions with skin necrosis
- 5. Major clinical systemic and neurologic complications
 - a. Arterial and venous thrombosis
 - b. May occur in the absence of thrombocytopenia
 - c. Greater occurrence in patients suffering cardiovascular disease
 - d. Arterial complications most common in large vessels that cause:
 - i. Gangrene of a limb
 - ii. Coronary artery thrombosis
 - iii. Ischemic arterial stroke
 - e. Venous complications:
 - i. Deep vein thrombosis
 - ii. Pulmonary embolism
 - iii. Clotting of dialysis shunts
- 6. Cerebral sinus thrombosis:
- 7. Rare systemic complications:
 - a. Hemorrhagic adrenal necrosis
 - b. Disseminated intravascular coagulation

- c. "White" clots in blood vessels (particularly evident in the retinal circulation)
- 8. Cerebrovascular sequelae:
 - a. Ischemic arterial stroke
 - b. Spinal ischemia
 - c. Transient global amnesia
 - d. No primary ICH

Laboratory Evaluation

- 1. Carbon 14-serotonin release assay (SRA test):
 - a. Heparin dependent HIT antibodies release carbon 14-labeled serotonin from platelets
 - b. Heparin induced platelet aggregation test
 - c. Serology

Primary Antiphospholipid Antibody Syndrome

General Characteristics

- 1. IgA, IgM, IgG antibodies are formed against platelet epitopes that include:
 - a. Phosphatidyl ethanolamine
 - b. Phosphatidyl serine
- 2. The specific antibodies measured are:
 - a. Lupus anticoagulant
 - b. Anticardiolipin
 - c. Anti-beta 2-glycoprotein I
 - d. Anti-prothrombin
- 3. There is no other causative autoimmune disease
- 4. Clinical criteria:
 - a. One or more clinical episodes of arterial, venous or small vessel thrombosis
 - b. Confirmed by appropriate imaging studies
 - c. Thrombosis without significant evidence of inflammation in the vessel wall
- 5. Pregnancy morbidity:
 - a. One or more unexplained deaths of a morphologically normal fetus at or beyond 10 weeks of gestation
 - b. One or more premature births of a morphologically normal neonate at or before the 34th week of gestation due to:
 - i. Eclampsia or pre-eclampsia
 - ii. Placental insufficiency
 - c. Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation that are not due to:
 - i. Maternal anatomic or hormonal abnormalities
 - ii. Maternal and paternal chromosomal abnormalities
- 6. Laboratory criteria:
 - a. Lupus anticoagulant is present in the plasma at two times at least 12 weeks apart
 - b. Anticardiolipin antibody of IgG or IgM isotype is present in serum or plasma in medium or high titer on two or more occasions at least 12 weeks apart
 - c. Anti-b2 GP-1 antibody of IgG and/or IgM isotype in serum or plasma is present in two or more occasions at least 12 weeks apart

- 7. Most thrombotic events are venous; if arterial they often occur in the cerebral circulation
- 8. Antiphospholipid syndrome (APS) is classified as secondary if it occurs with SLE or other collagen vascular diseases. They are similar clinically
- 9. Antiphospholipid antibodies may also be seen with infection or specific medicines and in normal subjects. They may not be pathogenic
- 10. B2 GP-1 is a phospholipid binding protein that is needed to detect most antiphospholipid antibodies

Clinical Manifestations

- 1. Cerebral vascular ischemia:
 - a. Can occur in any vascular territory
 - b. Cardiac valvular lesions may be an embolic source; primarily mitral valve thickening
 - c. Increased risk of first ever stroke in young patients
 - d. An increased risk is present in patients with anticardiolipin antibodies and lupus coagulants
 - e. Increased risk of stroke and TIA in women (absolute risk 4.5%)
 - f. Probably no increased recurrent stroke risk
 - g. Presence of Lupus Anticoagulant (LA) and other prothrombotic factors increase stroke risk
 - h. Antiphosphatidyl serine antibodies may be an important biomarker for ischemic stroke
 - i. Antiphosphatidyl serine correlate with LA
 - i. Antiphosphatidyl serine antibodies and b2GP-1 antibodies are a possible cause of arterial stroke
 - j. Antiphosphatidyl antibodies may be important antipathogenic factor for recurrent thrombosis in SLE patients
- 2. Recurrent thrombosis:
 - a. Relatively uncommon
 - b. The recurrence may be within the first year or late (5–10 years)
 - c. The recurrence is similar to the initial thromboembolic event
 - d. Risk factors for a recurrent arterial event:
 - i. Caucasian ethnicity
 - ii. High titers of antibodies in serum
 - e. Risk factors for recurrent venous thrombosis:
 - i. Oral contraceptives
 - ii. Puerperium
- 3. Secondary APS related to systemic lupus erythematosus (SLE):
 - a. Combined anticardiolipin antibodies and LA associated with thrombosis which is arterial
 - b. Venous sinus thrombosis:
 - i. Occurs at a younger age
 - ii. Maybe more severe than the usual causes of venous sinus thrombosis
 - iii. Hemorrhagic infarction

Laboratory Evaluation

1. Lupus anticoagulant
 - a. Clot based assays
 - i. Partial Thromboplastin Time – Lupus Anticoagulant (PTT-LA)
 - ii. dRVVT (Dilute Russell's viper venom time)
 - iii. Dilute prothrombin time (dPT) tests
 - b. Test confounders
 - i. Heparin affects the PTT-LA
 - ii. Vitamin K antagonist prolongs the dRVVT and the dPT tests
2. Anticardiolipin antibodies
 - a. Immune assay for IgM and IgG isotypes
 - b. Test confounders:
 - i. Serum preferably tested 12 weeks following the thrombotic event
3. Anti- β 2-GPI antibodies:
 - a. Immuno-assay for IgM and IgG isotypes
 - b. Test cofounders:
 - i. Serum preferably tested 12 weeks following a thrombotic event

Antiphospholipid Antibody Syndrome Associations*General Characteristics*

1. SLE associated in 1/3 of patients
2. SLE like syndrome in 5% of patients

Clinical Manifestations

1. Most patients have a higher frequency of:
 - a. Myocardial infarction
 - b. Arterial thrombosis of the lower extremities
 - c. After age 50 males are affected more than females
2. Migraine
3. Seizure
4. Chorea
5. Anterior ischemic optic neuropathy

Other Neurological Manifestations of APS

1. Sensorineural hearing loss:
 - a. Sudden or progressive sensorineural hearing loss
 - i. Sudden deafness occurs
 - ii. SLE patients with anticardiolipin antibodies may suffer sudden deafness:
 1. Possibly vascular basis
2. Transient global amnesia
3. Ocular signs:
 - a. Anterior ischemic optic neuropathy
 - b. Branch and central retinal artery occlusion
 - c. Cilioretinal artery occlusion
 - d. Amaurosis fugax
 - e. Combined artery and vein occlusion

Neuropathology

1. Antiphospholipid antibodies effect platelets, coagulation factors, and endothelial cells:

- a. Antiphospholipid antibody binding to phospholipid complexes on platelets and vascular endothelial cells:
 - i. Activates these cells through Fc-gamma receptors binding to phosphatidyl serine or b2GP-1
 1. Induces aggregation of platelets
- b. b2 GP-1
 - i. Binds to endothelial cells through heparin-sulfate proteoglycan
 - ii. Possible role in the function of VEGF (Vascular endothelial growth factor)
- c. Infection may trigger pathologic antiphospholipid antibody response
- d. Receptors, co-receptors, and accessible molecules are involved in the pathogenic effects of a PLA

*Neuroimaging***MRI**

1. Multiple small vessel infarction in all vascular territories
2. Rare hemorrhagic infarction
3. Cerebral atrophy with frontal lobe predominance
4. Small foci of high signal intensity on T2-weighted sequences noted in sub cortical white matter (WMH)
5. Greater than 8 mm (WMH) have been correlated with high anticardiolipin IgG levels

Catastrophic Antiphospholipid Syndrome*General Characteristics*

1. Multiple system involvement
2. Develops over a short period of time
3. Causes microthrombosis
4. Algorithm of Catastrophic Antiphospholipid syndrome
 - a. History of APS or persistently elevated antiphospholipid antibody levels
 - b. 3 or more organ system involvements in less than one week
 - c. Biopsy diagnosis of microthrombosis
 - d. Less than 1% of patients with APS develop catastrophic APS syndrome
 - e. The recurrence rate is low

Sneddon's Syndrome*General Characteristics*

1. Combination of skin and ischemic cerebral lesions in the absence of connective tissue or chronic infective disease
2. Categorized as idiopathic, autoimmune and thromboembolic
3. No definite ethnic predilection
4. In hospital-based series the incidence of .25% to .5% of stroke patients
 - a. 80% are women
 - b. Average age at onset: 40 years
 - c. Possible autosomal dominant genetics in familial cases

Clinical Manifestations

1. Livedo reticularis (mottling, bluish lace-like discoloration with pale center) is often the first manifestation of the dis-

ease and may precede neurological symptoms although it may occur concurrently or afterwards

2. Topography of the lesions:
 - a. Lower trunk, buttocks, proximal thighs
 - b. Lesions may generalize to upper body
 - c. Temporary vasoconstriction
 - i. Exacerbation with cold and concomitantly with exacerbation of neurologic symptoms
 - d. Some patients demonstrate area cyanosis and Raynaud's phenomena
3. Livedo reticularis is associated with:
 - a. Sneddon's
 - b. Divry–Van Bogaert syndrome
 - c. SLE
 - d. Antiphospholipid syndrome
 - e. Polyarteritis nodosa
 - f. Cholesterol embolization
 - g. Livedoid vasculopathy

Neurological Manifestations

1. Headache and vertigo in greater than 50% of patients
2. TIA in more than 50%
3. Cognitive dysfunction: dementia in some late stage patients
4. Multiple TIA and strokes
 - a. Cortical and subcortical topography in anterior and posterior circulations
 - b. Lacunar and white matter lesions
 - c. Spinal cord is rarely involved
 - d. Case reports of SAH and ICH
5. Recurrent transient global amnesia
6. Focal and generalized seizures
 - a. Tremor with a high incidence of seizure (rare)
7. Valvular heart disease
8. Retinal and mesenteric artery involvement
9. Patients with antiphospholipid syndrome may present with full syndrome
10. Cognitive dysfunction
 - a. Evidence for relationship between sustained titers of anticardiolipin antibody IgG levels and cognitive decline

Neuropathology

1. Non-specific cortical and subcortical infarction (data derived from one autopsy)
2. Cortical infarctions; occlusion of medium-sized arteries; focal smooth muscle hyperplasia
3. Putative pathogenesis
 - a. Hypercoagulable state
 - b. Small vessel vasculopathy

Neuroimaging

MRI

1. Multiple subcortical and white matter lesions in separate arterial territories
2. Lacunar infarction
3. Mild to moderate cortical and subcortical atrophy

Angiography

1. Normal in many patients
2. A subset demonstrate distal arterial occlusions with extension collaterals

Circulating Lupus Anticoagulant

General Characteristics

1. A lupus anticoagulant is;
 - a. An anti-IgA, IgG or IgM anticardiolipin (antiphospholipid antibody to phosphatidyl serine and phosphatidyl ethanolamine epitopes)
2. Requirement for laboratory diagnosis:
 - a. Prolongation of a phospholipid dependent screening assay
 - b. Demonstrate inhibitory activity when mixed with healthy pooled plasma
 - c. Documentation that the inhibitory activity is phospholipid dependent
 - d. Blocks the formation of the prothrombin activator:
 - i. Causes a prolonged activated partial thromboplastin time (aPTT) that is not corrected by added plasmin
 - ii. Positive dRVVT and/or dPT test
3. One third of the patients with these antibodies have SLE; these antibodies without another autoimmune disease constitute primary antiphospholipid antibody syndrome

Clinical Manifestations

1. Evidence of systemic venous clotting
2. Large and small artery occlusions
3. Mitral and aortic valve lesions

Neurologic Manifestations

1. Amaurosis fugax
2. Chorea
3. Migraine
4. Transverse myelitis
5. Intracranial occlusive arterial disease
6. Venous and sinus thrombosis
7. Atypical extracranial arterial occlusion
8. Binswanger leukoencephalopathy

Neuropathology

1. Thrombosis of large and small arteries

Neuroimaging

1. Topographical large vessel stroke
2. Generalized small vessel infarction

Diseases of Complement Activation and Thrombotic Microangiopathy (TMA)

Overview

Abnormal activation of complement causes vascular endothelial injury, exposure of the subendothelial matrix and platelet

activation. This deleterious sequence leads to thrombotic microangiopathy (TMA). The process affects arterioles and capillaries primarily and induces vessel wall thickening, detachment of endothelial cells from the basement membrane and intraluminal thrombosis. TMA occurs primarily in hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP). There are two major forms of HUS: 1. associated with Shiga toxin-producing *E. coli* (STEC-HUS) 2. atypical HUS with dysregulated complement activation. The kidney, lungs, gastrointestinal tract and brain are the most affected. In a full-blown attack there is platelet activation, aggregation, hemolysis and the development of a prothrombotic and inflammatory state. The usual precipitating causes are infection, pregnancy, drugs or trauma. Mutations in complement regulatory proteins (factor H, factor I, MCP/CD46, thrombomodulin) or those that increase it through alternative pathways (C3, factor B) as well as anti-factor H antibodies cause aHUS. The fundamental defect in aHUS is a complement attachment on cellular surfaces.

In paroxysmal nocturnal hemoglobinuria (PNH), there is dysregulation of complement generation. A variety of cancers demonstrate Terminal Complement (C5-9) deposition on both endothelial and tumor cell membranes which may contribute to their induction of a prothrombotic state. The antiphospholipid syndrome also demonstrates dysregulated complement activation.

These complement dependent diseases include:

1. Thrombotic Thrombocytopenic Purpura (TTP)
2. Atypical Hemolytic Uremic Syndrome (aHUS)
3. Shiga Toxin-producing *E. coli* Hemolytic Uremia Syndrome (STEC-HUS)
4. Disseminated Intravascular Coagulation (DIC)
5. Paroxysmal Nocturnal Hemoglobinuria (PNH)
6. Antiphospholipid Antibody Syndrome (APLA)

Paroxysmal Nocturnal Hemoglobinuria

General Characteristics

1. Non-immune hemolytic anemia with pancytopenia and venous thrombosis
2. Expansion of hematopoietic stem cells and progeny mature cells that are deficient in cell surface proteins that regulate complement activation
3. An acquired somatic mutation in the phosphatidyl inositol glycan (PIGA) gene in hematopoietic stem cells:
 - a. RBC cells derived from the clone form decreased anchored cell surface protein (CD55 and CD59) and are sensitive to complement mediated hemolysis
4. Decreased hematopoiesis
5. Budd-Chiari hepatic vein thrombosis may be prominent
6. Pulmonary hypertension
7. Renal dysfunction
8. Mortality is from thromboembolism
9. Associated myelodysplastic syndrome and leukemia may occur

Clinical Manifestations

1. Hepatic and cerebral vein thrombosis
 - a. Large paroxysmal nocturnal hemoglobinuria granulocytic clones (>50%) predict venous thromboembolism
2. Cerebral arterial thrombosis
3. Platelet counts of <50,000 mm³ in about 50% of patients and may be associated with ICH

Neuroimaging

1. Cortical vein thrombosis
2. Rarely large vessel cortical stroke

Laboratory Evaluation

1. Flow cytometry demonstrate absence of CD55, CD59 on RBCs and neutrophils
2. Absence of CD14, CD16, CD24, CD48, CD52 and CD66 on the surface of neutrophils

Atypical Hemolytic Uremic Syndrome (aHUS)

General Characteristics

1. Recognized by the laboratory signs of microangiopathic hemolysis that includes:
 - a. Schistocytes
 - b. Elevated lactic dehydrogenase
 - c. Low haptoglobin
 - d. Low hemoglobin
 - e. Thrombocytopenia

Clinical Manifestations

1. Focal strokes from small vessel pial involvement
2. Seizures
3. Altered mental status
4. Primarily kidney involvement but gastrointestinal and pulmonary involvement occurs

Neuropathology

1. Uncontrolled activity of the alternative complement pathway
2. Genetic defect in soluble and/or membrane-bound complement regulatory protein. Complement factor H is most often involved
3. Microthrombosis of arterioles and capillaries in affected organs
4. Excellent response to eculizumab that blocks complement activation

Neuroimaging

1. Primarily cortical small vessel infarction
2. Arteriole infarction

Differential Diagnosis

1. TTP often presents a diagnostic dilemma. The diagnosis is secured by demonstrating an ADAMTS13 inhibitor in TTP (less than 10% activity)

2. ADAMTS13 is:
 - a. A disintegrin and metalloproteinase with a thrombospondin type I motif, member 13
 - b. Inhibitor is present in both the idiopathic and acute forms of TTP
 - c. DIC is differentiated due to an increase in D-dimer and decreased factor V and VIII levels. Abnormal clotting profile
 - d. Antiphospholipid antibody syndrome is associated with clotting events and miscarriage

Shiga Toxin-Producing *E. coli* Hemolytic Uremia Syndrome (STEC-HUS)

General Characteristics

1. Arterioles and capillaries are affected
2. Thrombotic microangiopathy

Clinical Manifestations

1. Patients present with HUS signs and symptoms but have active severe diarrhea
2. Kidney injury by microthrombi occurs in all ages but is most severe in children *E. coli* O104
3. H4 was responsible for a large outbreak in Europe in 2011

Neuropathology

1. The Shiga toxin from the *E. coli* triggers endothelial complement deposition by:
 - a. Up regulation of P-selectin
 - b. Putatively interfering with complement regulatory proteins
2. Vessel wall thickening in arterioles
3. Endothelial detachment from basement membranes

Neuroimaging

1. Generalized WMH due to small vessel microangiopathy

Thrombotic Thrombocytopenic Purpura (TTP)

General Characteristics

1. Mutation in ADAMTS-13
 - a. vWF cleaving protease
2. Incidence in females is twice as high as in males; incidence rate about 4 to 6 cases/million individuals
3. Fever (interleukin 1)
4. Peripheral digit ischemia
5. Acute respiratory distress
6. Renal failure
7. Thrombocytopenia
8. Microangiopathic hemolytic anemia
9. Concomitant primarily cortical neurologic symptoms
10. Associated with:
 - a. Pregnancy
 - b. Bone marrow transplantation
 - c. HIV
 - d. SLE

- e. Sjögren's syndrome
- f. Rheumatoid arthritis
- g. Autoimmune disease
- h. Ticlopidine
- i. Influenza
- j. D-penicillamine
- k. Cyclosporine
- l. Cytomycin

Clinical Manifestations

1. Diffuse encephalopathy with:
 - a. Visual hallucinations
 - b. Headache
 - c. Seizure
 - d. Visual loss
2. Transient focal deficits:
 - a. Aphasia
 - b. Papilledema
 - c. Relapsing course
 - d. Posterior leukoencephalopathy

Neuropathology

1. Microvascular thrombosis in arterioles and capillaries
2. Non-familial form:
 - a. Antibodies to ADAMT-13
 - b. Inhibitor of von Willebrand factor cleaving protease
3. Familial form:
 - a. Constitutional deficiency of the protease
 - b. Large multimeres of von Willebrand factor (vWF) adhere to and aggregate platelets
4. Platelet rich thrombosis
5. Multi-focal microinfarctions

Neuroimaging

1. Primarily cortical microinfarcts
2. WMH throughout the brain above the tentorium

Laboratory Evaluations

1. Coombs-negative hemolytic anemia and severe thrombocytopenia due to platelet clumping ($<20,000/\text{mm}^3$ – $<10,000/\text{mm}^3$) thrombocytopenia may be correlate with levels of ADAMTS-13 activity
2. RBC fragmentation on peripheral blood smear
 - a. Anisocytosis
 - b. Poikilocytosis
3. Reticulocyte count and indirect bilirubin are high; haptoglobin is low
4. High lactate dehydrogenase levels

Disseminated Intravascular Coagulation

General Characteristics

1. Simultaneous clotting and activation of the fibrinolytic system
2. Causative disease entities:

- a. Sepsis
- b. Obstetrical emergencies (amniotic fluid emboli)
- c. Cancer (release of thromboplastic-like substances)
- d. Damage to blood vessel endothelium
- e. Severe brain injury or surgery
- f. Heat stroke (platelet activation)
- g. Treatment of leukemia and lymphoma (after IV chemotherapy)
- h. SAH
- i. Vascular malformations (Kasabach-Merritt syndrome)
3. Abnormal activation of intravascular thrombin and the fibrinolytic system
 - a. Deposition of fibrin throughout systemic and intracranial vasculature

Clinical Manifestations

1. Large and small vessel arterial thrombosis
2. SAH
3. SDH (subdural hematoma)
4. NBTE (emboli) in cancer patients
5. Intracranial hemorrhage in non-hypertensive areas
6. Multifocal encephalopathy
7. Severe acrocyanosis
8. Bleeding from prior venipuncture sites

Neuropathology

1. Infections:
 - a. Release of IL-1, IL-6 and TNF- α from macrophages, monocytes and lymphocytes during sepsis:
 - i. Converts antithrombotic endothelium to a pro-thrombotic state
 - ii. Lipopolysaccharides from gram negative cell walls and release of endotoxins activate TNF- α and IL-1 that induces coagulation
2. Tissue factor is released from endothelial cells with burns, trauma and cancer induced coagulation
3. Collagen vascular diseases, viremia, microangiopathic hemolytic anemias may all dysregulate the endothelial cell membrane and the high affinity thrombin receptor thrombomodulin to induce clotting
 - a. IL- β and TNF- α are increased in DIC and down regulate endothelial expressed thrombomodulin
 - b. Thrombomodulin and thrombin, when complexed, activate Protein C inhibit factor V and VIII_a. Lack of this inhibition from decreased thrombomodulin induces clotting
4. Increased fibrinolytic activity is induced by the release of plasminogen activators from endothelial cells
5. Fibrin is deposited throughout small arterioles and capillaries of the brain and systemic organs. Occasionally larger extracranial cerebral vessels may be occluded
6. Recent studies demonstrate:
 - a. Activation of vascular endothelial factors 1 and 2 and the angiotensin (Ang)-Tie ligand receptor system
 - b. Activation of vascular endothelial growth factor (VEGF) which increases vascular permeability during inflammation and ischemia

Neuroimaging

MRI

1. Large and small vessel strokes in all circulations
2. SDH
3. SAH

Laboratory Evaluation

1. Platelets and clotting factors
 - a. $<30\text{--}50,000/\text{mm}^3$
 - b. Decreased factors V and VIII
 - c. Decreased fibrinogen levels
 - d. Prolonged PT and partial thromboplastin time
 - e. D-dimer (new antigen) appears in the blood
2. Molecular hemostatic markers:
 - a. Thrombin-antithrombin complex
 - b. D-dimer
 - c. Soluble fibrin (SF)
 - d. Plasmin-plasmin inhibitor complex

Chronic Myeloproliferative Disorders

Overview

1. Myeloproliferative disorders are:
 - a. Clonal disorders
 - b. Myeloproliferative disorders include:
 - i. Essential thrombocythemia
 - ii. Polycythemia vera
 - iii. Chronic myeloid leukemia
 - iv. Myelofibrosis/myeloid metaplasia
 - v. Chronic neutrophilic, eosinophilic and basophilic leukemia
 - vi. Systemic mastocytosis
2. The most important in regard to coagulation dysfunction in the nervous system are polycythemia vera and essential thrombocythemia

Polycythemia Vera

General Characteristics

Genetics

1. Increased sensitivity of erythroid precursors to erythropoietin
2. Related to mutation in JAK2 V617F, a tyrosine protein kinase, other JAK mutations are found in patients with myeloproliferative neoplasms and leukemia
 - a. Janus kinases (JAKs) are involved in cytokine signaling
 - b. JAK2 – pivotal in hematopoiesis
 - c. JAK2 – JAK2 V617F point mutation is present in the majority of Philadelphia chromosome-negative myeloproliferative neoplasms that include:
 - i. Polycythemia vera
 - ii. Essential thrombocythemia
 - iii. Primary myelofibrosis
 - d. JAK2V617F is rarely found in:
 - i. Hypereosinophilic syndrome
 - ii. Chronic myelomonocytic leukemia

- iii. Acute myeloid leukemia
- e. JAK2V617F mutation is:
 - i. An acquired somatic event of hematopoietic stem cells

Clinical Manifestations

1. Mortality due to thrombosis, rare bleeding complications:
 - a. Thrombotic events occur in approximately 4–9% of patients
 - b. Low incidence in young patients less than 40 years of age; higher incidence in patients older than 70
 - c. Greater incidence in those treated with phlebotomy rather than hydroxyurea
 - d. Thrombosis reported 2 years preceding diagnosis
2. Thrombosis of large cerebral arterial vessels:
 - a. Posterior circulation infarctions are more common than anterior circulation infarctions
 - b. Scattered lesion pattern:
 - i. Suggestive of embolic microcirculation stroke
3. Retinal venous occlusions
4. Large arteries are involved in the cardiovascular and peripheral arterial systems
5. Ischemic stroke and TIA occur in 4–5% of patient/year
6. Cerebral venous thrombosis is frequent:
 - a. Aggravating factors are decreased cerebral blood flow and elevated hematocrit

Essential Thrombocytosis

General Characteristics

1. Sustained thrombocytosis of greater than 450,000 platelets/mm³ after exclusion of reactive causes
2. Persistently elevated levels of thromboxane A₂ due to platelet activation
3. Approximately 50% of patients have the JAK 2 V617F mutation
4. Aspirin more effective than Coumadin in treatment

Clinical Manifestations

1. Migraine or non-specific headache
2. TIA and arterial strokes
3. Ocular scintillating scotoma
4. Thrombotic events occur (15–89%) with a 5% annual incidence
 - a. Thrombosis more prevalent in patients older than 60
 - b. In those who have suffered previous events
 - c. Thrombotic risk is not proportional to platelet count >1,000,000 mm³
5. Cerebral venous sinus thrombosis

Neuropathology

1. Increased responsiveness of megakaryocytes to thrombopoietin
2. Thrombocythemia
 - a. Shortens platelet survival

- b. Increased beta-thromboglobulin in the serum
- c. Increased platelet factor 4 level in the serum
- d. Increased urinary tract excretion of thromboxane B₂ (TxB₂)
 - i. Marker of platelet activation
- 3. Most thrombotic events are in large arteries, platelet/thrombin clots also occur in arterioles

Neuroimaging

1. Large artery strokes
2. Venous sinus thrombosis

Short Clinical Classification of Thrombotic and Bleeding Disorders

1. Thrombophilia
 - a. Any disorder inherited or acquired with increased thrombosis
2. Coagulopathies
 - a. Common gene mutations:
 - i. Factor V (R1691A) mutation
 - ii. Prothrombin (G20210A) mutation
 - iii. Methylenetetrahydrofolate reductase (MTHFR) mutation
3. Rare Genetic Deficiencies
 - a. Protein C
 - b. Protein S
 - c. Antithrombin
 - d. Plasminogen
 - e. Homocysteine
4. Probable Genetic Risk Factors
 - a. Increased:
 - i. Fibrinogen
 - ii. Factor IX
 - iii. Factor VIII
 - iv. Decreased Factor XII
5. Most Common Deficiencies of Inhibitors of Clotting
 - a. Antithrombin III
 - b. Protein C
 - c. Protein S
 - d. Factor V Leiden

Organ-Specific Thrombosis and Hemostasis

1. Local organ expression of endothelial factors and receptors determine thrombosis and hemostasis in the face of systemic changes in coagulation parameters:
 - a. Differential expression of coagulant and anticoagulant factors in different locations within the vascular tree
 - b. Endothelial Protein C receptor
 - i. Predominately expressed in large arteries and veins
 - ii. Tissue factor pathway inhibitor
 1. Expressed in capillaries
 - iii. Nitric oxide
 1. Expressed in arteries
 - iv. vWF expressed in veins

- c. Protein C, Protein S or antithrombin III deficiency:
 - i. Predispose to venous thrombosis of the lower extremity at valve pockets due to concomitant stagnant blood flow and hypoxia
- d. Polycythemia vera, paroxysmal nocturnal hemoglobinuria and essential thrombocythemia:
 - i. Preferentially effect intra-abdominal veins (Budd-Chiari syndrome)
- e. Erythromelalgia:
 - i. Thrombotic occlusion of arterioles (not the painful Nav1.7 neuropathy) primarily localizes to the toes, fingers and is caused by myeloproliferative disease, polycythemia vera and essential thrombocythemia
- f. Warfarin induced skin necrosis:
 - i. Effects buttocks, thighs and the breast
 - ii. Caused by the thrombotic occlusion of venules
 - iii. Deficiency of protein C

Organ Specific Hemorrhage

1. Possibly dependent on deficiencies within the intrinsic or extrinsic pathways:
 - a. Murine model: decreased expression of VII and tissue factor cause hemorrhage in heart, lung testes, uterus and placenta
 - i. Low factor VIII and IX lead to hemorrhages in joint muscles and joints (tissue factor expression is low)
 - b. Subdural hematoma (often with minimal trauma)
 - c. Experimental evidence supports low levels of tissue factor and hemorrhage in:
 - i. Heart
 - ii. Lung
 - iii. Testis
 - iv. Uterus
 - v. Placenta

Antithrombotic Factors

1. Vascular endothelium is characterized by constitutive expression of antithrombotic factors:
 - a. Differentially expressed
2. Thrombomodulin:
 - a. Expressed in brain capillaries (low levels in areas of lacunar stroke)
 - b. Increased expression in small arteries occur with small vessel disease
 - c. Endothelial protein C receptor is:
 - i. Adjacent to thrombomodulin
 - ii. Enhances protein C deactivation of factors V and VIII
 - d. Preferentially expressed in the endothelium of arteries and veins
 - e. Minimal expression in brain capillaries

Fibrinolytic Pathway: tPA and Plasminogen Activator Inhibitor-1

1. tPA is the pivotal endothelial dependent serine protease that binds fibrin and activates the fibrinolytic system:
 - a. tPA capillary expression in the brain is absent
 - b. Alpha-thrombotin induces tPA release from endothelial cells
 - c. Brain microvascular endothelium expresses tissue plasminogen activator inhibitor-1
 - d. The BBB may be the regulator of the brain microvascular fibrinolytic system

Tissue Factor

1. The brain is a major source of tissue factor:
 - a. Astrocytes are the principal source in the CNS; also on the surface of pericytes
 - b. Brain hemostatic envelope

Tissue Factor Pathway Inhibitor (TFPI)

1. Synthesized by endothelial cells
2. Low expression in the brain

Antithrombin III – Heparin Sulfate – Polyglycan

1. Protease inhibitor synthesized by the liver:
 - a. Forms covalent complexes with coagulation factors
 - b. Function is amplified when bound to heparin-sulfate – polyglycan (HSPG) which is absent in brain capillaries (in rat)

Cerebral Venous Thrombosis (Genetic Causes)

1. Thrombophilia risk factors occur in approximately 30–60% of patients and include:
 - a. Antithrombin III deficiency
 - b. Protein C and S deficiency
 - c. Factor V Leiden mutation
 - d. Dysfibrinogenemia with increased factor VIII
 - e. Thrombomodulin mutations
 - f. Prothrombin G 20210A mutation
2. Acquired Prothrombotic Disorders:
 - g. Antiphospholipid antibodies
 - h. Lupus anticoagulant
 - i. APC resistance
 - j. Acquired deficiency of antithrombin III, protein C, S and hyper homocysteinemia

Cerebral Venous Thrombosis (Acquired)

1. All causes of venous stasis
2. Advanced age
3. Multiple trauma
4. Surgical procedures
5. Pregnancy (second and third trimester) and is further increased by inherited thrombophilia, increased CVST risk
6. During puerperium
7. Malignancy:
 - a. Risk increased if patients have Factor V Leiden or prothrombin G20210A mutations

Summary of Coagulopathies That Cause Arterial and Venous Strokes

Coagulopathies

1. General Categories:
 - a. Decreased inhibitors of activated coagulation factors
 - b. Hereditary fibrinolytic deficits
 - c. Clotting factor deficiencies
 - d. Approximately 5% of stroke
2. Autosomal Dominant Defects:
 - a. Heparin cofactor II
 - b. Protein C deficiency
 - c. Decreased release of plasminogen activator
 - d. Homozygote XII deficits (thrombotic tendency)
 - e. Prothrombin gene defect
3. Autosomal Recessive Defects:
 - a. Prekallikrein deficiency (Fletcher factor)
4. Propensity for Thrombosis:
 - a. Antithrombin III defects
 - b. Protein S deficiency
 - c. Plasminogen defects
 - d. Factor V Leiden defect
5. Acquired Causes of Hypercoagulability:
 - a. Diabetes mellitus
 - b. Hyperlipidemic states
 - c. Disseminated intravascular coagulation (consumption with fibrinolysis)
 - d. Platelet disorders
 - e. Vasculitis
 - f. Malignancy (thromboplastin-like substances released into the circulation)
 - g. Hyperaggregable (sticky) platelets
 - h. Endothelial damage
 - i. Cardiopulmonary bypass:
 - i. Increased fibrinolytic activity
 - ii. Decreased coagulant activity
 - iii. Increased plasminogen activator inhibitor level
 - iv. Platelets $>1,000,000 - 7 \times$ risk of bleeding
 - j. Antiphospholipid antibody
 - k. Anticardiolipin antibody
 - l. Lupus anticoagulant
 - m. Heparin induced thrombosis
 - n. Rheological Abnormalities
 - i. Hyperviscosity
 - ii. Deficits in laminar and pulsatile flow

Coagulopathies: General Categories That Warrant a Laboratory Screening

1. Comprehensive Procoagulant Screen:
 - a. Common gene mutations:
 - i. Factor V (R1691A) mutation
 - ii. Prothrombin (G20210A) mutation
 - iii. MTHFR (C677T); methyl tetrahydrofolate reductase mutation
 - b. Rare genetic deficiencies:

- i. Protein C
- ii. Protein S
- iii. Antithrombin III
- iv. Plasminogen
- c. Putative candidates for genetic thrombophilia:
 - i. Elevated lipoprotein
 - ii. Homocysteine

Probable Genetic Risk Factors

1. Increased:
 - a. Fibrinogen
 - b. Factor IX
 - c. Factor VIII
 - d. Decreased factor XII

Hereditary Cause of Hemorrhagic Stroke

General Characteristics

1. X-linked VIII and IX deficiency
2. AR-afibrinogenemia
3. Factor VII, X, XI, XIII deficiency

Clinical Manifestations

1. Rare bleeding in factor XI deficiency
2. VIII deficiency less than 10% of normal values are necessary to bleed
3. Latent period of deficits prior to stroke

Platelet Dysfunction

General Characteristics

1. Increased platelet counts – above 1 million:
 - a. Associated with hypercoagulability
2. Increased coagulability may occur with increased adhesion and aggregation:
 - a. Functional platelet abnormality more than absolute platelets number may be the important parameter:
 - i. Sticky platelets
3. Essential Thrombocythemia:
 - a. Associated with stroke and digital artery infarction
 - b. Transient ischemic attacks
 - c. Major ICH
4. Glanzmann Thrombocythemia
5. Bernard Soulier Thrombocythemia

Leukemia

General Characteristics

1. Rheological abnormalities occur with WBC $> 250,000/\text{mm}^3$
 - a. Capillary sludge
 - i. Infarction
 - ii. Small brain hemorrhages
2. SAH
 - a. Vaginal bleed prior to cerebral bleed at approximately $30,000 \text{ platelets}/\text{mm}^3$

Decreased Natural Inhibitors of Coagulation

1. Antithrombin III
2. Low levels of heparin releasable tissue factor inhibitor in young patients with thrombosis
 - a. Coincidence of defect with thrombosis is putative
3. Prekallikrein deficiency
 - a. Severely prolonged activated partial thromboplastin time (a PTT)
 - b. Due to Factor XII activation
 - c. No increased bleeding risk if defect is solitary
 - d. Bleeding risks occur in association with hereditary defects of:
 - i. VIII, IX, XI

Most Common Deficiencies of Inhibitors of Clotting

1. Antithrombin III
2. Protein C
3. Protein S
4. Factor V Leiden

Rheology*Overview*

1. Viscosity is the ratio of the shear stress to shear rate
 - a. Shear stress – the tangential force between flowing layers of a fluid
 - b. Shear rate – the velocity gradient between layers of flow
2. Whole blood viscosity varies as its shear rate
 - a. Low viscosity increase with low flow rates
3. Blood viscosity is determined by:
 - a. Hematocrit
 - b. Plasma protein
 - c. Fibrinogen concentration
 - d. Cellular aggregation
 - e. Red cell deformability
 - f. Axial migration
 - g. Vessel diameter
 - h. Flow rate
4. Viscosity in small blood vessels
 - a. Blood viscosity approximates plasma viscosity which becomes an important determinant of capillary flow
 - b. Red cell aggregation determines a major proportion of blood viscosity
 - i. Fibrinogen and globulin decrease electronic repulsion between RBCs (increase aggregation)
 - ii. In long blood vessels RBCs migrate to the vessel axis which increases fluidity and oxygen transport
 - iii. Higher velocities and shear rate break up RBC aggregation; the reverse occurs in low flow states
 - iv. RBC aggregation increases in most conditions with high sedimentation rates
 - v. Low flow rate increases viscosity logarithmically due to low shear rates which occur with:
 1. Arterial stenosis

2. Hypervolemia

3. Stasis or low shear rate causes RBC structural deficits that increase viscosity (stiffening of red blood cells)

Hyperviscosity Syndromes*Overview*

1. Three major categories:
 - a. Plasma viscosity abnormalities
 - b. Increased blood cellularity
 - c. Structural changes in RBCs (deformability)

Putative Associations

1. Binswanger disease
2. Pathogenesis and progression of atherosclerosis
 - a. Occurs in areas of low shear stress
3. Spontaneous echo contrast (smoke) in heart chambers
 - a. Increased risk for cardiac emboli
 - b. In atrial fibrillation, mitral stenosis, left atrial enlargement
 - c. Pathology is putative protein mediated RBC aggregation as a consequence of low shear force

Plasma Viscosity Abnormalities*General Characteristics*

1. Plasma viscosity is determined by positively charged, non-spherical, high molecular weight proteins:
 - a. Fibrinogen (principal determinant)
 - b. α -2 macroglobulins
 - c. Immunoglobulins
2. Increased high-molecular weight globulins occur in:
 - a. Lymphoma
 - b. Waldenström's macroglobulinemia
 - c. Multiple myeloma (uncommon)

Clinical Manifestations

1. Mucous membrane bleeding
2. Blurred vision and visual loss
3. Lethargy
4. Dizziness/vertigo
5. Tinnitus
6. Paraesthesias
7. Seizures (rare)

Clinical Signs

1. Enlarged tortuous retinal veins
2. Retinal hemorrhages
3. "Box-car" formation of RBC's in retinal veins (abnormal clumping; Rouleaux formation)
4. Bleeding gums and mucous membranes
5. Poor perfusion of distal extremities; acrocyanosis (particularly in cryoglobulinemia)
6. Lower leg petechiae (Waldenström's macroglobulinemia)
7. Altered mental states
8. Small vessel stroke

*Pathology***Pathological Mechanisms**

1. Increased plasma viscosity
2. Hypervolemia
3. Increased red cell aggregation (due to elevated paraproteins)
4. Intravenous Immunoglobulin Therapy
 - a. Possible association with strokes; mechanisms include:
 - i. Increased viscosity of plasma and whole blood
 1. Decreased cerebral blood flow
 - ii. Platelet activation
 - iii. Vasospasm

Neuroimaging

1. MRI
2. Large and small vessel stroke
3. Venous sinus thrombosis

Increased Blood Cellularity*General Characteristics*

1. Polycythemia vera
 - a. Increased peripheral blood cell counts and increased red cell mass that leads to:
 - i. Decreased vertebral blood flow
 - ii. Increased platelet counts and reactivity
2. Types of strokes recorded include:
 - a. Cerebral venous infarction, Binswanger disease, intracerebral hemorrhage, large cerebral artery thrombosis and watershed infarction
3. Increased white blood cell counts particularly in forms of leukemia that have hyperviscosity
 - a. WBCs less deformable than RBCs
 - i. Global dysfunction (poor perfusion)
 - ii. Microinfarcts
 - iii. Petechial infarction (particularly in white matter)

Structural Changes in RBCs (Decreased Red Cell Deformability)*General Characteristics*

1. In sickle cell disease with hypoxia or low pH:
 - a. Hemoglobins polymerize
 - b. Cell shape becomes sickled thus increasing viscosity, decreasing flow and causes sludging of the microcirculation and cerebral veins
2. Associated with occlusion of the distal internal carotid artery and Circle of Willis which may cause:
 - a. Moyamoya disease with distal carotid occlusion (lenticulostriate collaterals appear as a “puff of smoke” in the MCA territory)
 - b. Endothelial injury and possibly sickle cell stimulation of smooth muscle and fibrous elements of the vessel wall

- c. Stasis in the vaso vasorum (blood supply to blood vessels)
3. Sickle cell disease patient strokes occur:
 - a. Convexity border zones
 - b. Deep and subcortical territories
 - c. Brainstem, spinal cord and retinal territories

Differential Diagnosis of Strokes Associated with Hyperviscosity

1. Diabetes mellitus
2. Low flow states (dehydration, burns, shock)
3. Arterial hypertension
4. Lipoproteins including LDL, triglycerides, chylomicrons and VLDL which cause:
 - a. Concentration dependent increase of plasma viscosity (dehydration)
 - b. Red cell aggregation (increased LDL)
5. Smoking associated with:
 - a. Increased hemoglobin
 - b. Red cell aggregation
 - c. Increased fibrinogen
 - d. Increased leukocytosis
 - e. Increased plasma viscosity

Putatively Associations

1. Binswanger disease
2. Pathogenesis and progression of atherosclerosis
 - a. Occurs in areas of low shear stress
3. Spontaneous echo contrast (smoke) in heart chambers
 - a. Increased risk for cardiac emboli
 - b. In atrial fibrillation, mitral stenosis, left atrial enlargement
 - c. Pathology is putative protein mediated RBC aggregation as a consequence of low shear force

Bone Disorders and Cerebrovascular Disease*General Characteristics*

1. Low bone mineral density (BMD)
 - a. Predictor of cardiovascular mortality in older men
 - b. Low BMD is related to stroke mortality and incidence of stroke in women
 - c. Relationship between BMD and stroke has not been supported by some studies

Clinical Manifestations

1. Fibrocartilaginous emboli
 - a. Rare cause of stroke:
 - i. Source is nucleus pulposus
 - ii. 32 patient study demonstrated:
 1. Women affected more than men
 2. Bimodal age distribution (20's and 60's)
 3. Embolization was arterial and venous; some purely arterial
 - b. Ischemic myelopathy occurred
 - i. Cervical > lumbosacral areas

Neuropathology

1. Schmorl's nodes (nucleus pulposus eroding the vertebral body)
2. Larger volume of nucleus pulposus in younger patients
3. Prolonged flexed position during lumbar puncture

Neuroimaging

1. Large vessel embolic stroke

Osteopetrosis*General Characteristics*

1. An abnormal accumulation of bone mass
 - a. Diminished bone resorption
2. Autosomal recessive
 - a. Multiple genes have been described: SNX10 and TC1RG1 are related to osteoclast function

Clinical Manifestations

1. Associated cerebrovascular disease:
 - a. Compression of the carotid and vertebral arteries in transcervical and carotid canal from excessive bony overgrowth

Neuropathology

1. Communication between Ephrin type-B receptor 2 and Ephrin type-B receptor 4 within the osteoblast lineage are pivotal in bone mineralization

Neuroimaging

1. Entrapped arteries in their bony canals

Paget's Disease*General Characteristics*

1. Incidence appears to be decreasing
2. Genetic features:
 - a. Mutation in the SQSTM1 gene occur in 25–50% of familial Paget's disease
 - b. Disturbance of bone modeling and remodeling

Clinical Manifestations

1. Steal syndrome
2. Spinal epidural hematomas; reported case of subdural hematoma
3. Mechanical compression of cerebral vasculature in bony canals

Neuropathology

1. Overactivity of Pagetic osteoclasts
2. Focal and disorganized increases in bone turnover

Neuroimaging

1. MRI/CT
2. Arterial compression in bony canals with topographical stroke

Schimke Immuno-Osseous Dysplasia*General Characteristics*

1. Autosomal recessive
 - a. Biallelic mutation in SMARCAL1 (SWI/SNF-related matrix-associated, actin-dependent regulator of chromatin, subfamily-like 1)
 - b. Decreased regulation of elastin expression
2. Associated with atherosclerosis and emphysema
3. Atherosclerosis characterized by:
 - a. Intimal and medial hyperplasia
 - b. Smooth muscle cell hyperplasia
 - c. Disorganized elastin fibers
 - d. Microdontia, hypodontia, malformed deciduous and permanent molars
4. Associated medical conditions:
 - a. Spondyloepiphyseal dysplasia
 - b. Triangular face
 - c. Short neck and short limbs
 - d. Hyperpigmented macules

*Clinical Manifestations**Cerebrovascular Complications*

1. 2 girls described with Moyamoya disease
2. Several children described with TIA

Imaging Evaluation

1. PET study revealed hypoperfusion of cerebral and cerebellar arterial territories

Neuropathology

1. Low brain weight
2. Defective neuron-glial migration with:
 - a. Heterotopia
 - b. Irregular cortical thickening
 - c. Incomplete gyral formation
3. Cortical dysplasia

Camurati-Engelmann Disease*General Characteristics*

1. Autosomal dominant disorder
 - a. Chromosome 19q.13 gene mutations
 - b. Encodes TGFB1
 - c. Occasional incomplete penetrance
2. Progressive diaphyseal dysplasia
 - a. Cortical bone sclerosis of the diaphyses and metaphyses of long bones
 - b. Cranial hyperostosis (skull base)
 - c. Exophthalmos
 - d. Waddling gait
 - e. Muscle weakness
 - f. Leg pain
 - g. Cranial nerve constriction at the skull base

*Clinical Manifestations***Cerebrovascular Manifestations**

1. Premature onset of arteriopathy causing:
 - a. Dissection of vessels
 - b. Vertebral atherothrombosis

Neuropathology

1. TGFBI-dependent vascular remodeling
 - a. Thickening of the intima and media
 - i. Increase in extracellular matrix and proteoglycan synthesis

Neuroimaging

1. Dissection of vertebral vessels
2. Atherosclerotic circulation
 - a. Posterior > anterior

Cancer and Paraneoplastic Strokes*Overview*

1. The syndromes may develop in parallel with the development and growth of the tumor or precede it
2. 15% of patients with cancer have cerebrovascular disorders related to their neoplastic disease
3. Paraneoplastic strokes often present with specific clinical manifestations
4. The frequency of hemorrhages equals infarcts

Cerebrovascular Disease and Cancer

1. Brain infarction is more common in patients with carcinoma and leukemia
2. Leukemia most often is the cause of hemorrhage
3. Diffuse and progressive encephalopathy occurs with:
 - a. DIC, non-bacterial endocarditis and paraneoplastic vasculitis
 - b. Associated with or without focal deficits
 - c. Due to multiple infarcts
4. Approximately 10% of cancer patients suffer a stroke
5. Venous thrombotic disease:
 - a. Diffuse moderate to severe headache
 - b. Focal or generalized seizures:
 - i. Cortical vein induced seizures progressively incorporate a larger territory with each seizure
6. Strokes with disseminated intravascular coagulation:
 - a. Occur in both large and small vessels
 - b. Primarily anterior circulation
 - c. Associated with subarachnoid hemorrhage
 - d. Often accompanied by NBTE and emboli
 - e. May occur following chemotherapy and often with gram negative sepsis
 - f. Acrocyanosis and bleeding from peripheral venipuncture sites
7. Hemorrhagic stroke is as common as bland infarction:
 - a. More frequent with leukemia than lymphoma or solid tumors

- b. Myelogenous greater than lymphocytic leukemia
- c. Acute greater than chronic disease
- d. Hemorrhages are often smaller than with usual causes
 - i. Associated with diffuse encephalopathy
- e. Subdural hematoma occurs in all stages
- f. Subarachnoid hemorrhage (SAH) is the rarest form of hemorrhagic stroke with cancer

Mechanisms of Stroke in Cancer Patients

1. Autoimmune in primary paraneoplastic syndromes ("molecular mimicry")
 - a. Most common with small cell cancer of the lung and gynecological tumors
2. Secondary neurological paraneoplastic syndromes:
 - a. Most common cause of cerebrovascular disease and cancer
 - b. Autoimmune mechanism
 - c. Release of procoagulant proteins (tissue-factor VII like) by the tumor; occurs with breakdown of tumor cells during treatment – particularly with leukemia and lymphoma
 1. Cause both hemorrhagic and bland infarctions
3. Autoimmune blood element involvement occurs with:
 - a. Microangiopathic hemolytic anemia:
 1. Associated with mucinous adenocarcinomas of the stomach, breast and lung
 - a. Associated thrombocytopenia
 - b. Thrombocytopenia
 1. Usually platelets are less than 30,000/mm³
 2. Most common tumors are chronic lymphocytic leukemia, b-cell lymphoma, lung and rectal carcinoma
 3. Thrombotic thrombocytopenic purpura
 - a. Fibrin and platelet aggregates form throughout the brain microcirculation
 - b. Microinfarcts
 - c. Intracranial and subdural hemorrhages
 - d. Antibodies to vWF
 - i. Associated with lympho- and myeloproliferative neoplasms
 - ii. Systemic and intracranial bleeding
4. Antiphospholipid antibodies:
 - a. Associated with arterial and venous thrombosis
 - b. Venous sinus occlusion
5. Tumor induced vasculitis:
 - a. Immune complex deposition on vascular endothelium
 - b. Hodgkin's disease, lymphoma, hairy cell leukemia and lung cancer are the most common neoplasms
6. Granulomatous angiitis:
 - a. Herpes Zoster infection (distribution of V₁)
 - b. Delayed onset of proximal intracranial large vessel infarction
7. Temporal arteritis:
 - a. Estimated incidence concomitant with neoplasm is 3.5%–16%
 - i. TIA and infarction occur in less than 10% of these patients

Neoplasms and a Prothrombotic State

1. Tumor derived procoagulants
2. Non-bacterial thrombotic endocarditis:
 - a. Most common cause of symptomatic cerebral infarction in cancer patients
 - i. Fibrin-platelet deposits on cardiac valves (primarily mitral or aortic)
 - ii. Highest incidence
 1. Lymphomas
 2. Gastric and lung cancer
 3. Prostate adenocarcinoma
 4. Medullary thyroid cancer (rare)
 - iii. Associated with compensated disseminated intravascular coagulation (DIC) and intravascular thrombosis
 - iv. 1–2% of autopsied cancer patients
 1. Approximately 1/3 with cerebral emboli
 - v. May occur with any cancer at either the early or late stage of disease
 - b. 20% of acute leukemia patients develop DIC
 - i. Release of procoagulants
 - c. Compensated DIC:
 - i. Platelets approximately 30,000/mm³
 - ii. Increased fibrin degradation products
 - iii. Hyperfibrinogenemia; decreased factor V and VIII
 - iv. Infarction of small cerebral arteries and venules
 - v. Venous sinus thrombosis
 - vi. NBTE
 - vii. Second most common cause of vascular disease in cancer patients
3. Mechanisms of hypercoagulability in DIC
 - a. Fibrinopeptide A, a marker of thrombosis, is elevated in many neoplasms
 - b. Sialic acid residues released by mucinous tumors
 - c. Pancreatic enzyme release
 - d. Tissue factors and phospholipids
 - e. Inflammatory cytokines (IL-1, IL-6, IL-8, ICAM, tumor necrosis factor α) released by the neoplasms:
 - i. Activate platelets
 - ii. Induce clotting
 - f. IL-6 induces thrombosis
 - g. Paraproteins and immunoglobulins (Waldenström's, IgG and IgM)
 - i. Hyperviscosity syndrome
 - ii. Interferes with fibrin polymerization and causes hemorrhage

Intravascular Lymphoma*General Characteristics*

1. Extra nodal large B-cell lymphoma
 - a. Neoplastic lymphoid cells proliferate within the lumina of small to medium-sized vessels
 - b. Past terminology: angioendotheliomatosis
 - i. Presently intravascular lymphoma or intravascular lymphomatosis

2. Ischemic damage to various organ systems
3. Incidence of less than 1 case per million
4. Primary occurrence in sixth or seventh decade (range between 34 to 90 years of age)
5. No gender preference
6. An asian variant associated with:
 - a. Hemophagocytic syndrome
 - b. Less neurologic symptomatology
 - c. No cutaneous involvement
7. Women in Western countries may have:
 - a. Cutaneous variant
 - b. Good prognosis

Clinical Manifestations

1. Untreated patients: medium survival of 4 to 7 months
2. Poor prognostic factors
 - a. Greater than 60 years of age
 - b. Thrombocytopenia
3. Most common areas of involvement are skin and CNS
4. Non-neurologic presentations include:
 - a. Fever of unknown origin
 - b. Rash
 - c. Night sweats
 - d. Weight loss
 - e. Renal failure
 - f. Dyspnea

Neurological Features

1. Cerebral infarction:
 - a. Multifocal infarcts in greater than 75% of patients with neurologic symptoms
 - b. Recurrent focal deficits cause a progressive encephalopathy dementia
 - c. Supratentorial strokes most common
 - d. Differential diagnosis of vascular presentation
 - i. CNS angiitis
 - ii. Acute disseminated encephalomyelitis
 - iii. Creutzfeldt-Jakob disease
2. Encephalopathy and rapidly progressive dementia
 - a. Gradual cognitive decline, subacute encephalopathy or fluctuating level of consciousness
 - b. Encephalopathy in approximately 30% of patients
 - i. Focal deficits and seizures may occur
3. Spinal cord and radicular syndrome
 - a. Spinal cord involvement
 - i. Greater than 1/3 of patients with neurologic involvement
 - ii. Spastic or flaccid paraparesis associated with pain and incontinence
 - iii. Involvement of blood vessels with infarction of the cord or roots at any level
4. Neuropathy
 - a. Both peripheral and cranial nerve involvement
 - i. Vasa nervorum involved
 - b. Cranial nerve involvement

- i. VII, VI, VIII, III, V and II most often involved
 - ii. Axonal neuropathy
- 5. Venous stroke
 - a. Proliferation of lymphomatous cells within the venules and dural sinuses
 - i. Venous occlusion with infarction and hemorrhagic transformation

Neuropathology

1. Brain biopsy may be non-diagnostic (need involved tissue)
2. Occlusion of small vertebral and meningeal capillaries, arterioles and venules by malignant lymphocytes
 - a. β -cell phenotype
 - b. Rare T-cell or natural killer cell (NK) derivation
 - c. Infarctions may be hemorrhagic; distributed throughout the brain and spinal cord
- d. Extra-CNS involvement
 - i. Skin
 - ii. Liver
 - iii. Spleen
 - iv. Bone marrow
 - v. Kidney
 - vi. Lung
 - vii. Prostate
 - viii. Adrenal gland
 - ix. Thyroid
 - x. Gall bladder
 - xi. Lymph nodes are usually spared

Imaging Evaluation

MRI

1. May have high false negative rate
 - a. Spinal cord lesions are difficult to detect
 - b. Multifocal abnormalities:
 - i. Non-specific white matter hyperintensities: 45%
 - ii. Infarcts: 36%
 - iii. Focal mass lesions: 36%
 - iv. Meningeal/parameningeal enhancement: 64%
 - v. Multifocal lesions on DWI
 1. Fluctuation of lesions (resolution and recurrence) during the course of the illness
 - vi. Lesion enhancement with gadolinium
 - vii. One patient reported with posterior leukoencephalopathy

Laboratory Evaluation

1. Elevated ESR, lactic dehydrogenase and anemia
2. Bone marrow negative
3. CSF analysis:
 - a. May be normal
 - b. Most demonstrate elevated protein
 - c. 50% show mild to moderate pleocytosis:
 - i. Rarely malignant cells demonstrated
 - d. Elevated immunoglobulin G index

Differential Diagnosis

1. Intravascular lymphoma should be considered in the differential diagnosis of multifocal brain infarction and insidious or rapidly progressive dementia

Lymphomatoid Granulomatosis

General Characteristics

1. Angiocentric lymphoproliferative disease
2. Primarily affects the lungs
3. Abnormal lymphoid collections are centered around arteries and veins
4. Men are affected 2:1 more than women
5. Illness develops in the fifth or sixth decade (rarely adolescences)

Clinical Manifestations

1. Prolonged course but may be remittent
2. Pulmonary signs and symptoms are predominant
3. Skin lesions
 - a. Raised erythematous rash and rarely skin nodules (trunk)
4. Neurologic manifestations
 - a. Gradual onset of focal deficits including cognitive decline
 - b. Multifocal small and large lesions that involve the cerebral hemisphere more than the cerebellum and brainstem

Imaging Evaluation

MRI

1. Multifocal large and small mass lesions of the cerebral hemispheres and rarely the cerebellum and brainstem
2. Lesions in enhance with gadolinium
 - a. Punctate
 - b. Linear
 - c. Ring enhancement is rare
 - d. Brain atrophy occurs overtime
 - e. Enhancement of the leptomeninges and dura mater
 - f. Enhancement of cranial nerves
 - g. Lesions may involve the orbit and cavernous sinus

Neuropathology

1. Classified as an Epstein-Barr Virus associated form of lymphoproliferative disease
 - a. Lower grades: a β -cell proliferation
2. Severe disease: mature diffuse β -cell form of lymphoma associated with an extensive benign T-cell reaction
3. Areas of necrosis in the brain and lung
 - a. Related to infarction caused by the vascular infiltrate

Differential Diagnosis

Lymphomatoid Granulomatosis vs Intravascular Lymphoma

1. Lymphomatoid granulomatosis abnormal cells invade the vessel wall where as in intravascular lymphoma blood vessels are blocked by lymphomatous cells
2. Cranial and peripheral nerves may be involved with lymphomatoid granulomatosis

Hypereosinophilic Syndrome

General Characteristics

1. General eosinophilia is caused by
 - a. Allergic conditions
 - b. Neoplastic process (eosinophilic leukemia, Hodgkin's disease)
 - c. Drug reaction
 - d. Not clonal and are produced in response to eosinophilopoietic cytokines
2. Idiopathic hypereosinophilic syndrome (HES)
 - a. HES is a group of disorders
 - i. Sustained overproduction of eosinophils
 - ii. Eosinophilic degranulation; releases 4 major cationic proteins
 1. Causes organ damage
 - b. Requires:
 - i. Persistent eosinophilia of greater than 1,500/ μ l for longer than 6 months
 - ii. Lack of parasitic, allergic or other known causes of eosinophilia
 - iii. Signs and symptoms of organ involvement including diffuse or focal nervous system involvement

Clinical Manifestations

1. Cerebral infarction caused by:
 - a. Medial basic protein mediated endothelial damage
 - b. Eosinophil-cationic protein mediated hypercoagulability
 - c. Eosinophil cardiomyopathy
2. Loeffler's endomyocarditis (a restrictive cardiomyopathy) associated with:
 - a. Cardiac thrombi (rare emboli)
 - b. Peripheral small and large arterial occlusive thrombosis
3. Axonal peripheral neuropathy
4. Dementia

Neuropathology

1. Putative mechanisms:
 - a. Clonal eosinophilic proliferation
 - i. Primary defect in hematopoietic stem cells
 - ii. Overproduction of eosinophilopoietic cytokines (IL-5) or their dysfunction
 - b. Eosinophilic induced neural damage
 - i. Toxic proteins released by degranulation
 1. Medial basic protein
 2. Eosinophilic cationic protein
 3. Eosinophilic derived neurotoxic
 - c. Medial basic protein
 - i. Damages endothelial cells which promotes thrombosis and artery-to-artery emboli
 - ii. Eosinophil-cationic protein
 1. Prothrombotic
 - iii. Eosinophil-derived neurotoxin
 1. Direct toxin action on neuronal tissue and myelin

Neuroimaging

MRI

1. Large and small vessel stroke
2. Cranial nerve involvement (rare enhancement with gadolinium)
3. Increased white matter hyperintensities

Stroke in Young Patients

Overview

Approximately forty percent of cerebral thrombosis in young patients will be caused by HCVD 23%, diabetes mellitus 11%, and migraine 6%. Dissection certainly must be considered in a patient with neck or face pain. Carotid dissection will often be announced by oculosympathetic paresis. Posterior neck pain, occasionally accompanied by lateral eyebrow pain occurs with vertebral obstruction and dissection. Migraine headaches are characteristic of mitochondrial disease, collagen vascular disease and CADASIL. Sporadic hemiplegic migraine has a greater chance of permanent stroke than familial migraine. Migraine with multiple visual auras is suggestive of anticardiolipin antibody syndrome. Prothrombotic states should always be sought in the context of a family history of thrombophlebitis or venous clotting in the upper extremity or chest wall. Vasospastic occlusion as well as hemorrhage from underlying vascular malformation or aneurysms is characteristic of strokes from cocaine or other sympathomimetic drugs. Oral contraceptives, hypertension and diabetes cause strokes of PICA and the thalamoperforate and thalamogeniculate arteries. Cigarette smoking in this context exacerbates this risk in young patients.

Sickle cell disease, leukemia and lymphoma cause approximately 5–10% of thrombotic strokes in young patients. Sickle cell disease is particularly dangerous during pregnancy. Stroke is frequent during chemotherapy for leukemia and lymphoma possibly due to the release of thromboplastin from lysed neoplastic cells that cause DIC.

Cardiac causes of stroke in young patients are similar to those in adults except that congenital anomalies, infective endocarditis (drug use), mitral valve prolapse and PFO are more common.

General Characteristics

1. Approximately 3% of cerebral infarctions occur in patients <40 years of age
2. Specific age related vascular disease:
 - a. 70% of subarachnoid hemorrhage <40 years of age
 - b. 97% of cerebral infarction >40 years of age
 - c. 60% of cerebral infarctions occur between 65 to 84 years of age
3. Differential diagnosis of cerebral thrombosis in young patients:
 - a. HCVD (23%)
 - b. Diabetes mellitus (11%)
 - c. Migraine (6%)

- d. Collagen vascular disease (5%)
- e. Cryptogenic (10–30%)
- f. Dissection of carotid or vertebral artery (10%)
- g. Prothrombic states (5%)
- h. Hematologic diseases (5%)
- 4. Stroke in women (15–45 years old)
 - a. Aneurysm or AVM without hemorrhage in 3.4%
 - b. Hemorrhage – 42%
 - c. SAH – Berry aneurysm > AVM
 - d. Intracranial hemorrhage
 - i. Leukemia
 - ii. Thrombotic thrombocytopenia
 - iii. Aplastic anemia
 - e. Infarction – 18%
 - f. Embolism – 56% cardiac (33% from cardiovascular surgery)
 - g. Thrombosis
 - i. Carotid 30%
 - ii. Vertebrobasilar 7%
- 5. Early onset atherosclerosis with or without HCVD associated with:
 - a. Evidence of: coronary artery disease, peripheral vascular disease or arterial occlusive disease
- 6. Oral contraceptive risk (general)
 - a. 1/10,000 women
 - b. Death from stroke

Causes of Stroke in Young Patients

Migraine

- 1. 5% of stroke in young women
- 2. No relation to specific attack
- 3. Vasospasms, vessel occlusion, platelet hyper aggregability (subset of migraine patients)

Pregnancy

- 1. Pregnancy and the puerperium
 - a. 3% of cerebral thrombosis in young women
 - b. 4% within 30 days

Cardiac Source – High Risk

- 1. Ischemic heart disease and dyskinetic left ventricular segment
- 2. Atrial Fibrillation (AF)
- 3. AF with dilated left atrium
- 4. Mechanical prosthetic valve with AF
- 5. Rheumatic mitral stenosis, atrial fibrillation, dilated left atrium
- 6. Left ventricular thrombus
- 7. Dilated cardiomyopathy with left ventricular clot
- 8. Atrial myxoma
- 9. Infective endocarditis
- 10. Congenital heart disease – atrial septal defect perioperative
- 11. Congenital heart disease – Ebstein's anomaly
- 12. Congenital heart disease – Tetralogy of Fallot

Cardiac Source – Medium Risk

- 1. Patent foramen ovale (PFO)
- 2. Atrial septal aneurysm and PFO
- 3. Mitral valve prolapse (MVP)
- 4. Hypertensive heart disease and hypokinetic left ventricular segment

Cardiac Valve Tumors

- 1. Have risk of cardiac emboli:
 - a. Aortic > mitral > pulmonary > tricuspid
 - b. Mean age 52 (2–88 years)
 - c. Male patients more than female
 - d. Less aggressive than non-valve tumors
 - e. Less than 10% of cardiac tumors are on the valve
- 2. Clinical presentation
 - a. Most are asymptomatic
 - b. Cardiopulmonary symptoms
 - i. Coronary artery occlusion
 - ii. Congestive heart failure
 - c. Embolic stroke (usually pial vessels)
 - d. Rare occurrence of sudden death
 - e. Left-sided more symptomatic than right-sided lesions
 - f. A few patients have multiple tumors

Differential Diagnosis

Cardiac Tumors

- 1. Papillary fibroelastoma (most common)
- 2. Myxoma (medium stroke risk)
- 3. Fibroma
- 4. Sarcoma (rhabdomyosarcoma; tuberous sclerosis)
- 5. Hemangioma
- 6. Histiocytoma
- 7. Undifferentiated

Age Relation to Stroke in Young Patients

Ages 15–29	Approximate percentages
1. Atherosclerosis	3%
2. Lacunar infarction	3%
3. Cardiac Embolism	30%
4. Other determined causes	25%
a. Dissection	
b. Sickle cell disease	
c. Arteritis	
d. Infection	
5. Undetermined	17%
Ages 15–40	
1. Hematologic disorder	
2. Arterial dissection	
3. Vasculitides	
4. SLE	
5. Primary antiphospholipid antibody syndrome	
6. Migraine	
7. Neurocysticercosis (specific populations)	
8. Eclampsia	
9. Oral contraceptives	

10. Extracranial carotid aneurysm
11. Central venous thrombosis
12. Vasospasm after subarachnoid hemorrhage
13. Complication of angiography
14. Moyamoya disease

Cerebral Embolism (Ages 15–40 Order of Frequency)

1. Apical aneurysm
2. Segmental hypokinesia
3. Acute myocardial infarction
4. Aseptic endocarditis (NBTE)

Ischemic Stroke Due to Deficiency of Coagulation Inhibitors (Young Patients)

1. Thromboses secondary to hematologic or clotting disorders occurs in approximately 4% of young patients
2. Hematologic disturbances young stroke patients:
 - a. Abnormalities of platelet function
 - b. Coagulation inhibitors
 - c. Fibrinolysis defects
3. Free protein S enhances inhibition of V and VIII by activated Protein C; oral contraceptives and inflammatory conditions may decrease its concentration
4. Antithrombin III; inhibits thrombin (factor Xa, IXa, XIa, XIIa – minor effect) deficits may be AD; acquired deficits
 - a. Inhibits thrombin
 - b. Minor effect inhibits clotting factors
 - c. AD form
 - d. Acquired deficits
 - i. Failure to synthesize due to cirrhosis
 - ii. Diabetes
 - iii. Age
 - iv. Protein malnutrition
 - v. Low serum albumin
5. Acquired deficiencies of coagulation inhibitory proteins occur with:
 - a. Malignancies
 - b. Plasmapheresis
 - c. Hemolysis
 - d. Nephrotic syndrome
 - e. Hepatic failure
 - f. Oral contraceptives
6. Factor V Leiden defect (effects on protein C)
7. Prothrombin gene defect
8. Increased fibrinogen and factor VIII levels and acquired hyperfibrinolysis occur in young adults with ischemic stroke
9. Strong predictors of myocardial infarction and stroke:
 - a. Plasma levels of fibrinogen (increased)
 - b. Tissue plasminogen activator concentration (decreased)
 - c. Plasminogen activator inhibitor type I (PAI-1) concentrations (decreased)
10. Decreased fibrinolytic factors:
 - a. Obesity

b. Hyperlipidemia

11. Young stroke patients (subgroup) have:
 - a. Generalized defect in fibrinolytic system
 - b. Diurnal circadian rhythm of tPA and PAI-1 tPA
 - i. PA I-1 activity doubles from early morning until afternoon
 - c. Genetic control of circulating PAI-1 (plasminogen activator inhibitor type I)

Differential Diagnosis of Stroke from Cross Section of Community or Referral Hospitals

1. Stroke in patients (15 to 44); heterogeneous population
 - a. 50% probable cause
 - b. 20% possible cause
 - c. 30% (cryptogenic); arch of aorta source, PFO and atrial septal aneurysm discovery are decreasing this percentage
2. First Stroke
 - a. 50% women
 - b. 60% black patients (38% of population studies)
 - c. 35% Caucasian patients (60% of population studied)
3. Patients with recurrent stroke:
 - a. 60% women
 - b. 70% black patients
 - c. 16% <30 years old
 - d. <2% more than one probable cause
4. Probable cause (approximately percentage)
 - a. Cardiac embolism – 16%
 - b. Lacunar stroke – 10%
 - c. Hematologic – 10%
 - d. Non-atherosclerotic vasculopathy – 6%
 - e. Illicit drug use 5% (probably much higher)
 - f. Oral contraceptive 5%
 - g. Large artery atherosclerosis <2%
 - h. Migrainous <1% (probably higher)

Stroke and Substance Abuse

Heroin

General Characteristics

1. Heroin is a semisynthetic derivative of opium
2. Crosses the BBB easily
3. Heroin most widely abused opiate
 - a. Administration:
 - i. I.V. or subcutaneously
 - ii. Smoked or sniffed
4. When injected the initial effect or “rush” occurs within minutes and peaks in approximately 10 minutes
 - a. Sedation then ensues and last for about one hour
5. Heroin and other opiates cause death from violence, suicide, its association with HIV, sepsis and overdose

Clinical Manifestations

1. Hypotension
 - a. Decreased peripheral vascular resistance

2. Bradycardia (inhibits the baroreceptor reflex)
3. Respiratory depression (decreased respiratory centers response to carbon dioxide and low oxygen)
4. Infective endocarditis
5. Pulmonary hypertension
6. Foreign bodies injected with heroin include:
 - a. Starch
 - b. Sugar
 - c. Ajax
 - d. Quinine
 - e. Lactose
 - f. Mannitol caffeine
 - g. Lidocaine
 - h. Strychnine
 - i. Talcum powder
7. Induced lung granulomatous reaction that induces pulmonary hypertension
 - a. Causes or exacerbates a right-to-left pulmonary shunt

Cerebrovascular Complications

1. I.V. use:
 - a. Septic embolization with staphylococcus aureus and candida that cause:
 - i. Mycotic aneurysm (may have premonitory symptoms)
 - ii. Infectious vasculitis
 - b. Septic aneurysms are peripheral and may rupture with or without treatment
2. Hemorrhagic stroke:
 - a. Consequence of hepatitis (decreased production of clotting factors)
 - b. Heroin nephropathy (hypertension and uremia)
 - c. Meningitis
 - d. HIV/AIDS
3. Decreased perfusion of the medial prefrontal cortex; anterior cingulate cortex and precuneus
4. Increased arterial stiffness which contributes to vascular aging

Neuropathology

1. Septic emboli (I.V. use)
2. Hypotension and hypoxic changes induced by overdose (hypoxic-ischemic injury) in vulnerable brain regions (hippocampus layers III, V of the cortex, Purkinje cells of the cerebellum and globus pallidus)
3. Minimal evidence for vasculitis

Imaging Evaluation

MRI

1. Areas of signal change on T1 and T2 sequences in brain areas vulnerable to ischemia/hypoxic injury
2. Some patients demonstrate "beaching" on arteriography
3. Topical large vessel stroke from septic emboli
4. Mycotic aneurysms
 - a. Most common in MCA territory (peripherally)
5. Cerebral hemorrhage in areas of septic embolic infarction
6. Hemorrhagic stroke

Angiography

1. Some patients demonstrate large or small vessel arteritis
 - a. Possible autoimmune etiology (eosinophilia, hypergammaglobulinemia)
2. Stroke mechanisms in heroin abuse:
 - a. Vascular aging
 - b. Hypotension and hypoventilation (acute)
 - i. Bilateral GP infarction
 - c. Infective endocarditis with mycotic aneurysm
 - d. Embolization of adulterants:
 - i. Pentazocine and antihistamines
 - ii. Parenteral paregoric, meperidine and hydromorphone
 - e. Heroin myelopathy:
 - i. Some patients with ischemia of the anterior spinal arteries
 - ii. Acutely associated with pulmonary edema

Cocaine

General Characteristics

1. Blocks reuptake of monoamine neurotransmitters at synaptic nerve endings (binds to transporter proteins)
2. Intranasal preparation
 - a. Cocaine hydrochloride
 - b. Ischemic stroke; intracranial hemorrhage
3. Smokeable form:
 - a. Alkaloid form "crack"
 - b. Can be utilized in large doses over a long duration (hours to days)
 - c. Ischemic and hemorrhagic stroke

Clinical Manifestations

Cerebrovascular Complications

1. TIA
2. Infarctions of cortical and subcortical territories that include the hemispheres; thalamus, brainstem, spinal cord and retina
3. Strokes in pregnant women and neonates
 - a. Vasospasm
 - b. Premature separation of the placenta (cocaine taken prior to delivery)
4. Rare vasculitis
5. Delayed vasospastic ischemic infarction is common (hours to days)
6. Hemorrhagic stroke
 - a. Intracerebral and subarachnoid hemorrhage
 - b. 20% of hemorrhages have underlying
 - i. Vascular malformation
 - ii. Saccular aneurysm
 1. Increase vasospasm after aneurysmal rupture
 - iii. Bleeding into embolic infarction or glioma
 - c. Other cocaine induced stroke mechanisms:
 - i. Myocardial infarction and cardiomyopathy with embolus
7. Multiple infarcts occur:

- a. High incidence of hemorrhagic transformation
- 8. Aggregation and de-aggregation of platelets; effects on antithrombin III, protein C, NF- κ B (nuclear factor kappa-light-chain-enhancer of activated B-cells), activator protein-1
- 9. Platelet rich arterial thrombi
- 10. Activates the endothelium that promotes platelet vWF interaction
- 11. Vasoconstrictive metabolites can last for days to weeks

Neuropathology

- 1. Hyperintense surge (ICH)
- 2. Hyperintensive surgery
 - a. Most common cause of ICH and SAH
 - i. Possibly 20% have underlying vascular malformation or aneurysm
 - ii. ICH occurs in the usual locations
- 3. Vasospasm
 - a. Sudden and usually reversible changes in vascular caliber
 - i. Due to smooth muscle dysfunction
 - ii. Tunica media and elastic lamina changes damage in arteries in multiple vascular territories
 - b. Effects on calcium channels in smooth muscle cells of arteries and arterioles by release of calcium from the endoplasmic reticulum
 - c. Accumulation of catecholamines occur due to prevention of reuptake
 - d. Effects of endothelin-1
 - e. Vasospasms induces:
 - i. Endothelial injury that resulting in:
 - 1. Intimal hyperplasia
 - 2. Platelet activation which then causes:
 - a. α -granule release
 - b. Increased platelet responsiveness to arachidonic acid
 - c. Platelet release of thromboxane, β 2 and plasminogen activity factor-1 inhibitor (PAI-1)
 - d. Facilitates thrombosis
- 4. Enhanced platelet aggregation
 - a. Caused by platelet activation
- 5. Cerebral vasculitis
- 6. Vasculitis
 - a. Biopsy demonstrates
 - i. Hypersensitivity vasculitis
 - ii. Rarely demonstrated
- 7. Accelerated atherosclerosis
 - a. Cocaine causes increased permeability to atherogenic lipoproteins
- 8. Cardiac emboli
 - a. Infective endocarditis (injection of the hydrochloride forms)
 - b. Arrhythmia
 - c. Acute and chronic dilated cardiomyopathy
- 9. Endocarditis
 - a. Septic cerebral arteritis
 - b. Mycotic aneurysms

Neuroimaging

MRI

- 1. Dose-dependent vasoconstriction of cerebral vessels on MRA
- 2. Microvascular white matter changes in chronic users
- 3. ICH in standard hypertensive locations
- 4. SAH (hypertension)
- 5. Ischemic and hemorrhagic stroke of cerebral vessels

Amphetamines

General Characteristics

- 1. Amphetamines have a chemical similarity to epinephrine and dopamine
- 2. Synthetic modifications have different properties and effects
- 3. They are weak bases that can be absorbed through different routes
- 4. Drug half-life is dependent on the specific drugs used and its dosages
 - a. Half-life varies between 10 to 30 hours depending on the above
- 5. These agents include:
 - a. Dextroamphetamine
 - b. Methamphetamine
 - c. Methylphenidate
 - d. Ephedrine
 - e. Pseudoephedrine
 - f. Phenylpropanolamine (PPA)
- 6. Methamphetamine is the most potent and most frequently abused:
 - a. Half-life of 12 hours
 - b. Metabolized in the liver
 - c. Has an active metabolite that is hallucinogenic
- 7. Blocks the presynaptic uptake of dopamine, epinephrine and serotonin
- 8. Administration is oral, sniffed or smoked
 - a. Crystalline form ("ice", "crystal meth")

Clinical Manifestations

- 1. Acute ischemic stroke
- 2. ICH
- 3. SAH
- 4. Disproportionate rate of hemorrhagic stroke
- 5. Approximately 75% of patients with methamphetamine induced stroke are hypertensive at admission

Neuropathology

- 1. Necrotizing periarteritis
 - a. Spontaneous ICH (hypertensive surge)
 - i. Usual locations for hypertensive hemorrhages
 - b. Chronic use causes:
 - i. Vessel wall necrosis
 - ii. Microinfarcts in small vessels
 - iii. Atherosclerosis is accelerated

Neuroimaging

1. ICH and cerebral edema
 - a. Usual areas of hypertensive hemorrhage
 - b. Petechial hemorrhages in white matter

Angiography

1. "Beading" of cerebral cortical vessels consistent with arteritis
2. Embolic thrombosis in large vessels in patients with cardiomyopathy
3. SAH

*Phencyclidine***General Characteristics**

1. Chemical name: 1-(1-phenylcyclohexyl)piperidine
2. Dissociative anesthetics similar to ketamine
3. Effects NMDA (antagonist), nACh (antagonist) and dopamine (agonist) receptors
4. Possible PCP receptors on cerebral vessels
5. Stored in fat and therefore re-mobilization can occur with recurrent symptoms for days or months

Clinical Manifestations*Cerebrovascular Disease*

1. Hypertension occurs following use or can be delayed
2. Hypertensive encephalopathy
3. Transient monocular blindness
4. PCP related SAH
5. Hemorrhagic stroke

Neuropathology

1. Experimental:
 - a. Neuronal degeneration on retrosplenial cortex, posterior cingulate gyrus, entorhinal cortex and hippocampus

Neuroimaging

1. Edema (occipital lobe) from hypertensive encephalopathy
2. SAH
3. Cortical hemorrhagic stroke

*Lysergic Acid Diethylamide (LSD)***General Characteristics**

1. Chemical name: (6aR,9R)-N,N-diethyl-7-methyl-4,6,6a,7,8,9-hexahydroindolo-[4,3-fg]quinoline-9-carboxamide
2. An ergotamine derivative that causes hypertension
3. Potent hallucinogen

Clinical Manifestations*Cerebrovascular Disease*

1. Ischemic vascular disease (patients less than 25 years of age)
 - a. Large artery involvement
 - b. Delayed stroke occurs
2. Mechanism:
 - a. May effect serotonin receptors to cause vasospasm

Neuropathology

1. Binding to serotonin receptors in the brainstem (5HT_{2A} receptor) and the cerebral cortex

Neuroimaging*Angiography*

1. Progressive narrowing and occlusion of ICA
2. Generalized arterial beading

*Marijuana***General Characteristics**

1. Most widespread recreational drug in the USA
2. Active component: tetrahydrocannabinol (THC) or (-)-(6aR,10aR)-6,6,9-Trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-1-ol
3. Cannabinoids have physiological role in:
 - a. Cerebral circulatory autoregulation
 - b. Vascular tone
 - c. Cardiac physiology

Clinical Manifestations

1. Associations with stroke, myocardial infarction and lower limb arteritis
 - a. Myocardial infarction may occur with concomitant use
 - b. Extremity arterial disease occurred in younger male patients primarily in one extremity

Cerebrovascular Disease

1. Ischemic stroke; majority of reported cases
2. Reversible vasoconstriction syndrome (described in 2 patients)
3. Stroke associated with concomitant anabolic steroid use
4. PRES reported

*Synthetic Cannabinoids***General Characteristics**

1. Heterogeneous group of compounds
2. "Spice" and "K2" synthetic cannabinoids
 - a. Not detectable by standard screening
 - b. Greater binding affinity at the CB₁ receptor than does Δ^9 tetrahydrocannabinol
 - c. Greater binding affinity at the CB₁ receptor than CB₂ receptor
 - d. Animal studies demonstrate 2-100x greater potency than THC

Clinical Manifestations

1. Nausea and vomiting
2. Shortness of breath
3. Depressed breathing
4. Hypertension
5. Tachycardia
6. Chest pain
7. Cognitive dysfunction
8. Acute renal failure
9. Cerebral vascular manifestations
 - a. Ischemic stroke

Neuropathology

1. No specific pattern of infarct distribution
2. Putative mechanisms for marijuana-ischemic stroke
 - a. Hypotension
 - b. Vasospasm
 - c. Arrhythmia
 - d. PRES
 - i. Possible vasospasm

Neuroimaging

1. Large vessel thrombotic stroke (rare reports: associated myocardial infarction)

MDMA (“Ecstasy”), MDMC (“Methylone”) and MDPV (“Bath Salts”)**General Characteristics**

1. Chemical names:
 - a. MDMA: *N*-methyl-1-(3,4-methylenedioxyphenyl)propan-2-amine or methylenedioxymethamphetamine; most used
 - b. MDMC: 3,4-methylenedioxy-*N*-methylcathinone
 - c. MDPV: (RS)-1-(Benzo[d][1,3]dioxol-5-yl)-2-(pyrrolidin-1-yl)pentan-1-one or Methylenedioxypyrovalerone
2. Alternatives to cocaine and methylenedioxymethamphetamine
 - a. 3,4 methylenedioxymethcathinone (methylone)
 - b. 3,4-Methylenedioxypyrovalerone (MDPV)
3. Increases the release and inhibits uptake of NE, serotonin, DA
4. Peak concentration at two hours after ingestion
5. Synthetic cathinones
 - a. Target plasma membrane transporters for DA, NE and serotonin
 - i. Mephedrone and methylone act as non-selective transporter substrates
 - b. Stimulates non-exocytotic release of DA, DA and serotonin. Effects are analogous to amphetamines
 - c. MDPV only blocks dopamine and norepinephrine

Clinical Manifestations

1. Mechanisms of stroke similar to those of cocaine and amphetamine
2. Cardiac arrhythmias and embolism may be important
3. Causes both ischemic and hemorrhagic stroke
4. I.V. use of crushed methylphenidate tablets: microembolization of talc in lungs

Neurological Complications

1. Hallucinations
2. Delirium
3. Euphoria
4. Tachycardia
5. Hyperthermia
6. Delayed responses
7. Agitation/psychosis
8. Cardiomyopathy
9. Myoclonus/seizures

Cerebrovascular Effects

1. Ischemic and hemorrhagic stroke
2. Cardiac dysfunction and hypertension are prominent

Neuropathology**Ecstasy**

1. Increases the release and reuptake of serotonin and norepinephrine; lesser effects on dopamine
2. Ischemic and hemorrhagic stroke
 - a. Cardiac arrhythmia with embolus
 - b. Cardiomyopathy in Ecstasy users with stroke (CHF and arrhythmia)
3. Vasospasm and necrosis in the vasculature of the globus pallidus
4. Chronic Vasospasm
 - a. Thrombosis and aneurysmal dilation of cerebral vessels
 - b. High fever that triggers DIC
 - i. Microinfarctions throughout the brain
 - c. Minimal evidence for vasculitis
5. Hypertensive surge:
 - a. ICH in hypertensive locations
 - b. SAH – underlying aneurysm
 - c. Microinfarction from DIC

Neuroimaging

1. ICH (hypertensive locations)
2. Ischemic and hemorrhage large vessel stroke
3. Microinfarctions (DIC)
4. SAH underlying aneurysm, AV malformation or hypertension

Ethanol**General Characteristics**

1. Ethanol consumption and coronary artery disease fits a “J-shaped” curve (a small amount is protective and larger amounts are detrimental)
 - a. Cardioembolic risk from MI occurs in heavy drinkers (>300 grams/week)
 - b. Thromboembolism in alcoholic cardiomyopathy
2. A J-shaped curve exists for ischemic stroke and ethanol consumption:
 - a. Linear correlation with ICH
 - b. Greater than 60 grams per day increased stroke risk for ischemic and hemorrhagic stroke

Clinical Manifestations

1. Heavy ethanol consumption:
 - a. Increases carotid artery atherosclerosis
 - b. Hemorrhagic stroke from thrombocytopenia
 - c. Subdural hematoma
2. Causes hypertension cardiomyopathy and atrial fibrillation

Neuropathology

1. SDH
2. Petechial hemorrhage in white matter
3. Ischemic and hemorrhagic stroke

Neuroimaging*MRI*

1. SDH
2. Atrophy (primarily white matter) with ventricular megally
3. Mammillary body hemorrhage (Wernicke's syndrome)
4. SAH (trauma)
5. Topographical ischemic and hemorrhagic stroke

Laboratory Evaluation

1. Lowers LDL and increases HDL
2. Lowers fibrinogen activity
3. Decreases plasma fibrinogen levels
4. Increases factor VIII levels
5. Increases platelet reactivity to adenosine diphosphate
6. Increases prostacyclin
7. Stimulates endothelial release of endothelin
8. Alcohol withdrawal
 - a. Causes hemoconcentration
 - b. Rebound platelet hyperaggregability

*Tobacco***General Characteristics**

1. Active component: (S)-3-[1-Methylpyrrolidin-2-yl]pyridine or nicotine
2. Heavy use is defined as smoking more than half a pack per day or 10 packs a year
3. Smokers have a higher incidence of coronary artery disease, peripheral vascular disease, chronic obstructive pulmonary disease as well as specific cancers (>30 carcinogens)
4. Tobacco smoke injures all major organs of the body

Clinical Manifestations

1. Linked to both small and large vessel atherosclerosis
2. Induces aneurysm formation

Neuropathology

1. In cultures smooth muscle cells (SMC) exposure to cigarette smoke causes
 - a. Decreased promoter activity and mRNA expression of key SMC contractile genes (SM-a-actin, SM-22a, SM-MHC)
 - b. Decreased transcription factor myocardin in a dose dependent manner
2. Induced proinflammatory/matrix remodeling genes (MCP-1, MMPs, TNF- α , IL1 β , NF- κ B)
3. Increased expression of KLF4, a regulator of SMC differentiation
4. Cigarette smoke causes phenotypic modulation of cerebral SMC through myocardin and KLF4 dependent mechanisms
5. Impairs the baroreflex sensitivity which may increase blood pressure
6. Decreases vasodilatory response to carbon dioxide
7. Smokeless tobacco:

- a. Increases ischemic stroke risk and acute coronary dysfunction
- b. Accelerates atherothrombosis
- c. Increases HCVD and metabolic syndrome

Cerebrovascular Disease

1. Mechanisms for smoking and cerebrovascular disease
 - a. Ischemic and hemorrhagic stroke is increased with concomitant oral contraceptive use
 - b. Increases atherosclerosis
 - c. Decreases blood oxygen carrying capacity (carbon monoxide from smoke has a higher affinity for hemoglobin than does oxygen)
 - d. Nicotine damages the vascular endothelium
 - e. Increased platelet reactivity
 - f. Decrease prostacyclin
 - g. Increases blood fibrinogen levels
 - h. Induced polycythemia increases blood viscosity
 - i. Paradoxical benefit effect on in-hospital mortality
 - j. May have benefit in blood pressure and flow in MCA
 - i. Changes in baroreflex sensitivity (lowers)

Neuroimaging

1. Large and small vessel ischemic stroke patterns
2. Exacerbate or induce aneurysm formation

Autoimmune Disease and Stroke*Overview*

Almost all autoimmune diseases are associated with stroke, especially during exacerbations of the dysimmune process. The patient's symptoms and signs may be dominated by organ system failure or by the other aspects of cerebral involvement such as seizures, dementia or movement disorder. The specific pattern of organ, central and peripheral nervous system involvement are the clinical clues that differentiate the entities. Neurologic manifestations and stroke frequently occur in the setting of:

1. Systemic Lupus Erythematosus (SLE)
2. Periarthritis Nodosa
3. Microscopic Polyangiitis
4. Sjögren's syndrome
5. Neurosarcoidosis
6. Rheumatoid Arthritis
7. Scleroderma
8. Churg-Strauss syndrome
9. Henoch-Schönlein Purpura
10. Kawasaki's disease
11. Wegener's granulomatosis
12. Allergic arteritis
13. Thrombotic thrombocytopenia purpura (TTP)
14. Mixed connective tissue disease
15. Reiter's syndrome
16. Relapsing polychondritis
17. Ulcerative colitis and regional enteritis
18. Celiac disease

Systemic Lupus Erythematosus (SLE) is generally dominated by renal, cardiac and serosal surface involvement. If there is a rash in the hand it is between the interphalangeal joints as opposed to dermatomyositis where the rash is over the joint (Groton's sign). The malar rash is characteristic. Periungual telangiectasia and fingertip pain occur with disease activity. Pial vessel strokes occur although seizures, psychosis and proximal myopathy are the most common neurologic features. A vasculopathy rather than a vasculitis is the predominant pathology of cerebral blood vessels.

Periarteritis nodosa usually affects the peripheral nervous system with mononeuritis multiplex or a multiradicular pattern of involvement. Renal medullary artery involvement with severe hypertension dominates the active phase of the disease. Late onset asthma, testicular and hepatic artery infarctions occur. Eosinophilia is common. Stroke is rare.

Microscopic polyangiitis is a variant of periarteritis nodosa that affects venules, arterioles and small arteries. It is the most common pulmonary renal vasculitic syndrome. It, like periarteritis nodosa, most commonly affects the peripheral nervous system, but ischemic and hemorrhagic infarction may be seen secondary to hypertension.

Sarcoid affects both the PNS and CNS. It usually comes to medical attention from its diffuse infiltrative or periaortic node involvement. Ankle pain is characteristic as are cardiac conduction abnormalities. MRI evaluation demonstrates posterior hypothalamic, chiasmatic and parenchymous granulomata. Characteristically, the dura is involved. It is associated with a cerebral vasculitis and retinal inflammation (a periphlebitis). A VIIth nerve palsy in association with uveitis (Heerfordt's syndrome) is diagnostic.

Sjögren's syndrome is very prevalent in the population and is most often associated with rheumatoid arthritis. Its cardinal diagnostic feature is keratoconjunctivitis sicca and xerostomia (dry mouth). Peripherally there is a large fiber sensory loss with dorsal column spinal cord involvement. Both conducting and pial vessels may be involved in the CNS.

Rheumatoid arthritis is most often associated with a severe motor neuropathy of the hands that causes intrinsic muscle wasting in association with CTS. Subluxation (atlantoaxial) at C2–C3 is a feared complication. Localized vasculitis is rare.

Scleroderma produces a microvascular pathology that produces characteristic fibrosis of multiple organ systems. Gastrointestinal tract and renal involvement as well as its skin manifestations are characteristic. It frequently affects the Vth cranial nerve (as does Sjögren's syndrome). A disseminated cerebral vasculitis has been noted.

Churg-Strauss syndrome should be considered in a patient presenting with asthma, eosinophilia and pituitary infarction. A CNS small vessel necrotizing arteritis may accompany the medical triad.

Henoch-Schönlein is usually a disease of childhood and presents with abdominal pain, arthritis and prominent purpura. Allergies to drugs may be a precipitant. Rare small vessel stroke has been reported.

Wegener's granulomatosis should always be borne in mind in the setting of refractory chronic sinus disease. The usual medical evaluation reveals upper respiratory tract necrotizing vascular lesions. Orbital involvement is common with extraocular muscle and Vth nerve paresthesia. A cerebral arteritis with pial vessel infection occurs.

Hypersensitivity vasculitis primarily affects the skin in the form of a purpuric skin rash. Specific allergies trigger the process (particularly sulfa). The extremities are symmetrically swollen, erythematous and painful. Stroke is rare.

Mixed connective tissue disease is an overlap of SLE, scleroderma and polymyositis. Encephalopathy, seizure and aseptic meningitis are much more common CNS manifestations than stroke from vasculitis. Peripheral nerve involvement is more common than are CNS manifestations.

Thrombotic thrombocytopenic purpura often has a dramatic explosive onset manifested by seizures, hallucinations, fever and renal failure. Transient focal neurologic deficits dominate its course. Multifocal microinfarctions of the cortex are seen pathologically.

Reiter's syndrome should be suspected in a patient with diarrhea and heel pain associated with optic neuritis, encephalitis and pial artery stroke.

Relapsing polychondritis is an autoimmune disease of cartilage. It may present with inflamed sore ear lobes (also occurs in ochronosis) conjunctivitis, lip scleritis and laryngotracheal involvement. Stroke is rare.

Ulcerative colitis and regional enteritis are associated with both venous and cerebral sinus thrombosis as well as large vessel stroke.

Celiac disease presents most commonly with severe diarrhea. Its neurologic manifestations are proximal myopathy and ataxia. Occasionally, patients suffer conducting vessel and pial strokes.

The following is a detailed description of the major neurologic and general medical features that differentiate the autoimmune entities that cause stroke.

Systemic Lupus Erythematosus

General Features

1. A complex disease characterized by autoantibodies and multisystem involvement
2. A central role for β cells in pathogenesis as evidenced by early breakdown of β tolerance
3. Autoantibodies pathogenic role in autoimmunity include:
 - a. Immune complex mediated type III hypersensitivity reactions
 - b. Type II antibody-dependent cytotoxicity
 - c. Innate immune cell production of inflammatory cytokines
4. A role for toll-like receptors in the link between the innate and adaptive immune systems in SLE immunopathogenesis
5. Associated neurologic manifestations
 - a. Psychosis

- b. Proximal myopathy
- c. Mononeuritis multiplex
- d. Migraine headaches
- e. Sensorimotor neuropathy
- f. Chorea
- g. Seizures
- h. Stroke (pial arteries; multifocal)
- i. Retinal findings:
 - i. Cytoid bodies
 - ii. Increased nicking of arterioles

Clinical Features

1. Stroke

- a. Embolic stroke (Libman-Sacks endocarditis)
- b. Coagulopathy
 - i. Lupus anticoagulant
 - ii. Anticardiolipin antibody
- c. Non-inflammatory vasculopathy
- d. Small deep infarcts
 - i. Associated HCVD
- e. Intracranial branch artery occlusion
- f. Cortical and subcortical infarcts (arteritis)
- g. Large Vessel Stroke (Atherosclerosis)
 - i. In approximately 86% of patients the disease is active at stroke occurrence
 - ii. Stroke occurs after 4–5 years of disease
 - iii. Headache is common at onset
 - iv. Often associated with low protein S activity
 - v. Antiphospholipid antibody associated with Libman-Sacks endocarditis
 - vi. Global depression of left ventricular function
 - 1. Cardiac small vessel arteritis
 - 2. Poor ejection fraction and embolus
 - 3. Thrombogenic cytokines
- h. Unusual Vascular Manifestations:
 - i. Vertebrobasilar territory infarction at presentation
 - ii. Vascular monocular or binocular optic neuropathy
 - iii. Posterior ischemic optic neuritis

Pathology

- 1. Widespread microinfarcts in the cerebral cortex and brainstem
 - a. Destructive and proliferative changes in arterioles and capillaries
 - b. Attachment of immune complexes to the vessel walls in mechanism of vascular injury
 - c. Immune components to hemispheric white matter and spinal cord lesions
 - d. Endocarditis (Libman-Sacks)
 - e. Hypertensive changes
 - f. Active necrotizing vasculitis

Neuroimaging

- 1. Territorial localization of cortical, border zone infarcts and basal ganglia lesions

- a. More common in patients with antiphospholipid antibodies
- 2. Lacunar infarcts
- 3. Focal cortical infarcts (vasculitis)
- 4. Longitudinal involvement of the spinal cord

Laboratory Evaluation

- 1. CSF is normal or has a mild lymphocytic pleocytosis with slight increase in protein
- 2. Antibodies to double-stranded DNA (anti-ds DNA)

Periarteritis Nodosa

General Features

- 1. Prevalence of 6.3 per 100,000 individuals
- 2. Association with hepatitis B virus surface antigen
- 3. Putatively associated with hairy cell leukemia, Sjögren's syndrome and rheumatoid arthritis
- 4. Male and females are equally affected
- 5. Onset between 40 and 60 years of age
- 6. Organ-limited varieties:
 - a. Lobar liver
 - b. Testicular
 - c. Cutaneous (ulcers/livedo reticularis)
 - d. Striated muscle
 - e. Primary angiitis of the CNS
- 7. Multisystem involvement:
 - a. Late onset asthma
 - b. Testicular infarction
 - c. Lobar hepatic infarction
 - d. Eosinophilia
 - e. Severe hypertension from renal involvement
 - f. Palpable arteriolar lesions in the skin
 - g. May occur with hepatitis B and C infection

Clinical Features

- 1. Peripheral nerve involvement
 - a. Mononeuritis multiplex
 - b. Guillain-Barré-like syndrome
 - c. Mixed polyneuropathy
- 2. CNS involvement is rare
 - a. Stroke is rare but may occur in less than 1 year of illness
 - b. Ischemic and hemorrhagic strokes may occur late in the illness
 - i. Hemorrhagic strokes in one third of patients that suffer stroke
 - ii. Often secondary to renal induced severe hypertension
 - iii. Illness never presents with stroke
- 3. Ocular manifestations
 - a. Conjunctivitis
 - b. Episcleritis
 - c. Extraocular muscle palsy
 - d. Optic neuritis
 - e. Orbital pseudotumor

Pathology

1. Involvement of medium-sized arteries
 - a. Disease occurs at branch points
2. Necrotizing arteritis:
 - a. Increased levels of adhesion molecules
 - b. Invasion of arterial wall by leukocytes and monocytes
 - c. Fibrinoid destruction of the vessel wall
 - d. Endothelial proliferation with thrombosis
3. Rare ANCA antibodies (pANCA); anti-nuclear cytoplasmic antibodies
4. Cerebral miliary microaneurysms (Charcot–Bouchard aneurysms)
5. Microinfarcts

Genetics

1. Recessive mutation in:
 - a. CECRI gene
 - i. Encodes adenosine deaminase 2 (ADA2)
 - ii. A growth factor

Neuroimaging

1. Microinfarcts of the cortex
2. Spinal cord infarcts (rare)
3. Posterior reversible encephalopathy

Angiography

- a. Microaneurysms of the renal vasculature

Laboratory Evaluation

1. Elevated C-reactive protein and erythrocyte sedimentation rate
2. Skin biopsy
3. Renal arteriogram

*Microscopic Polyangiitis (Periarteritis Nodosa Variant)***General Features**

1. A form of necrotizing small vessel vasculitis
 - a. Affects venules, arterioles and small arteries
 - b. Rarely medium-sized arteries are affected
2. Fever, weight loss and fatigue in the majority of patients
3. Associated medical conditions:
 - a. Immune necrotizing and crescentic glomerulonephritis
 - b. Hemorrhagic, pulmonary capillaritis
 - c. Most common cause of pulmonary renal vasculitic syndrome

Clinical Features

1. Optic neuritis
2. Peripheral nervous system involvement
 - a. Guillain-Barré syndrome
 - b. Mononeuritis multiplex
 - c. Vasculitic induced sensorimotor neuropathy
3. Ischemic and hemorrhagic infarction

Pathology

1. Vasculitis similar to:
 - a. Wegener's Granulomatosis
 - b. Churg-Strauss disease

- a. Wegener's Granulomatosis
 - b. Churg-Strauss disease
2. Putative role for neutrophils/monocytes in vascular injury
 - a. Enzymes and proteins within the cytoplasmic granules
 3. Minimal immunoglobulin in vessel walls

Neuroimaging

1. Microinfarcts of the cortex
2. Spinal cord infarcts (rare)

Laboratory Evaluation

1. Elevated C-reactive protein and erythrocyte sedimentation rate
2. pANCA titer
 - a. Myeloperoxidase is in the epitope that pANCA binds
3. Hematuria > 10 red blood cells per high powered field

*Kawasaki's Disease***General Features**

1. A systemic vasculitis complicated by coronary and peripheral aneurysms
2. An infectious trigger in a genetically predisposed patient
3. Necrotizing panarteritis affecting all vessels
 - a. Coronary arteries in particular
4. More common in Asians; 80% of patients less than 5 years of age
5. Rare recurrence (against autoimmune etiology)

Clinical Features*Systemic Features*

1. Erratic high fever
2. Conjunctivitis
3. Involvement of vallate papillae ("strawberry tongue")
4. Confluent erythematous lesions of the palms and soles
5. Painful swelling of the hands and feet
6. Acute cervical lymphadenopathy (50–75%)
7. Later in the course:
 - a. Coronary artery aneurysms
 - b. Left ventricular dysfunction
 - c. Mortality from coronary disease
8. Hyponatremia
9. Nephrotic syndrome

Neurological Signs and Symptoms

1. Mild encephalopathy in children
2. Aseptic meningitis (30–40%)
3. Myositis
4. Peripheral VIIth nerve palsy
5. Hearing loss
6. Seizures

Cerebrovascular Signs and Symptoms

1. Subdural hemorrhage
2. Ischemic stroke:
 - a. Hemiparesis in children
 - i. Associated with coronary aneurysms
 - ii. No demonstrated cerebral aneurysms

Pathology

1. Coronary artery aneurysm (25%)
2. Antigen-driven IgA oligoclonal response directed against cytoplasmic inclusions
3. Vasculitis of cerebral vessels

Neuroimaging

1. Aseptic meningitis (increased T-2 weighted hyperintensities of the dura)
2. Topographic stroke
3. Demonstration of coronary artery aneurysms by ECHO

Laboratory Evaluation

1. Thrombocytosis and increased liver enzymes
2. Decreased plasma total cholesterol and HDL
3. Elevation of triglycerides

Neurosarcoidosis**General Characteristics**

1. An inflammatory granulomatous disease
2. CNS involvement (neurosarcoidosis) occurs in approximately 25% of afflicted patients with systemic sarcoidosis (often subclinical)
3. Systemic involvement includes:
 - a. Pulmonary diffuse infiltration pattern
 - b. Periaortic nerve involvement
 - c. Cardiac conduction abnormalities
4. Diffuse infiltrative lung pattern
5. Articular (rheumatologic) manifestations (ankle involvement is prominent)
6. Skin manifestations (neck and nose)

Clinical Features**Neurological Signs and Symptoms**

1. Peripheral nervous system involvement:
 - a. Cranial nerve VII (with uveitis is Heerfordt's syndrome)
 - b. Optic nerve (compression by meningeal infiltration)
 - c. Sensorimotor neuropathy
 - d. Myopathy
 - e. Optic chiasmatic involvement
2. Central nervous system involvement:
 - a. Chiasm
 - b. Parenchymatous granuloma occur in the:
 - i. Posterior hypothalamus
 - ii. Pituitary
 - iii. Hemisphere
 - c. Meningeal involvement; may compress optic nerves
 - d. Compressive myelopathy
 - e. Meningitis inflammation results in CSF elevation:
 - i. Glucose 30–40 mg%
 - ii. Slightly elevated protein 60–80 mg%
 - iii. Lymphocytic pleocytosis (30 cells mm³)

Vascular Features

1. Stroke:
 - a. Cerebral vasculitis
 - b. Associated with pleocytosis
 - c. Retinal inflammation (periphlebitis)
 - d. Spread of inflammatory cells from the meninges through the Virchow–Robin spaces to pial vessels
 - e. Predilection for veins (phlebitis)
2. Stroke pattern
 - a. TIA
 - b. Superficial pial artery stroke
 - c. Dural sinus thrombosis
3. Retinal changes:
 - a. Periphlebitis (diffuse sheathing of retinal veins)
 - b. Hard exudates (“taches de bougie”; candle wax dripping)
 - c. Chorioretinal scars

Pathology

1. Active sarcoid granuloma
 - a. A central mass of epithelioid cells and multinucleated giant cells surrounded by lymphocytes (β and T-cells), monocytes and fibroblasts
 - b. Multinucleated giant cells less frequent in neural lesions. Less fibrous tissue in neural lesions

Neuroimaging**MRI**

1. T2-weighted hyperintense parenchymal lesions are the most common lesions
2. Pituitary and posterior hypothalamic involvement
3. Meningeal enhancement

Sjögren's Syndrome**General Characteristics**

1. May affect 3% of population
2. Women > men
3. In 50% of patients it is secondary (occurring with other diseases)
4. Lymphoid invasion of exocrine tissues of the body:
5. Characterized by:
 - a. Keratoconjunctivitis sicca
 - b. Xerostomia
6. Associated with other connective tissue diseases
 - a. Otitis (eustachian tube dysfunction)
 - b. Recurrent bronchial infection
 - c. Dryness of genital mucosa
 - d. Atrophic gastritis
 - e. Atrophy of the oral mucosa

Clinical Features**Neurological Manifestations**

1. Peripheral nervous system:
 - a. Large fiber sensory loss
 - b. Dorsal column involvement

- i. Dorsal root ganglionitis
- c. Autonomic impairment
 - i. Adies pupil (tonic pupil)
 - ii. Anhidrosis
 - iii. Orthostatic hypotension
- d. Vth nerve involvement
 - i. Gasserian ganglionitis
- 2. Central nervous system involvement:
 - a. Myelitis
 - b. Seizure
 - c. Dementia
 - d. Meningoencephalitis
 - e. Focal brain infiltrates
 - f. Associated with primary progressive multiple sclerosis (putative)
- 3. Vascular Features
 - a. Pial vessel stroke
 - b. Large vessel occlusion
 - c. Spontaneous ICH
 - d. Hemiparesis, aphasia, ataxia
 - e. Cognitive and behavioral deficits

Neuroimaging

MRI

- 1. T2-weighted signal hyperintensities throughout the hemispheres
- 2. Longitudinal extensive spinal cord lesions (dorsal column)
- 3. Lesions resemble those of MS
- 4. Discrete cortical lesions that resemble infarcts

Pathology

- 1. Autopsy dorsal root ganglion biopsy
 - a. Mononuclear and lymphocytic infiltration associated with neural loss

Laboratory Evaluation

- 1. Elevated SSA/SSB antibodies in the serum
- 2. Lip biopsy
- 3. Peripheral nerve biopsy
 - a. Necrotizing vasculitis

Rheumatoid Arthritis

General Features

- 1. Crippling arthritis associated with:
 - a. Ocular manifestations (keratoconjunctivitis)
 - b. Cardiac involvement
 - c. Vasculitis of the bowel
- 2. Possibly affects 1% of the population

Clinical Features

Associated Neurological Manifestations

- 1. Myopathy (proximal)
- 2. Neuropathy (severe atrophy of intrinsic hand muscles)
- 3. Atlantoaxial subluxation (C2–C3; spinal cord compression)

- 4. Rheumatoid pachymeningitis
- 5. Rheumatoid dural nodules (seizures)
- 6. Encephalopathy
- 7. Generalized sensorimotor neuropathy
- 8. Mononeuritis multiplex (rare)
- 9. C2 pannus with spinal cord compression
- 10. Carpal Tunnel syndrome
- 11. Rheumatoid vasculitis
 - a. Occurrence of cerebral vasculitis in rheumatoid arthritis is 1 to 8%
 - b. Usually occurs in long-standing, active and erosive rheumatoid arthritis and in patients with extra-articular manifestations

Pathology

- 1. Arteritis of small vessel fibrinoid type
- 2. Immunoglobulins are demonstrated in vessel walls

Neuroimaging

MRI

- 1. T2-weighted sequences demonstrate high signal intensity in cortical and subcortical junctional areas

Laboratory Evaluation

- 1. Increased C-reactive protein, IgM rheumatoid factor, IgG and IL-1 β , IL-1RA, IL-2, IL-8 and MIP-1 α

Scleroderma

General Features

- 1. Microvascular pathology and diffuse tissue fibrosis that affects:
 - a. Skin
 - b. Gastrointestinal tract
 - c. Lungs
 - d. Heart
 - e. Kidneys

Clinical Features

Neurological Manifestations

- 1. Peripheral nervous systems:
 - a. Myopathy in 17% of patients
 - b. Cranial nerve involvement
 - i. Vth nerve most often involved
 - 1. Mental nerve involvement causes “numb chin” syndrome
 - c. Sensorimotor neuropathy
 - d. Mononeuritis multiplex
 - e. Carpal tunnel syndrome
 - f. Cranial neuropathies (Vth nerve)
 - g. Autonomic neuropathy
 - h. Myelopathy (rare)

Vascular Feature

- 1. Stroke
 - a. Disseminated cerebral arteritis (debated point)

- b. Hemorrhage (due to severe hypertension from renal involvement)
- c. SAH (rare)
- d. Cardiac emboli (rare)
- 2. Coagulopathy
- 3. Vasospasm

Pathology

- 1. Progressive fibrinosis of the skin and internal organs
- 2. The pathogenesis of systemic sclerosis (SSC) involves 3 interrelated processes:
 - a. Inflammation and autoimmunity
 - b. Vasculopathy
 - c. Increased extracellular matrix deposition
- 3. Dendritic cells, T-cells and macrophages are involved in an inflammatory response that activates fibroblasts and myofibroblasts
- 4. Transforming growth factor growth β (TGF β) stimulates fibroblasts and myofibroblasts to produce large amounts of ECM which leads to fibrosis
- 5. The intracellular pathways that cause fibrosis include:
 - a. TGF β
 - b. Type I interferon
 - c. Wnt/catenin
 - d. Cadherin

Neuroimaging

- 1. Topographical pial vessel stroke
- 2. Cerebral vasculitis (rare)

Laboratory Evaluation

- 1. SSC autoantibodies in the serum
 - a. Topoisomerase I
 - b. Centromere
 - c. RNA polymerase

Churg-Strauss Syndrome

General Characteristics

- 1. Also known as eosinophilic granulomatosis with polyangiitis (EGPA) is a systemic small-vessel vasculitis
- 2. Associations include:
 - a. Asthma
 - b. Eosinophilia
 - c. Previous allergic disorder
 - d. Lung involvement
 - e. Pituitary infarction
- 3. >60% of patients have CNS involvement

Clinical Features

- 1. EGPA most commonly presents with upper airway and lung involvement
- 2. Cardiac dysfunction
- 3. Skin lesions

Neurological Manifestations

- 1. Encephalopathy

- 2. Distal sensorimotor neuropathy
- 3. Small vessel stroke

Neuroimaging

MRI

- 1. Microinfarction
- 2. Intracranial hemorrhage
- 3. SAH (2 patients)

Laboratory Evaluation

- 1. Increased CRP and ESR
- 2. Eosinophilia
- 3. Antibodies p-ANCA

Henoch-Schönlein Disease

General Characteristics

- 1. A systemic vasculitis of small vessels
- 2. Primarily affects children
- 3. If adults are affected:
 - a. More severe illness
 - b. Associated with cancer

Systemic Features

- 1. Adult involvement may be preceded by a mucosal infection of the upper respiratory tract
- 2. Palpable skin purpura
- 3. Abdominal pain
- 4. Arthritis
- 5. Renal involvement
- 6. Carcinoma of respiratory and GI tract

Clinical Features

- 1. Occasional small vessel stroke
- 2. ICH (children)
- 3. Factor XIII deficiency
- 4. Vasculitis possible cause of ICH
- 5. Peripheral nerve involvement; facial palsy

Pathology

- 1. Leukocytoclastic vasculitis that involves venules, capillaries and arterioles
- 2. Deposition of immune IgA complexes

Neuroimaging

Angiography

- 1. Magnetic resonance angiography (MRA) and digital subtraction angiography (DSA) demonstrate vasculitis of blood vessels (if negative standard angiography)

MRI

- 1. T2-weighted sequences with bilateral hyperintensities that are diffuse
- 2. PRESS has been demonstrated
- 3. Vascular lesions involve two or more blood vessels
- 4. Thrombosis of superior sagittal sinus

Laboratory Evaluation

1. Elevated IgA
2. High sed rate, proteinuria

Behçet's Disease**General Features**

1. Behçet's disease is a systemic chronic relapsing vasculitis. This inflammatory disorder is characterized by painful oral and genital ulcers, uveitis, well circumscribed skin lesions, large artery stroke and vasculitis
2. Diagnostic criteria:
 - a. Oral ulcers at least 3 times in 12 months and any 2 of the following:
 - i. Recurrent genital ulcers or sores
 - ii. Eye inflammation (loss of vision)
 - iii. Skin lesions
 - iv. Positive pathology (skin prick test)
3. Involvement of the CNS occurs in 11 to 50% (pediatric patients)

Clinical Features

1. Clinical manifestations of neuro Behcet's
 - a. Cranial nerve palsies
 - b. Altered consciousness
 - c. Seizures
 - d. Meningoencephalitis
 - e. Focal cortical/brainstem deficits
 - f. Neurologic manifestations may occur from 1 to 10 years after onset of the disease
 - g. Cerebral venous thrombosis

Pathology

1. Vasculitis in both arterial and venous system (venous disease more common than arterial)
2. Thrombosis and false aneurysms
3. Perivascular infiltration of memory T-cells

Neuroimaging**MRI**

1. T2-weighted sequences reveal high intensity lesions scattered throughout the basal ganglia, brainstem and internal capsule
2. Topographic stroke
3. White matter hyperintensities may enhance with gadolinium
4. Cerebral venous thrombosis

Laboratory Evaluation

1. Association at IL23R and IL12RB2 locus from GWAS studies
2. CSF
 - a. IL-21 and IL-17A producing T-cells; elevated protein and normal glucose
 - b. Usually lymphocytic pleocytosis
3. Rarely the ESR, CRP and acute phase reactants are elevated in serum

4. Rarely there is elevated factor VIII, immune circulating complexes and cryoglobulins
5. Positive HLAB%1 allele is not diagnostic
6. Skin biopsy may demonstrate vasculitis with immune complex deposition

Wegener's Granulomatosis (Granulomatous Polyangiitis)**General Characteristics**

1. Granulomatous polyangiitis is a necrotizing vasculitis that primarily effects the sinuses, lungs, upper respiratory tract and kidneys

Clinical Features

1. Approximately one third to one half of affected patients suffer neurologic complications
2. Neurologic complications include:
 - a. Peripheral neuropathy and mononeuritis multiplex
 - b. Cranial nerve involvement from direct extension of nasal and sinus granulomas
 - c. Episodic hemicrania with periorbital ecchymosis
 - d. Intracranial spread causes:
 - i. Seizures
 - ii. Cerebritis
 - iii. Spastic paraparesis
 - iv. Horner's syndrome
 - v. Papilledema
 - e. Orbital involvement occurs in 20% of patients – similar to orbital pseudotumor, cellulitis or lymphoma
 - i. Extraocular muscle palsies
 - ii. Retinal involvement
 - iii. Optic nerve ischemia
 - iv. Posterior ischemic optic neuropathy
 - f. Cerebral arteritis and pial vessel infarcts

Pathology

1. Involves small arteries and veins
2. Fibrinoid necrosis of vessel walls with neutrophilic and histiocytic infiltration

Neuroimaging**CT and MRI**

1. Evaluation of the nasal sinuses
 - a. Mucosal thickening
 - b. Air-fluid level and opacification of the sinus
 - c. Bony destruction of the nasal septum
 - d. Sclerosing osteitis

MRI

1. Orbit
 - a. Granulomatous infiltration is hypo intense in both T1 and T2-weighted sequenced but enhance with gadolinium
2. Cerebral MRI
 - a. Diffuse linear dural thickening with enhancement contiguous with orbital, nasal and paranasal sinuses
 - b. T2-weighted sequences reveal high intensity lesions in the cortex and brainstem
 - c. Cerebral vasculitis

Laboratory Evaluation

1. Elevated c-ANCA levels in the serum
2. Sed rate: a good measure of disease activity
3. Overlap with other serum markers of hypersensitivity disease

*Hypersensitivity Vasculitis***Overview**

Hypersensitivity vasculitis (HV) and Henoch-Schönlein purpura (HSP) are the most common cutaneous vasculitides.

General Features

1. Palpable purpuric skin lesions
 - a. Legs more commonly affected than arms
 - b. Extremities may be symmetrically swollen and erythematous
2. Precipitants are specific allergens (Penicillin and sulfa drugs are common)

Clinical Features

1. Sensorimotor neuropathy
2. Plexopathy
3. Diffuse petechiae in centum semiovale
4. Low platelets

Pathology

1. Leukocytolytic vasculitis
 - a. Medium and small-sized vessel
 - b. Due to IgG or IgM containing immune complexes; has less systemic involvement
2. IgA deposition is predictive of associated renal and gastrointestinal organ involvement

Neuroimaging*MRA or Conventional Arteriogram*

1. Demonstrates vasculitis

MRI

1. T2-weighted sequences with diffuse hyperintensities
2. Large vessel stroke (rare)

Laboratory Evaluation

1. Skin biopsy
2. Determination of immune globulin complex type and vessel wall

Differential Diagnosis

1. Cryoglobulinemia
2. Urticaria
3. ANCA-associated
4. Leukocytolytic vasculitis associated with vasculopathy and coagulopathy in scleroderma/SLE
5. Bacteria/sepsis

*Mixed Connective Tissue Disease***General Features**

1. Mixed connective tissue disease has components of:

- a. SLE
 - b. Scleroderma
 - c. Polymyositis
2. Frequently there are concomitant high titers of antibody to:
 - a. V1 snRNP proteins
 - b. ds DNA

Clinical Features

1. Raynaud's phenomenon
2. Arthralgia
3. Swollen joints
4. Esophageal dysmotility
5. Muscle weakness

Neurological Manifestations

1. Headache
2. Seizure
3. Psychosis
4. Encephalopathy
5. Traverse myelitis
6. Ataxia
7. Aseptic meningitis
8. Monocular blindness
9. Vth nerve involvement
10. Sensorimotor neuropathy
11. Entrapment neuropathy
12. Stroke
 - a. Cerebral vasculitis
 - b. Rare association with thrombotic thrombocytopenic purpura

Pathology

1. Dependent on the manifestations of primarily SLE, scleroderma or polymyositis

Neuroimaging

1. Cerebral vasculitis
2. Topical stroke

Laboratory Evaluation

1. High titer of anti-V1-RNP antibody

*Thrombotic Thrombocytopenic Purpura (Moschcowitz Syndrome)***Overview**

A disease of small blood vessels combined with microangiopathic hemolytic anemia. Dominated by fever, anemia, renal and hepatic signs and symptoms and thrombocytopenia.

General Features

1. Caused by an acquired circulating IgG inhibitor of the von Willebrand factor cleaving protease
 - a. A disintegrin and metalloproteinase with thrombospondin type 1 motif member 13: ADAMTS13

- b. There is a rare familial deficit of ADAMTS13 (Upshaw-Schulman syndrome)
- 2. 3.8–6.5 cases per million individuals (2:1 ratio of females to males)

Clinical Features

- 1. Fever (interleukin I)
- 2. Renal failure
- 3. Thrombocytopenia
- 4. Microangiopathic hemolytic anemia
- 5. Associated with:
 - a. Pregnancy
 - b. Bone marrow transplantation
 - c. SLE
 - d. Ticlopidine
 - e. Sjögren's syndrome
 - f. Influenza vaccination
 - g. D-penicillamine
 - h. Cyclosporine
 - i. Rheumatoid arthritis
 - j. Mitomycin
 - k. Cancer
 - l. Autoimmune disease
 - m. HIV

Neurological Manifestations

- 1. Diffuse encephalopathy:
 - a. Visual Hallucination
 - b. Headache
 - c. Seizures
 - d. Visual loss
 - e. Transient focal deficits
 - f. Aphasia
 - g. Papilledema
 - h. Posterior leukoencephalopathy
 - i. Relapsing course
 - j. Non-convulsive status epilepticus
- 2. Overlap occurs with:
 - a. Hemolytic uremia syndrome
 - b. Hemolytic anemic with elevated liver function and platelets (HELLP syndrome)
 - c. Toxemia of pregnancy
 - d. Hyperintensive encephalopathy
 - e. Posterior reversible leukoencephalopathy (PRESS)

Pathology

- 1. Arteriolar and capillary involvement
- 2. Platelet rich thrombi in small vessels
- 3. Multifocal microinfarctions
- 4. Thrombosis affects the microvessels of both gray and white matter
 - a. Cortical and subcortical infarcts
- 5. Branch occlusions of the MCA/PCA (rare)
- 6. Restricted ischemia of the brainstem or cerebellum (rare)
- 7. Hemorrhagic presentation (rare)

- 8. Renal involvement less frequent and severe than neurological
- 9. Pathogenesis
 - a. Non-familial form (antibodies to ADAMTS-13)
 - i. Inhibitor of von Willebrand factor (cleaving protease)
 - b. Familial form
 - c. Large multimeres of von Willebrand Factor adhere to and aggregate platelets
 - i. Microvascular thrombosis in arterioles and capillaries
 - ii. Mutation in ADAMS-13 (a metalloproteinase)

Neuroimaging

- 1. Diffuse microinfarction
- 2. Large vessel stroke (rare)

Laboratory Evaluation

- 1. Microangiopathic hemolytic anemia
- 2. Assay for ADAMS13
- 3. Coombs negative hemolytic anemia
- 4. Severe thrombocytopenia
- 5. Elevation of serum LDH
- 6. Schistocytosis of RBCs
- 7. Gingival biopsy demonstrates microvascular thrombosis

Differential Diagnosis

- 1. Between thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndrome (HUS)
 - a. Both are thrombotic microangiopathic disorders
- 2. HUS:
 - a. Severe renal dysfunction always (not common in TTP)
 - b. Primarily in children after an incidence of severe bloody diarrhea
 - i. E. coli strain or Shigella dysenteriae that produces Shiga toxin

Reiter's Disease (Reactive Arthritis)

Overview

A classic triad of arthritis, urethritis and conjunctivitis that usually occurs within six weeks of a genitourinary or gastrointestinal infection.

General Characteristics

- 1. May follow GI illness
- 2. Severe heel pain
- 3. Conjunctivitis
- 4. Arthritis
- 5. Urethritis
- 6. Balanitis and sacroiliitis occur commonly

Neurologic Complications

- 1. Optic neuritis
- 2. Encephalitis
- 3. Ascending motor paralysis (GBS like syndrome)

4. Seizures
5. Brainstem dysfunction
6. Acute transverse myelitis
7. Neuralgic amyotrophy
8. Large vessel vasculitis

Pathology

1. Large vessel vasculitis
2. Aortitis
3. Inflammatory synovium

Vascular Features

1. Pial vessel stroke

Neuroimaging

1. Sacroiliitis (PET/CT)
2. Thoracic magnetic imaging (aortic involvement)
3. Large vessel vasculitis

Laboratory Evaluation

1. Ferritin antibodies demonstrated in patient with aortitis
2. HLA-B27 positive

Relapsing Polychondritis

Overview

An illness that causes inflammation of cartilage throughout the body.

Clinical Characteristics

1. Predominant systemic manifestations include:
 - a. Auricular chondritis (pain and tenderness of cartilaginous portions of the ear in 85% of patients)
 - b. Polyarthritits
 - c. Nasal chondritis ("saddle nose deformity")
 - d. Ocular inflammation
 - e. Audiovestibular involvement
 - f. Tracheal and laryngeal inflammation

Clinical Features

1. 40% of patients suffer inner ear disease with:
 - a. Hearing loss
 - b. Tinnitus
 - c. Vertigo
 - d. Rarely deafness
2. Ocular involvement:
 - a. Conjunctivitis, episcleritis, scleritis
 - b. Iritis and iridocyclitis
 - c. Keratoconjunctivitis sicca
 - d. Choroiditis
 - e. Optic neuritis
 - f. Retinal vasculitis
 - g. Orbital pseudotumor (proptosis)
3. Nasal cartilage inflammation
 - a. 70% of patients
 - b. Saddle nose deformity
4. Aortic insufficiency
5. Laryngotracheal involvement in 50%

Neurologic Signs and Symptoms

1. Occurs in 3% of patients
2. Extraocular muscle palsy
3. Optic neuritis
4. Bilateral VIIIth nerve
 - a. Associated with inner ear disease
5. Mononeuritis multiplex
 - a. Associated with PAN

CNS Manifestations

1. Meningoencephalitis
2. Headache
3. Altered consciousness
4. Papilledema
5. Seizure
6. Ischemic stroke
7. IIIrd and Vth cranial neuropathy
8. Meningeal signs

Pathology

1. Perivascular lymphocytic cuffing and infiltration of small vessels and hemispheric white matter
2. Inflammatory destruction of myelin sheaths
3. Neuronal loss and gliosis
4. Pathogenesis
 - a. IL-6 involvement

Neuroimaging

MRI

1. Brain atrophy

Associated Diseases

1. Rheumatoid Arthritis
2. Systemic lupus erythematosus
3. Reiter's syndrome
4. Ankylosing spondylitis
5. Ulcerative colitis
6. Hashimoto's thyroiditis
7. 25% have myelodysplastic syndrome

Ulcerative Colitis and Regional Enteritis

Overview

Also known as inflammatory bowel disease.

General Characteristics

1. Dominant bowel symptoms
2. Extra intestinal and bowel features:
 - a. Large joint arthritis
 - b. Keratoconus
 - c. Primary sclerosing cholangitis
 - d. Rare non-neurologic complications
 - i. Acute pancreatitis
 - ii. Gluten-sensitive enteropathy
 - iii. Pulmonary bronchiectasis
 - e. Thrombosis
 - i. Deep vein thrombosis

- ii. Pulmonary embolism
- f. Coagulation dysfunctions
- 3. Extra intestinal manifestations may be the first manifestations of disease
- 4. Neurologic complications are more common in men and occur in approximately 3% of patients

Clinical Features

1. The risk of arterial and venous thrombosis and thromboembolic disease is increased in IBD
2. Cerebrovascular events have been documented in .12 to 4% of all IBD patients
3. Active disease is the most important predisposing factor
4. Arterial thromboembolism:
 - a. More frequent in younger patients
 - b. Total colitis a risk factor
 - c. Large vessel emboli
 - i. Hypercoagulable state
5. Venous and sinus thrombosis
 - a. More common in ulcerative colitis than Crohn's disease
 - b. Superior sagittal and lateral sinuses most frequently affected
 - c. Accompanied at times by cerebral infarction

Pathology

1. Embolic stroke
2. Ischemic stroke mechanisms
 - a. Large artery disease
 - b. Small vessel disease
 - c. Endocarditis with embolus
 - d. Vasculitis
 - e. Associated with anti-TN α therapy

Neuroimaging

1. Topologic large vessel stroke (ischemic)
2. Embolic stroke
3. Cerebral vasculitis

Laboratory Evaluation

1. Endoscopy with biopsy
2. Low sensitivity of p-ANCA and anti-Saccharomyces cerevisiae antibodies are not useful for diagnosis of VC or CD

Celiac Disease

General Features

1. An immune-mediated enteropathy
2. Approximate prevalence of 1% in USA and European populations
3. Increased disease prevalence in high risk groups that include patients with:
 - a. Autoimmune conditions
 - i. Insulin dependent diabetes
 - ii. Addison's disease
 - iii. Thyroid disease
 - iv. Sjögren's syndrome

- b. Osteoporosis
- c. First degree relatives of Crohn's disease patients
4. Diarrhea abdominal pain and constipation are common symptoms

Clinical Features

Neurologic Manifestations

1. Proximal myopathy
2. Sensorimotor peripheral neuropathy
3. Spinal cord dysfunction
4. Cerebellar degeneration with ataxia
5. Celiac disease, epilepsy and cerebral calcifications (CEC)
 - a. Primarily in patients from Italy, Spain and Argentina
6. Approximately 10 to 20% of patients have neurological disease

Vascular Features

1. Stroke
 - a. Large conducting and pial vessel stroke

Pathology

1. Gluten ataxia is a distinct disease process and may occur without enteropathy
 - a. Associated with anti-gliadin antibody
2. Cerebellar atrophy
3. Lymphocytic infiltration and perivascular cuffing in the cerebellar cortex and peripheral nerves
4. Anti-gliadin antibodies are directed against gluten
5. Association with other autoimmune diseases

Neuroimaging

1. Celiac disease, epilepsy and cerebral calcification
2. Possible vascular calcification malformation (a type of Sturge-Weber like phacomatosis)

MRI

1. Diffuse T2-weighted sequence hyperintensities seen in 20% of 75 diet-treated patients
2. Consistent with vasculitis or inflammatory demyelination

Laboratory Evaluation

1. High titers of serum and CSF anti-gliadin antibodies
2. Small bowel biopsy to document villous atrophy
3. Anti-endomysium and anti-transglutaminase are markers for sprue but do not correlate with neurologic disease

Temporal Arteritis (Giant Cell Arteritis)

General Features

1. Primarily affects the external carotid system (particularly the temporal branches) in older patients
2. It may involve the aortic arch, axillary, iliac and femoral arteries
3. Incidence is approximately 1 to 20 patients per 100,000 populations in the USA
4. Rare familial patients

5. Presents as a systemic illness
 - a. Low grade fever
 - b. Weakness of proximal muscles (coexisting polymyalgia rheumatica)
 - c. Weight loss
 - d. Onset of headache
 - i. Painful burning scalp
 - ii. Not pulsatile headache
 - e. Jaw claudication (facial artery involvement)
 - f. Perforated nasal septum
 - g. Ischemic tongue lesions (similar appearance to carcinoma)
 - h. Painful cord-like superficial temporal arteries (only 30 to 40% positive by blind biopsy)
 - i. Rare sites of involvement
 - i. Pial and brainstem arteries
 - j. Extracranial giant cell arteritis
 - i. Occurs in 10 to 15% of patients with polymyalgia rheumatica
 - k. Relapses may occur after successful treatments
- c. Ischemic tongue lesion
 - i. Similar to squamous cell carcinoma in appearance
8. Facial pain:
 - a. Arteritis of the facial branch of the external carotid artery
9. Myelopathy:
 - a. Vasculitis of the vertebral and anterior spinal artery with cervical cord infarction
10. Peripheral neuropathy:
 - a. Distal symmetrical sensorimotor neuropathy
 - b. Mononeuritis multiplex
 - c. One month after onset
11. Myopathy:
 - a. Steroid related proximal myopathy
12. Encephalopathy
 - a. Arteritis of pial and superficial arteries
13. Multiinfarct dementia
14. Infarction of major branches of both anterior and posterior circulations
 - a. Posterior circulation most often affected at:
 - i. Top of the basilar distribution
 - ii. Lateral medullary stroke
 - iii. Occipital lobe infarction
 - b. Arteries with the most internal elastic membrane are affected most severely
15. Carotid bruits noted in 10–20% of patients:
 - a. Bilateral bruits:
 - i. 60% of these patients have associated involvement of the aortic arch
16. Vertebrobasilar arterial involvement may present with:
 - a. Acute confusional state
 - b. Coma
17. Mechanism:
 - a. Arteritis
 - b. Hypercoagulable state

Clinical Features

Neurological Manifestations

1. Blindness from:
 - a. Occlusion of the posterior ciliary arteries (derived from the internal carotid) or their collaterals (from the external carotid)
 - b. Central retinal artery occlusion
 - c. Ischemic optic neuropathy from infarction at the optic disc
 - d. Visual loss occurs suddenly:
 - i. May occur in the second eye within minutes or at approximately 2 months
 - ii. Men > women with severe ocular problems
 - iii. Visual loss is permanent due to infarction of the optic nerve head and retina
2. Visual field deficits
 - a. Altitudinal rather than central
3. Anterior optic nerve involvement:
 - a. Mild papilledema
 - b. Infrequent disk hemorrhage
 - c. Resolves over 10 days
4. Retrobulbar ischemic optic neuropathy:
 - a. Gradual optic pallor and atrophy
5. Diplopia:
 - a. 2–14% of patients
 - b. Vasculitis of extraocular muscles with total ophthalmoplegia (rare)
6. Cranial nerve palsies:
 - a. Rare that VIIIth cranial nerve is involved
 - b. Infarction of the internal auditory artery (origin is AICA)
7. Tongue:
 - a. Hemianesthesia of the tongue (lingual artery)
 - b. Lingual paralysis
- Pathology
 1. Subacute Granulomatous inflammatory exudate affecting the involved arteries
 - a. Lymphocytes and monocytes, neutrophils and giant cells are seen in the artery
 - b. Thrombosis occurs at the most severely affected part of the artery
 - c. Intracranial arteries are rarely affected
 - d. Posterior ciliary artery branches of the ophthalmic artery and the choroidal circulation that supplies the anterior optic nerve may be infarcted
- Neuroimaging
 1. Vertebral artery stroke and anterior circulation strokes occur
 2. Embolic stroke
 3. Less than 1% of patients suffer cerebral vein thrombosis
 4. Rare intracranial arteritis
- Laboratory Evaluation
 1. The sedimentation rate is usually above 80 to 120 mm/hr

- a. Some patients have documented disease with an ESR of less than 50 mm/hr
- 2. Elevated sedimentation rate (or may be normal)
- 3. Mild normocytic anemia
- 4. Mild peripheral leukocytosis
- 5. Biopsy of the temporal artery is the gold standard

Isolated Angiitis of the CNS

General Features

- 1. This is putatively an immune-mediated arteritis of strictly cerebral blood vessel
- 2. Other names for the process:
 - a. Isolated granulomatous angiitis
 - b. Giant cell granulomatous angiitis of the CNS
- 3. Mean age of onset 49; any age can be affected
- 4. Male predominance 2:1
- 5. Vasculitis isolated to the CNS:
 - a. Exclusion of systemic inflammation, infection or other causes of CNS vasculitis; rarely associated with angiod angioopathy
- 6. Segmental necrotizing granulomatous vasculitis that involves:
 - a. Cortical arteries
 - b. Spinal arteries
 - c. Leptomeningeal arteries may be predominant
 - d. Usual vessel size involved is 200–500 μm (microns)
 - i. Any size vein or artery may be involved
 - ii. Precapillary arterioles of less than 500 μm are involved
 - e. Intima and adventitia of arteries are infiltrated with:
 - i. Lymphocytes, giant cells, and granulomas
 - ii. Granulomas may invade the cortex
 - f. Veins may be affected in 50% of patients

Clinical Features

Neurologic Manifestations

- 1. Earliest symptoms:
 - a. Headache
 - b. Phonophobia
 - c. Photophobia
 - d. Unusual stroke-like presentation
 - e. Diffuse encephalopathy (usual presentation)
 - f. Gradual onset
 - g. Retinal perivascular lesions
 - h. SAH
 - i. Root pain
- 2. Later signs and symptoms:
 - a. Altered mental status
 - b. Dementia
 - c. Myelopathy
 - d. Hemiparesis
 - e. Diffuse encephalopathy
 - f. Rare: territorial stroke
 - g. Pathology of intracranial vessels
 - i. Thrombosis

- ii. Rare: small aneurysms develop on arteries
- h. Myelopathy may precede encephalopathy
- i. Seizures occur
- j. Usual progression
 - i. Step-like deterioration of a progressive encephalopathy
- k. SAH (rare)

Pathology

- 1. Infiltration of vascular wall by lymphocytes, macrophages and histiocytes
- 2. Occasional fibrinoid necrosis
- 3. 85% of patients demonstrate granulomas with:
 - a. Epithelial cells
 - b. Giant Langerhans cells
- 4. Inflammatory lesions preserve the media
- 5. Small and middle sized arteries are involved
 - a. Involvement of veins and vessels occur
 - b. Arteries less than 500 microns may be solely affected
- 6. Non-specific T-cell mediated inflammatory reaction important in pathogenesis

Imaging Evaluation

- 1. MRI
 - a. Positive 68% of the cases
 - b. Infarcts demonstrated (ischemic)
 - c. Hemorrhagic infarction (rare)
 - d. Small hematoma (rare)
 - e. Intracerebral aneurysm (rare)
 - f. Combination of ischemic and hemorrhagic stroke
 - g. Increased diffuse number of T2-weighted lesions
 - h. Intracranial hemorrhagic is more frequent than that seen with infectious etiologies
 - i. Linear and punctate pattern of leptomeningeal enhancement associated with:
 - i. Hemispheric and penetrating vessel involvement
 - ii. Diffuse DWI lesions
 - j. Unusual MRI patterns
 - i. Pseudotumoral
 - ii. Multiple sequential parenchymal and ventricular hemorrhages
 - iii. Miliary appearance from multiple small lesions
 - iv. Diffuse white matter involvement
- 2. Arteriogram
 - a. Positive in approximately 50% of patients; involved vessels of less than 500 μm may be negative
 - b. Segmental narrowing, dilatation and beading
 - c. Rare: intracranial aneurysm

Laboratory Evaluation

- 1. Elevated sed rate in 2/3 of patients; increased incidence of anticardiolipin antibodies
- 2. CSF
 - a. Mononuclear and lymphocytic pleocytosis
 - b. CD4+ lymphocytes involved
 - c. Protein elevated in 80% of patients to >100 mg/dl

*Nongranulomatous Angiitis of the CNS***General Characteristics**

1. Segmental necrotizing angiitis without granulomata
2. Male: female 1.8 to 1
3. Multiple small but occasionally large foci of infarction throughout the CNS
4. Mean age at onset 49
5. Evolution of the disease
 - a. Stepwise occurrence of focal neurologic deficits

Neurological Manifestations

1. Acute presentation
 - a. Stupor or coma within days to weeks
2. Classic presentation:
 - a. Fever and weight loss are uncommon
 - b. Mental status change
 - c. Headache
 - d. Hemiparesis
 - e. Impairment of consciousness
 - f. Focal, multifocal or diffuse encephalopathy
3. Rare neurologic presentations:
 - a. Increased intracranial pressure (ICP)
 - b. Chronic meningitis or arachnoiditis
 - c. Cerebral hemorrhage
 - d. Radiculopathy

Vascular Features

1. Rare vascular presentation:
 - a. TIA
 - b. Large vessel stroke
 - c. SAH
 - d. Multiinfarct stroke

Imaging Evaluation

1. MRI:
 - a. White and gray matter involvement
 - b. Occasional hemorrhage
 - c. Bilateral subcortical lesions
 - d. Enhanced meninges
2. Arteriography
 - a. Abnormal in approximately 60%
 - i. Segmental narrowing and sausage shaped dilatation (beading)
 - ii. Rarely: avascular mass or intracerebral aneurysm
 - iii. Affected vessels < 500 μm
3. Leptomeningeal biopsy more often positive than brain biopsy

Laboratory Evaluation

1. Mild elevation of ESR in 2/3 of patients
2. CSF mononuclear pleocytosis (mean of 70 monocytes/mm³)

*Differential Diagnoses of Mimicking Conditions***Overview**

The following are different conditions that mimic immune vasculitis and vasculitis differentiated by pathologic process,

association with neoplastic disease, site of involvement, topography, vessel size and segmental narrowing on arteriogram.

Differential Diagnosis of Conditions Mimicking Vasculitis

1. Dissecting aneurysm
2. Antiphospholipid syndrome
3. Drugs
 - a. Methamphetamine
 - b. Sympathomimetic drugs
 - c. Ginseng
 - d. Ephedrine
 - e. Propylethanolamine
 - f. Cocaine
4. Cholesterol emboli
5. Intravascular lymphomatosis
6. Coll-Fleming syndrome

Differential Diagnosis of Arteritis Associated with Autoimmune Diseases

1. SLE
2. Polyarteritis Nodosa
3. Neurosarcoidosis
4. Sjögren's
5. Rheumatoid arthritis
6. Scleroderma
7. Churg-Strauss
8. Wegener's granulomatosis
9. Hypersensitivity arteritis
10. Mixed connective tissue disease
11. Giant cell arteritis
12. Reiter's syndrome
13. Relapsing polychondritis
14. Ulcerative colitis
15. Regional enteritis
16. Celiac disease
17. Serum sickness
18. Henoch-Schönlein purpura
19. Cryoglobulinemia
20. Polyangiitis

Differential Diagnosis of Systemic Necrotizing Arteritis

1. Wegener's granulomatosis
2. Lymphomatoid granulomatosis
3. Sarcoid
4. Hairy cell leukemia

Differential Diagnosis of Arteritis with Neoplasia

1. Hodgkin's disease
2. Non-Hodgkin's lymphoma
3. Neoplastic angioendotheliosis
4. Hairy cell leukemia
5. Angiocentric endothelial lymphomatosis

Differential Diagnosis of Isolated Angiitis of the CNS

1. Necrotizing vasculitis

2. HZ
3. Hodgkin's disease
4. HIV
5. Sarcoid
6. Hypersensitivity arteritis
7. PAN
8. Lymphomatoid granulomatosis
9. Methamphetamine
10. Sympathomimetic drugs
11. Coll-Fleming syndrome
12. Wegener's granulomatosis
13. Multiple Sclerosis
14. Behçet's disease
15. Giant cell arteritis
16. Posterior leukoencephalopathy

Differential Diagnosis of Systemic Vasculitis Resembling Isolated Angiitis of the CNS

1. Vasculitis with connective tissue disease
2. PAN
3. Wegener's granulomatosis
4. Giant cell arteritis
5. Takayasu's disease
6. Behçet's disease

Differential Diagnosis of Vasculitis Associated with Granulomatous Parenchymal Lesions

1. Wegener's granulomatosis
2. Sarcoid
3. Lymphomatoid granulomatosis
4. Granulomatous angiitis
5. Hodgkin's disease

Differential Diagnosis of Vasculitis by Characteristic Sites of Involvement

1. Takayasu's disease:
 - a. Arch of the aorta
 - b. Mid common carotid artery
 - c. Mid descending aorta
2. Sneddon's syndrome
 - a. Skin (livedo reticularis)
3. Köhlmeier–Degos syndrome
 - a. Atrophic skin lesions
4. Giant cell arteritis
 - a. Primarily external carotid system
 - b. May affect the ICA, and arch of the aorta

Differential Diagnosis of Vasculitis by Topography

1. Focal:
 - a. Herpes Zoster
 - i. Proximal MCA; ACA (occur on the side of the skin lesions)
2. Multifocal:
 - a. SLE
 - b. Primarily separate areas of the cortex
3. Disseminated:
 - a. Isolated or primary angiitis of the CNS

Differential Diagnosis of Vasculitis of Medium-Sized Arteries

1. PAN
2. SLE
3. RHA
4. Sjögren's syndrome
5. Buerger's disease

Differential Diagnosis of Vasculitis of Small-Sized Arteries

1. Churg-Strauss
2. Polyarteritis nodosa (microangiopathic variant)
3. Wegener's granulomatosis
4. Hypersensitivity arteritis

Differential Diagnosis of Segmental Narrowing of Cerebral Arteries on Arteriogram

1. Arteritis (infective; inflammatory; necrotizing)
2. Leptomeningitis (infective, chemical, carcinomatous)
3. Vasospasm:
 - a. SAH
 - b. Migraine
 - c. Hypertensive encephalopathy
 - d. Coll-Fleming syndrome
4. Atherosclerosis
5. Fibromuscular dysplasia
6. Recanalization of emboli
7. Sickle cell disease
8. Sympathomimetic drug abuse
9. Neoplasms:
 - a. Angioendotheliosis
 - b. Glial and meningeal tumors
 - c. Atrial myxoma
10. Closed head injury
11. Radiation therapy (X-RT)
12. Neuroectodermal dysplasia
 - a. Neurofibromatosis
 - b. Tuberous sclerosis

Infectious Disease and Stroke

Overview

The differential diagnosis of the infections that cause stroke rests on the specific pathologic mechanisms induced or associated with each infection. The neurological manifestations of each infection are different and often the extracranial manifestations of the infection provide the clue to the specific diagnosis. Bacteria, viruses and fungi cause stroke as do spirochetes and protozoa.

Stroke may occur in the setting of bacterial meningitis. Pus may directly involve the pial vessels and encase them on the cortex. Pneumococcal meningitis may be associated with endocarditis that causes mycotic aneurysms that hemorrhage. Stroke may occur 6–8 weeks after the primary infection due to endocarditis.

Meningococcal infection occurs frequently in settings in which young healthy adults are living in close quarters. The

evolution of the infection (headache to coma) may occur within hours. The clinical course is dominated by the meningitis. Stroke is rare.

Listeria infections occur following head and neck surgery and during pregnancy and delivery. The seminal feature is brainstem infarction with dorsal pontine involvement. *Bartonella henselae* infection follows exposure or inoculation from cats. Seizures and retinitis are the seminal features following extremity lymphadenitis.

Syphilis has made a comeback as a serious cause of infection due to HIV. It may be telescoped where in all three stages are seen within a short period of time. In the past, brainstem strokes were noted in the meningovascular stage. This pattern persists, but may be more associated with gumma formation and less with syphilitic optic nerve and pretectal involvement (Argyll-Robertson pupils). If meningitis is seen concomitantly, the CSF sugar is usually normal.

Lyme's disease is the most common vector borne infection in the United States and has protein manifestations. If VIIth nerve palsy and characteristic rash and large joint arthritis is present diagnosis is straight forward. Unfortunately, many patients present in later stages with asthenia and low grade encephalopathy weeks or months after the infection. Strokes are rare, but are described.

Tuberculosis causes strokes because of cortical and basilar exudates. It is a more chronic illness in Western countries and is often seen as a low grade dementing illness. It should always be suspected in HIV infected patients with lower cranial nerve abnormalities (particularly the VIIIth nerve).

Fungal infections occur most frequently in the immunocompromised host. Disorders of B-lymphocyte function are associated with encapsulated bacterial pathogens. Impaired T-lymphocyte or macrophage function causes infection by intracellular pathogens such as aspergillus, nocardia (bacterial), viruses and parasites (toxoplasmosis gondii).

Extra-CNS sites of infection suggest aspergillus and nocardia both of which may present subacutely or chronically. T-lymphocyte dysfunction with meningitis is *Listeria* or *Cryptococcus*. *Aspergillus* can present as a CNS mass lesion or stroke but most often as meningitis.

Mucormycosis is associated with all forms of immunosuppression, but particularly with diabetic ketoacidosis and renal failure. The fungus is associated with sinus infection and venous infarction. It should be suspected in this circumstance in a patient with ophthalmoplegia.

Aspergillosis infects isolated lung abscesses and is associated with osteomyelitis of the base of the skull. It is notorious for fungal hyphae occluding cerebral conducting vessels. Fungal balls from valve leaflets are large enough to occlude peripheral extremity arteries.

Cryptococcus usually presents as a chronic dementia in the setting of immunocompromise. It spreads through the Virchow-Robin spaces to involve the basal ganglia. This is most helpful in the setting of stroke and T2 enhancement of the caudate and putamen. Proximal MCA branches and ves-

sels in the posterior perforated substance are most frequently involved.

Coccidiomycosis is common in the American SW. Extracranially it affects lungs and joints. Sacral involvement is frequent as is involvement of the jaw. Proximal MCA and the arteries of the perforated posterior substance are most often involved.

Histoplasmosis is most often encountered in the Mississippi Valley. It may be associated with adrenal failure with concomitant splenic calcification. Arteries are inflamed in the chronic basilar exudate.

Viral infections cause stroke by direct invasion of the vessel wall or its endothelium, an immune response triggered by vessel epitopes or immune complex deposition.

Herpes Zoster causes a middle cerebral artery stroke ipsilaterally to the Vth nerve involvement. This characteristically occurs 6–8 weeks following the rash, but has been seen within two weeks. Both anterior and posterior circulation large vessels may be involved. Immune compromised HIV patients may suffer small vessel disease. One mechanism is involvement of the vessel wall endothelial antithrombotic systems.

HIV itself is associated with stroke from various mechanisms:

1. Immune complex formation
2. Cell mediated vasculitis
3. Inflammation from direct viral invasion
4. Associated infections that cause stroke

Most often the pathology is in medium-sized arteries. The clinical manifestations of severe HIV infection suggest the diagnosis.

Cerebral malaria may be the most widespread CNS infection with stroke as a consequence. It most often occurs with *plasmodia falciparum* and occurs due to obstruction of capillaries by parasitized RBC.

The following is a more detailed description of the various infections that cause stroke.

Clinical Manifestations of Stroke Inducing Infections

1. Bacterial meningitis
 - a. *Pneumococcus*:
 - i. Early hematogenous spread from the lung
 - ii. Simultaneous infection of the heart valve (may occur); later SBE
 - iii. Stroke of superficial pial vessels
 - iv. Course clinically dominated by meningitis
 - b. Meningococcal infection:
 - i. Early headache, nausea and vomiting; "flu-like"
 - ii. Rapid progression to lethargy in 6–12 hours
 - iii. Pial artery strokes
 - iv. Adrenal failure (Waterhouse-Frederickson syndrome)
 - v. Clustered infection
 1. Close living quarters (army barracks' camp, college dormitories)

- vi. Bacteria may be seen in cerebral spinal fluid prior to neutrophils
- c. *Listeria monocytogenes*
 - i. Head and neck cancer patients
 - ii. Abrupt onset of symptoms
 - iii. Clinical involvement of:
 - 1. Medulla
 - 2. Pontine tegmentum (seminal feature)
 - 3. Lower cranial nerve palsies
 - 4. Arteritis of the brainstem with multiple infarcts
 - 5. Focal encephalitis
 - 6. Monocytic cerebral spinal fluid pleocytosis
- d. *Bartonella henselae* (cat-scratch fever)
 - i. Lymphadenopathy in drainage area of the scratch
 - ii. Seizures (generalized)
 - iii. Retinitis
 - iv. Intracranial stenosis and arteritis

Syphilis

General Characteristics

1. Most prominent in HIV patients
2. All stages may occur simultaneously
3. 3 major stages:
 - a. Stage 1 (primary infection)
 - i. Dissemination throughout the CNS from the primary lesion (2 to 12 weeks)
 - b. Stage 2 ("early neurosyphilis")
 - i. Syphilitic meningitis
 - ii. Asymptomatic neurosyphilis
 - iii. Last for up to 2 decades after the initial infection
 - c. Stage 3
 - i. Asymptomatic neurosyphilis
4. Genome is a single circular chromosome that lacks transposable elements
5. Rare transmission: from mother to fetus; accidental inoculation, close contact with a primary lesion
6. Neurosyphilis begins in the second stage
 - a. Meningitis
 - b. Asymptomatic neurosyphilis
 - c. Meningovascular syphilis
 - d. Lasts for two decades
7. Late neurosyphilis
 - a. Spirochete involvement of the brain and spinal cord

Clinical Manifestations

1. Dissemination from the primary lesion (2 to 12 weeks)
2. Secondary syphilis (12 weeks to 2 decades)
3. Tertiary stage (late syphilis) decades

Meningovascular Syphilis

1. Most patients do not develop meningitis
2. Subgroups develop:
 - a. Aseptic meningitis
 - b. Unilateral or bilateral cranial palsies (VII; VIII; difficulty protruding or maintaining the tongue protruded ("tombone tongue"))
 - c. Strokes

Cerebrovascular Disease with Meningovascular Syphilis

1. Syphilitic endarteritis involves medium-to-large arteries (Heubner's endarteritis)
2. Basilar meninges are often concomitantly involved with a perivascular infiltrate that causes brainstem strokes and cranial nerve palsies
3. Young age at stroke onset (90% are between 30 and 50 years of age)
4. Patients may have a prodromal headache, dizziness and emotional disturbance

Spinal Cord Stroke

1. Rare in isolation: usually associated with cerebral syphilis
2. Insidious or sudden onset of transverse myelitis (usually at a thoracic level)
 - a. Chronic spinal cord meningitis
 - b. Heubner's arteritis
 - c. MRI evaluation
 - i. Enhancement of the superficial spinal cord
 - ii. Extremely rare cervical cord gumma or syphilitic hypertrophic pachymeningitis

HIV and Concomitant Syphilis

1. Cause of neurosyphilis (accelerates the infection)
2. Higher HIV load
3. CSF-VDRL and FTA-ABS are diagnostic
4. 10% have cranial palsies (VIIIth and cranial nerve; 30% have abnormal pupils)
5. Stroke may evolve over days
6. Cognitive decline in some patients

Neuropathology

1. Syphilitic endarteritis
 - a. Medium-to-large arteries (Heubner's endarteritis); concentric collagen thickening of the intima with thinning of the media
 - b. Elastic lamina intact
 - c. Endothelial proliferation
 - d. MCA most often causative of stroke; also ACA, PCA, BA branches are involved
 - e. Meningeal involvement:
 - i. Involved at base of the brain with chronic inflammation
 - ii. Heubner's arteritis affects some vessels
 - iii. Perivascular infiltrate may occur around brainstem vessels (lymphocytes and plasma cells)

CSF Evaluation in Meningovascular Syphilis

1. Mononuclear cell pleocytosis (20 to several hundred cells/mm³)
2. Normal glucose
3. Protein normal to 250 mg/dl
4. Oligoclonal bands are often present
5. Increased IgG
6. CSF-VDRL is diagnostic

*Neuroimaging***Angiography**

1. Compatible with CNS vasculitis

MRI

1. May demonstrate meningeal enhancement
2. Spinal cord stroke
 - a. Enhancement of the superficial spinal cord
 - b. Extremely rare cervical cord gumma or syphilitic hypertrophic pachymeningitis

*Laboratory Evaluation***CSF Evaluation in Meningovascular Syphilis**

1. Mononuclear cell pleocytosis (20 to several hundred cells/mm³)
2. Normal glucose
3. Protein normal to 250 mg/dl
4. Oligoclonal bands are often present
5. Increased IgG
6. CSF-VDRL is diagnostic

Lyme's Disease*General Characteristics*

1. The most common vector borne infection in the United States:
 - a. 15,000 cases/year
 - b. Three distinct foci in the USA
 - i. Maine to Maryland
 - ii. Wisconsin and Minnesota
 - iii. Northern California and Oregon
2. *Borrelia burgdorferi*:
 - a. Tick borne spirochete
 - i. Ixodes ricinus complex
 - b. Vectors are:
 - i. Deer; white footed mice; dusky footed wood rats

*Clinical Manifestations***Medical Complications**

1. Early infection
 - a. Localized erythema migrans (stage 1)
 - b. Disseminated infection (stage 2):
 - i. Nervous system
 - ii. Heart
 - iii. Joints
 - iv. Occurs within days or weeks of infection
 - c. Late or persistent (stage 3)
 - i. Weeks or months after infection

Medical System Involvement

1. Skin
 - a. Erythema migrans
2. Cardiac
 - a. AV block; subendocardial myocarditis
3. Joints
 - a. Oligoarticular arthritis
 - b. Treatment resistant arthritis in 10% of patients
4. Asymptomatic infection about 10% of patients

Neurological Complications

1. Acute phase:
 - a. Severe headaches
 - b. Meningitis (lymphocytic)
 - c. Neck stiffness
 - d. Radiculoneuritis
 - e. Mononeuritis multiplex
 - f. Cerebellar ataxia
 - g. Myelitis
 - h. There is very little evidence that Lyme's disease is associated with stroke
2. Chronic phase:
 - a. Uni or bilateral VIIth nerve palsy
 - b. Encephalopathy
 - c. Cognitive dysfunction
 - d. Sensory polyneuropathy
 - i. No acrodermatosis

Neuroimaging

1. Generalized white matter hyperintensities; often larger than those of small vessel disease

Laboratory Evaluation

1. An antibody response to *B. burgdorferi* by enzyme-linked immunoabsorbent assay (ELISA)
2. Western blotting of CSF (positive)
3. Intrathecal production of IgM, IgG or IgA antibody
4. Post antibiotic treatment:
 - a. Antibody titers fall slowly and may persist for years

Tuberculosis*General Characteristics*

1. HIV pandemic has caused a resurgence of the disease; an increase in all developing countries
2. Tuberculosis meningitis (TBM):
 - a. Most important and common cause of neurotuberculosis (about 70 to 80% of cases)
 - b. TBM is secondary to primary infection most often of the lung
 - c. The cause of the infection is determined by:
 - i. Time between infection and treatment
 - ii. Virulence of the bacillus and its drug sensitivity
 - iii. Immune status of the host
 - iv. Age of the patient

Neuropathology

1. Exudate at the base of the brain encompassing MCA > ACA > PCA
 - a. MCA and its branches preferentially involved
2. Microscopic evaluation:
 - a. Endarteritis
 - b. Periarthritis
 - c. Fibrinoid necrosis of blood vessels

- d. Vascular edema
- e. Thrombosis
- 3. "Throttling and occlusion" by exudate of MCA and its branches:
 - a. Basal ganglia infarction
 - b. Vasospasm-induced by eicosanoids or cytokines
 - c. Immunological injury to blood vessels
 - d. HIV infected patients:
 - a. Minimal inflammatory response in the brain
 - b. Basal ganglia and cortical infarction

Clinical Manifestations

1. Prodromal fatigue and low grade fever
2. Tubercular meningitis
3. Cranial nerve palsy (VII & VIII)
4. Hydrocephalus (late)
5. Depressed consciousness
6. Dementia
7. Strokes usually occur in moderate to severe stages (2 and 3)
8. Stroke characteristics
 - a. Focal deficits occur in 10 to 47% of patients with TBM
 - b. Occur acutely and involve basal ganglia and subcortical structures
 - c. Infarction in vertebrobasilar circulation; intracerebral hemorrhage is rare
9. Seizures in 37% of patients with stroke
10. HIV infected patients have the same clinical phenomenology

Neuroimaging

1. Majority of infarcts are in the territory supplied by the lenticulostriate and thalamoperforating arteries of the MCA
2. TB zone:
 - a. Caudate/putamen/genu and posterior limb of the internal capsule

CT and MRI Evaluation

1. Enhancement of the base of the brain
2. Communicating and non-communicating hydrocephalus
3. Cerebral infarcts
4. Tuberculoma (rare)

MRI

1. HIV infected patients
 - a. Less basal exudate
 - b. Ventricular dilatation from atrophy
 - c. Tuberculoma and toxoplasma granulomas (in HIV patients)

Angiography

1. Angiographic evidence of arteritis

Cerebral Nervous System (CNS) Infections in the Immunologically Compromised Host

General Characteristics

1. General neurological manifestations:
 - a. Meningeal signs
 - b. Mass lesions
 - c. Encephalopathy
 - d. Seizures
 - e. Stroke-like presentation
2. Presentation depends on specific characteristics of the organism
3. CNS mass lesions
 - a. Subacute or chronic presentation
4. Meningitis and encephalitis
 - a. Acute presentation
5. Disorders affecting B-lymphocyte function:
 - a. Meningitis caused by encapsulated bacterial pathogens
 - b. Bacterial meningitis similar presentation in normal and compromised hosts
6. Impaired T-lymphocyte or macrophage function:
 - a. Infection caused by intracellular pathogens
 - i. Aspergillus and fungi
 - ii. Nocardia (bacteria)
 - iii. Viruses:
 1. HSV
 2. JC
 3. CMV
 4. HH-6
 - iv. Parasites
 1. Toxoplasmosis gondii
7. Extra-CNS sites of infection
 - a. Lung and brain infection:
 - i. Aspergillus
 - ii. Nocardia
 - iii. Subacute or chronic presentation
8. T-lymphocyte dysfunction with meningitis:
 - a. Listeria
 - b. Cryptococcus
9. Failure of anti-toxoplasmosis therapy for a mass lesion:
 - a. Probable central nervous system lymphoma
10. Aspergillus presentation:
 - a. Mass lesion
 - b. Stroke
 - c. Rare as meningitis

Fungus Infections

Mucormycosis

General Characteristics

1. Ubiquitous, angioinvasive filamentous fungi; found in soil, manure, decaying matter
2. Airborne and most commonly infects immunocompromised patients through the lungs and sinuses
3. Mortality in disseminated disease is 95%

4. Usual pathogens in the Mucorales order are: Rhizopus, Absidia, and Rhizomucor
5. Usual risk factors are:
 - a. Diabetes
 - b. Immunosuppression (steroid use, renal failure)
 - c. Hematological disorders
 - d. Leukemia
 - e. Bone marrow and transplantation (rare)

Clinical Manifestations

1. Most common presentation is rhinocerebral
 - a. Fungus enters the brain from nasal passages, sinus and orbit
 - b. Extends from the cavernous sinus into the carotid artery which causes complete ophthalmoplegia
 - i. Infarcts vascular supply from the meningo-hypophyseal trunk
 - c. Brain abscess and meningitis are presentations
 - d. Hematogenous spread to the brain following pulmonary infection

Neuropathology

1. Arteritis
 - a. Branch hyphae in affected blood vessels
 - b. Often hemorrhagic lesions

Neuroimaging

1. Hemorrhagic infarction; bland infarction
2. Intracranial vessel thrombosis
3. Intracranial hemorrhage
4. Septic emboli
5. Frontal lobe lesions with diffusion deficits

Aspergillus

General Characteristics

1. The most likely fungus to present as stroke
 - a. Most common pathogen is *Aspergillus fumigatus* (also reported with *A. flavus*, *A. niger*, *A. terreus*)
 - b. Malignancy and bone marrow transplant are the most common settings
 - c. Foci of fungus may be in hospital ventilation systems
2. Pulmonary infection leads to hematogenous spread; rare airborne spores infect open wounds; inhalation of spores from the environment

Clinical Manifestations

Cerebrovascular Disease

1. Hemorrhagic stroke due to:
 - a. Direct invasion of the artery
 - b. Rupture of mycotic aneurysm
2. Invasion from the orbit or ethmoid sinus to the cavernous sinus
3. Rupture of arteries from inflammation
4. Subacute mycotic endocarditis
5. Skull-based infection from sinuses:
 - a. Stroke
 - b. Brain abscess

Associated Clinical Features

1. Cranial nerve involvement
2. Skull-based osteomyelitis
3. Rare spinal involvement

Neuropathology

1. Necrotizing arteritis

Neuroimaging

1. Multifocal hemorrhagic lesions

Differential Diagnosis

Differential Diagnostic Clues for Aspergillosis

1. Gradual extension of an infarction over a few days
2. Involvement of different vascular territories
3. A setting of organ transplantation, depressed immune system, sinus involvement and malignancy
4. CSF pleocytosis: minimal, if any

Cryptococcus

General Characteristics

1. Common in all immunocompromised patients (especially those with HIV and organ transplantation)
2. Spores inhaled from the ground
3. "Flu-like" illness

Clinical Manifestations

1. Chronic dementia with headache
2. Pial vessel stroke
3. Basal ganglia involvement
4. Affects cranial nerve II

Neuropathology

1. Spreads to the basal ganglia through Virchow-Robin space from cortical meningitis
2. Possible Heubner's proliferative endarteritis of vessels in the anterior and posterior perforated substance

Neuroimaging

1. Basal ganglia thin-walled cysts
2. Pial territorial strokes
3. Basilar meningitis

Laboratory Evaluation

CSF

1. Sugar 30–40 mg%
2. Mild lymphocytic pleocytosis
3. Moderate protein elevation of 50–80 mg%
4. PCR positive

Coccidioidomycosis (Coccidioides immitis)

General Characteristics

1. Endemic in deserts of SW USA
2. Spores inhaled from the soil
 - i. Pulmonary route of infection presents as "flu-like" illness

Clinical Manifestations

1. Propensity to invade bone (jaw, knee and sacrum); erythema nodosa
2. Chronic basilar meningitis
3. Proximal MCA and arteries of the posterior perforated substance involved

Neuropathology

1. Thin-walled spherules filled with endospores

Neuroimaging

1. Musculoskeletal findings are non-specific
 - a. Multiple lytic punched out lesions (lumbosacral)
 - b. Hypertrophied synovium of joints
 - c. Meningitis with enlargement of the basal cistern

Laboratory Evaluation

1. Serologic testing reveals IgM antibodies in the acute stage and IgG in the chronic stage

Candida**General Characteristics**

1. One of the most frequent infections in immunosuppressed patients
2. Causes 8 to 10% of nosocomial blood stream infections
3. Superficial and minimal clinical manifestations include:
 - a. Esophageal infection
 - b. Oropharyngeal candidiasis
4. Serious infections include:
 - a. Blood stream infections
 - b. Disseminated candidiasis
 - c. Endocarditis
 - d. CNS infections and endophthalmitis
 - e. Osteomyelitis

Risk Factors

1. Host related (immunosuppression)
2. Health care associated factors that include
 - a. Catheter use
 - b. Total parenteral nutrition
 - c. Surgical interventions
 - d. Antimicrobial drugs

Clinical Manifestations

1. Neurologic manifestations
 - a. Usually candida causes meningitis
 - b. Rarely it causes a cerebritis and stroke-like syndrome
2. Chronic mucocutaneous candidiasis
 - a. 2 reported patients with stroke

Neuropathology

1. Hemorrhagic infarction
2. Not angioinvasive

Imaging Evaluation

1. Numerous microabscesses of less than 3 mm in the cortico-medullary junction, basal ganglia or cerebellum

Histoplasmosis (*Histoplasma capsulatum*)**General Characteristics**

1. Endemic in the Mississippi Valley of USA
2. Pulmonary route of infection
3. Histoplasmosis of the CNS occurs in 10 to 20% of patients with disseminated histoplasmosis or an association with immunocompromised patients

Clinical Manifestations

1. Clinical neurological manifestations:
 - a. Meningitis
 - b. Arachnoiditis
 - c. Hydrocephalus
 - d. Relapses following therapy are common
 - e. Proximal great vessel involvement (infected emboli)
 - f. Pontine infarction

Neuropathology

1. Parenchymal abscess
2. Meningitis

Neuroimaging

1. Hydrocephalus and basilar meningitis
2. Isolated ring enhancing lesions

Laboratory Evaluation

1. Antigen and serologic tests: low sensitivity of CSF culture

Fungal Aneurysms**General Characteristics**

1. Fusiform in shape
2. Involve longer and more proximal segments of intracranial vessels
3. Intradural portion of the carotid artery is most common site of a fungal aneurysm

Clinical Manifestations

1. Vessel invasion occurs from extension of the hyphae into the lumen which cause:
 - a. In situ thrombosis
 - b. Embolization of hyphal masses
 - c. Major portions of vessels are involved
 - i. Large infarctions

Neuroimaging**CT and MRI**

1. Signs of Fungal Infection of a Sinus
 - a. Sclerotic thickening
 - b. Erosion
 - c. Remodeling
 - i. All of the above are rare in bacterial infections
 - d. Central area of high density within the sinus cavity
 - e. Low signal on MRI in all sequences
 - i. Paramagnetic substances within fungal mycetomas
 - f. Aggressive extension of fungus from the sinus to:

- i. Orbit
- ii. Facial tissues
- iii. Intracranial cavity
- g. Vascular invasion

Viral Infections and Stroke

Overview

1. Vasculitis from a viral infection effected by:
 - a. Direct invasions of central nervous system vessels
 - b. Triggering an immune response to epitopes of the vessel wall
 - c. Immune complex deposition

Varicella

General Characteristics

1. Annual incidence of 1010/100,000 people aged 80–90 years of age
2. Immunocompetent host CNS involvement occurs in 1.5 to 4% of patients
 - a. Higher incidence in immunocompromised patients
3. Thoracic dermatomes are most commonly involved: severely painful with dynamic mechanoallodynia

Clinical Manifestations

Neurological Complications

1. Cranial neuropathy
2. Post herpetic neuralgia
3. Encephalomyelitis
4. Optic neuritis
5. Leukoencephalopathy
6. Ventriculitis
7. Traverse myelitis

Cerebrovascular Manifestations

1. Delayed brain infarction following infection
2. Contralateral hemiplegia from ipsilateral MCA involvement
3. Days to 6–8 weeks following onset of the rash
4. Concomitant encephalitis
5. Rash may occur in V2 or V3 as well as V1
6. Rare involvement of posterior cerebral artery (PCA) or the vertebrobasilar territory

Neuropathology

1. Productive virus in infected cerebral arteries (both large and small)
2. Occasional signs of arteritis
3. Concomitant VZV infiltration into the parenchyma (frontal and temporal lobe)
4. Rare SAH
5. Basilar meningitis (rare)

Neuroimaging

1. Stenosis of proximal MCA and basilar artery
 - a. Induce large infarction

2. Occlusion of the supraclinoid ICA:
 - a. May be preceded by TIA
 - b. Usual clinical onset is that of an abrupt stroke
3. Stenosis of intracranial large conducting vessels
4. Small artery involvement is less common
5. Multiple superficial and deep infarcts

HIV

General Characteristics

1. Clear increased risk of stroke in HIV infected individuals
2. Putative mechanisms:
 - a. Associated vasculitic changes from concomitant viral infection that includes:
 - i. Epstein-Barr Virus
 - ii. Hepatitis B
 - iii. HS
 - iv. CMV
 - b. Prothrombotic state:
 - i. Associated decrease of protein S (probable epiphenomenon)
 - c. Cardiac emboli
 - i. HIV associated cardiomyopathy
 - ii. Infective endocarditis
 - iii. NBTE (Non-bacterial thrombotic emboli)
 - d. Opportunistic organisms
 - i. Usual CD4+ count is less than 200 mm³
 - ii. Causes infective vasculitis with ischemic/hemorrhagic infarction
 1. Angioinvasive
 - a. Aspergillosis
 - b. VZV
 2. Constriction of proximal vessels by basilar meningitis
 - iii. Associated malignancies
 1. Primary CNS lymphoma
 2. Metastasis from Kaposi sarcoma
 - e. Hypercoagulable state
 - i. Decreased protein S (minimal evidence)
 - ii. Increased antiphospholipid antibodies
 - iii. Possible DIC
 - iv. Dehydration, cachexia and cerebral vein thrombosis
 - v. Associated substance abuse (cocaine, heroin, methamphetamine)
 - vi. Accelerated atherosclerosis with combination antiretroviral therapy are associated with:
 1. Increased glucose
 2. Insulin resistance
 3. Increased cholesterol and triglycerides
 4. Increased peptide C
 5. Abnormal deposition of body fat
 6. Derangement of lipid metabolic and inflammatory cytokine networks

Neuropathology

HIV Associated Vasculopathy/Vasculitis

1. Possible HIV association with systemic vasculitis:

- a. Polyarteritis
- b. Chung-Strauss
- c. Hypersensitivity vasculitis
- d. Primary angiitis of the CNS
2. HIV-specific vasculitis
 - a. Direct involvement of the vascular endothelium
 - b. Endothelial cell release of chemotactic factors promoting an autoimmune response
3. Small Vessel HIV associated vasculopathy
 - a. Hyaline small vessel wall thickening
 - b. Perivascular space dilatation
 - c. Perivascular cell infiltrate
 - d. Microinfarction
 - e. Concomitant VZV infiltration into the parenchyma (frontal and temporal lobe)
 - f. Rare SAH; basilar meningitis
4. HIV associated large and medium vessel vasculopathy in children
 - a. Vasculopathy with aneurysm
 - b. Fusiform dilatation of the arteries of the Circle of Willis; less common – saccular aneurysm
 - i. Destruction of the internal elastic membrane
 - ii. Medial fibrosis loss of the muscularis
 - iii. Intimal hyperplasia
 - iv. HIV genomic material found in 2 of 4 autopsied patients
5. Large and medium vessel HIV associated vasculopathy in adults
 - a. Adult age range 18–38 years
 - i. Aneurysms (often multiple)
 - ii. Occlusive disease
 - b. Clinical presentation
 - i. TIA
 - ii. Aneurysmal rupture
 - iii. Hypertension
 - iv. Ischemia of the lower extremities
 - v. Most affected arteries are: the carotid, abdominal aorta, iliac, femoral and popliteal

Herpes Zoster

General Characteristics

General Vascular Manifestations

1. Delayed brain infarction following infection
 - a. Contralateral hemiplegia from ipsilateral MCA involvement
 - b. Days to 6–8 weeks following onset of the rash
 - c. Occlusion or stenosis of the carotid siphon, ACA or MCA
 - i. May be preceded by a TIA
 - ii. Usual clinical onset is that of an abrupt stroke
 - d. Concomitant encephalitis
 - e. Recurrent and multiple infarcts
 - f. Rash may occur in V2, V3 or vertebrobasilar territory
 - g. Rare involvement of PCA or vertebrobasilar territory
 - h. Infarct and stenosis may occur in young adults

Clinical Manifestations

Herpes Zoster Cerebral Vascular Disease in HIV-Infected Patients

1. HZ ophthalmicus:
 - a. Delayed contralateral stroke (1 week to 6 months)
 - i. Granulomatous arteritis
 - ii. Patient's may have no preceding rash prior to stroke
 - iii. Similar pathology to non-infected patients
 1. Segmental arteritis of the carotid siphon
 - iv. Concomitant acute retinal necrosis
2. Immune competent HZ patients
 - a. Large vessel disease (usually MCA)
3. HIV patients
 - a. Small vessel diseases
 - b. Leukoencephalitis
 - c. Ventriculitis
4. Children with concomitant HIV and HZ
 - a. Dilatation arteriopathy with fusiform aneurysms of intracranial arteries
 - b. Subarachnoid hemorrhage
5. Children with non-HIV, VZV stroke
 - a. Typical delayed proximal intracranial arteritis

Neuropathology

1. Leukocytoclastic vasculitis of the vaso vasorum causing ischemia of the media
2. Fragmentation of the internal elastic lamina
3. Occlusive disease of large arteries (internal and external carotid)
4. Some patients have aneurysmal dilatation of the terminal carotid
5. Ectasia and focal stenoses of the medium and small-sized cerebral arteries

Neuroimaging

MRI

1. Atrophy out of proportion to age
2. Severe periventricular WMH
3. Opportunistic infections
4. Aneurysms of the carotid and abdominal aorta

Arteriographic Evaluation

1. Stenosis of proximal MCA and basilar artery
 - a. Induces large infarction
2. Occlusion of the supraclinoid ICA
3. Stenosis of intracranial large conducting vessels
4. Small artery involvement

Parasitic Infections

Cysticercosis (Taenia solium)

General Characteristics

1. Infection with the larval stage of *Taenia solium* (the pork tapeworm)
2. Humans are definitive hosts and may carry the adult parasites in the small intestine
3. In one large study from Mexico, 2.5% of ischemic strokes were secondary to neurocysticercosis

Clinical Manifestations*Cerebrovascular Presentations*

1. May cause ischemic or hemorrhagic stroke
2. Transient ischemic attacks caused by:
 - a. Intermittent stenosis of major intracranial arteries secondary to meningeal inflammation; may proceed to infarction
 - b. Lacunar stroke:
 - i. Inflammatory occlusion of small penetrating MCA branches
 - ii. Posterior limb of the internal capsule
 - iii. Large artery occlusion of the ICA, ACA or MCA
 - iv. Inflammatory occlusion of small branches of the basilar artery
 1. Due to subarachnoid cysticerci
 - v. Hemorrhagic stroke
 1. Rupture of a mycotic aneurysm
 - vi. Intracranial hemorrhage due to small artery rupture in a parenchymal cyst

Neuropathology

1. Parenchymal brain cysticerci (less than 10 mm) lodge in the cerebral cortex and basal ganglia
2. Subarachnoid cysticerci lodge within the cortical sulci in cisterns at the base of the brain
3. Ventricular cysticerci (attached to the choroid plexus or are free floating)
4. Rarer locations:
 - a. Subdural space
 - b. Sellar region
 - c. Spinal cord
5. Meningeal cysticerci cause a severe inflammatory reaction in the subarachnoid space resulting in leptomeningeal thickening
 - a. Small and medium-sized arteries from the Circle of Willis are affected by this inflammatory reaction
 - b. Penetrating arteries are involved by inflammatory cells that lead to endarteritis (fibrosis of the media, endothelial hyperplasia)
 - c. Large vessels may be occluded by atheroma-like material from the endothelium
 - d. Mycotic aneurysms develop from cysticerci adherence to subarachnoid blood vessels
 - e. MCA > PCA > ACA infarctions

Neuroimaging*MRI*

1. Enhancement of leptomeninges
2. Hydrocephalus
3. Cystic lesions at the Sylvian fissure or basal cisterns
4. Magnetic resonance angiography or arteriography
 - a. Segmental narrowing or occlusion of the intracranial arteries

*Cerebral Malaria (Plasmodium falciparum)***General Characteristics**

1. Plasmodium falciparum is the most prominent organism
2. Anopheles mosquitos is the vector

Clinical Manifestations*Signs and Symptoms*

1. Signs and symptoms begin approximately 8 to 25 days following infection and include:
 - a. Vomiting
 - b. Fever and shivering
 - c. Retinal damage (retinal whitening)
 - d. Convulsions
 - e. Coma
2. Sudden coldness followed by shivering, fever and sweating
 - a. Occurs every two days in P. vivax and P. ovale and every 3 days in P. falciparum
3. Severe malaria most often caused by P. falciparum

Associated Medical Conditions

1. Respiratory distress in 25% of adult patients
 - a. Concomitant pneumonia
 - b. Severe anemia
 - c. Non-cardiogenic pulmonary edema
2. Splenomegaly
3. Renal failure
4. Hepatomegaly/liver dysfunction
5. Severe anemia
6. Circulatory collapse
7. Acidosis
8. Hypoglycemia

Neurologic Manifestations

1. Neurologic manifestations of P. falciparum
 - a. Retinal whitening
 - b. Encephalopathy
 - c. Rare: hemiparesis, cranial nerve and brainstem signs and symptoms
 - d. Seizures
 - e. Cerebellar ataxia
 - f. Cognitive impairment
 - g. Coma

Neuropathology

1. Mechanical
 - a. Obstruction of the cerebral microvasculature and impaired brain perfusion
 - i. Neuropathological analysis that demonstrates brain capillaries packed with parasitized RBCs. Interaction between RBCs and vascular endothelium
 - ii. Pivotal are parasitic proteins expressed from infected RBCs (P. falciparum erythrocyte membrane protein-1 (PEMP-1))
 - iii. Host receptors that include intracellular adhesion molecule-1 (ICAM-1) and vascular cellular adhe-

- sion molecule – (VCAM-1); Thrombospondin-1, CD36 and E-elastin
- iv. Cytoadherence and decreased pliability are major mechanisms of vasculature obstruction
- v. Patients surviving cerebral malaria do not have signs of cerebral ischemia
- b. Vascular permeability putative mechanisms:
 - i. BBB damage is the underlying mechanism of cerebral malaria
 - 1. Allows toxic molecules to invade the parenchyma
 - 2. Possible histamine involvement
 - ii. Humoral hypothesis
 - 1. Proinflammatory mediators, cytokines and chemokines enter the brain through the damaged BBB
 - 2. Possible role of nitric oxide
 - iii. Evidence exists for the role of matrix metalloproteins (MMPs) in pathogenesis of cerebral malaria

Neuroimaging

Children

1. Children with retinal involvement
 - a. Cerebral edema
 - b. Basal ganglia involvement (Globus pallidus)
 - c. Thalamic and brainstem (T2 sequence abnormalities)
 - d. Corpus callosum (T2-weighted sequence lesions and seen on DWI sequences)

Adults

1. Periventricular white matter involvement
2. Corpus callosum lesions
3. Cortical hemorrhages
4. Thalamic involvement

Chaga's Disease (American trypanosomiasis)

General Characteristics

1. Caused by *Trypanosoma cruzi*
2. Transferred to humans by bites from a bug (family Reduviidae); bites are often around the face
3. Other means of transmission:
 - a. Blood transfusion
 - b. Organ transplantation
 - c. Pregnancy
 - d. Oral outbreaks (contamination from fecal material of the insect)

Clinical Manifestations

1. Acute phase is associated with fever, myalgia, hyperhidrosis, hepatosplenomegaly and swollen lymph glands (severe parasitemia)
2. Chronic stage
 - a. Cardiomyopathy (dilated)
 - b. Mega esophagus and megacolon

3. Approximately 30% of *T. cruzi*-infected individuals develop the chronic stage of the disease
4. Neurologic presentation includes:
 - a. Encephalitis
 - b. Meningoencephalitis
 - c. Tumor-like chagoma
5. Cardiomyopathy
 - a. Progressive to dilated cardiomyopathy
 - b. Arrhythmias
 - c. Intraventricular conduction defects
 - d. Sudden death

Cerebrovascular Disease

1. Stroke occurs in 5 to 15% of patients
2. MCA most affected territory
3. Cardiac embolism is the primary mechanism
 - a. Apical aneurysm is the hallmark of the cardiomyopathy

Neuroimaging

MRI

1. White matter hyperintensities (increased in those with parasympathetic disease)
2. Top of the basilar topology has been described
3. Embolic stroke pattern

Bacterial Infections

Periodontal Disorders

General Characteristics

1. Gingivitis
 - a. Mildest form of periodontal disease
 - i. A bacterial biofilm (dental plaque) that forms on teeth adjacent to the gingiva
 - b. Periodontitis
 - i. Loss of connective tissue and bone structure of the gum
 - ii. An independent risk factor for cardiovascular disease or stroke
2. Putative stroke mechanisms:
 - a. Systemic increase of bacteria, endotoxin and bacterial products
 - b. Periodontal bacteria
 - i. Found in atheromatous plaque of stroke patients
 - ii. Increased C-reactive protein; fibrinogen, C-reactive protein that promote atherogenesis
 - iii. *Actinobacillus actinomycetemcomitans* frequently found in edentulous stroke patients
 - iv. Associated periodontal disease causes increased IL-6 and s-ICAM in the serum of stroke TIA patients

Neuropathology

1. Maintenance of a proinflammatory state
2. Promotion of atherogenesis
3. Includes an increase of IL-6 and/or ICAM in the serum of stroke patients

Neuroimaging

1. Accelerated atherosclerosis of large vessels
2. Thrombotic stroke
3. Increased white matter hyperintensities

Stroke in Association with Named Vascular Syndromes

Overview

It is surprising how many named stroke syndrome have seminal skin manifestations. Köhlmeier-Degos syndrome is associated with characteristic whitish or erythematous papules with a porcelain white center. Associated severe gastrointestinal symptoms are diagnostic. Mencke's syndrome has diagnostic coarse, stiff hair associated with severe hypotonia, seizures, and branch artery occlusion. There is often survival to early adulthood. Vogt-Koyanagi disease is distinguished by a white forelock, eye lashes and eyebrows. The skin manifestations are noted with a uveal meningeal presentation, ocular and brainstem signs; if symptoms of the VIIIth nerve occur then the syndrome becomes Vogt-Koyanagi-Harada disease.

Sneddon's syndrome is characterized by severe livedo reticularis in the extremities and is associated with stroke in young adults. Divry-Van Bogaert disease is seen in older patients, has livedo reticularis and is associated with seizures and dementia.

The skin is clearly hyperelastic in pseudoxanthoma elastica (Grönblad-Strandberg disease) and has a characteristic cigarette paper thinness in the posterior neck area. Hyperelastic skin may also be noted in Ehlers-Danlos Type I and IV as well as Marfan's syndrome. Characteristic dissections of extracranial arteries (often bilateral), aortic disease and aneurysms distinguish these entities. Fabry's disease has characteristic angiomas in the bathing suit distribution and other seminal features of heat sensitivity, renal failure, premature coronary artery disease and painful neuropathy.

Hemorrhage rather than a stroke syndrome is characteristic of Von Hippel-Lindau disease, Sturge-Weber, Cobb's disease and Klippel-Trénaunay-Weber syndrome. The strawberry hemangioma covers the upper eyelid (V1) distribution in Sturge-Weber syndrome. Its most characteristic features are intractable seizures, mental retardation and tram-track calcification of the parieto-occipital cortex. Von Hippel-Lindau has characteristic retinal artery venous malformations with lesions also noted in the cerebellum and spinal cord. Associated renal carcinoma is expected. Wyburn-Mason is characterized by strawberry hemangioma on the face or trunk with a mid-brain hemangioma. Cobb's syndrome presents with a massive truncal hemangioma and spinal AVM. Osle-Weber-Rendu often presents with telangiectasia of the lower lip, conjunctiva and nasal mucous membrane. Stroke may be embolic from pulmonary shunts.

Thrombophlebitis with dilated veins in the upper extremity or chest wall (Mondor's syndrome) suggests non-bacterial

thrombotic endocarditis from an underlying malignancy. Well known in this regard is pancreatic cancer.

Petechiae and purpura are frequently associated with syndromic stroke. Thrombotic thrombocytopenic purpura (Moschcowitz's syndrome) presents with generalized purpura, seizures, hallucinations, focal neurologic signs and renal failure. Waldenström's macroglobulinemia may be associated with rheological causes of stroke and difficulty with perfusion of capillaries due to high concentrations of IgM. The petechiae are characteristically noted below the knee. Cryoglobulinemia may present similarly, but often with acrocyanosis. The Bing-Neel syndrome is inclusive of all disease processes that interfere with cerebral perfusion. The syndrome is primarily associated with lymphoplasmacytoid cell infiltration. Bleeding from the gums, petechiae and depressed consciousness are diagnostic. Small cortical strokes may occur. Kawasaki's disease frequently presents with an explosive course and mucous membrane involvement. Unusual coronary artery occlusion and stroke occur. Behçet's syndrome may present with painful erythematous, well demarcated skin lesions and stroke. Most frequently mouth and genital ulcers are seen concomitantly.

Eye findings and named stroke syndromes are common. Susac disease is a combination of retinitis and VIIIth nerve involvement with stroke. It is a microangiopathy of the main vestibulocochlear complex and retina. There is striking obliteration and amputation of retinal vessels. Acute posterior multifocal placoid pigment epitheliopathy affects young adults and is a putative autoimmune process. The patients may suffer arteritic strokes. The major pathology is in the retinal pigment epithelium although the optic nerve may be involved concomitantly.

Cogan's syndrome and its variants affect young adults and cause an acute interstitial keratitis as well as vestibular and auditory dysfunction. Central retinal artery or vein occlusion occurs in association with pial artery stroke. Atypical variants have vasculitis and systemic manifestations.

Eales disease occurs in young men and is prevalent in the Middle East and India. Retinal periphlebitis and vitreous hemorrhage are common with occasional large vessel stroke. The ophthalmologic symptoms predominate.

Eye findings in association with stroke occur in osteogenesis imperfecta (robin's egg blue sclera); PXE (angioid streaks-disruption of Bruch's membrane); homocystinuria and Marfan's syndrome (lens dislocation), cat-scratch fever (infectious retinitis) and syphilis (retinitis pigmentosa, Argyll-Robertson pupil, optic atrophy).

The defects in Ehlers-Danlos disease cause arterial dissection, intracerebral and extracranial aneurysm and cavernous sinus fistula. Gastric hemorrhage, skin manifestations, mitral valve prolapse due to elongated chordae tendineae and aortic root ectasia occur. Marfan's, osteogenesis imperfecta, Ehlers-Danlos type I and IV are the primary named entities associated with arterial dissection.

Strokes and bowel defects are related most often due to protein losing enteropathy known as Ménétriér's syndrome. Ulcerative colitis and regional enteritis are associated with large vessel stroke due to loss of protein C and S. Behçet's disease may affect the gastrointestinal tract with mucosal ulcers. Köhlmeier–Degos disease frequently is initiated by abdominal pain and diarrhea and blue rubber bleb nevus syndrome is also associated with gastric hemorrhage. Henoch–Schönlein purpura may be attended by early and severe joint and abdominal pain.

Loeffler's syndrome and Churg–Strauss disease are associated with pulmonary interstitial disease, eosinophilia and stroke. Pituitary infarction is peculiarly common with Churg–Strauss disease. Vasculitic sarcoid affects the lung and cerebral vessels as does the hyper eosinophilic syndrome (20,000 eosinophil/mm³).

Arterial involvement as the primary disease process occurs in both Moyamoya syndrome and Buerger's disease. In Moyamoya disease there is progressive relentless occlusion of the proximal carotid arteries. The resulting collateral circulation and exuberance of lenticulostriate arteries produce the characteristic "puff of smoke" on arteriograms. In the United States it is seen with sickle cell disease, tuberculosis that affects the origin of the great vessels as well as X-ray therapy. Frequently it is idiopathic. Surprisingly, it may present in elderly patients and as a primary subarachnoid hemorrhage rather than occlusive ischemic stroke. Buerger's disease often presents with severe occlusive disease below the knee rather than the distal 1/3 of aorta or iliac arteries that is characteristic of atherosclerosis. A dementia secondary to a generalized granular cortical atrophy is more common than conducting vessel stroke.

Erdheim-Gesell syndrome is medial cystic necrosis. Dissection of the great vessel is common. Arterial thickening of the radial artery at the wrist and aortic insufficiency bolster the diagnosis. As noted above, osteogenesis imperfecta, Marfan's syndrome and homocystinuria (accelerated atherosclerosis) all present as primary disease of blood vessels. May-Thurner disease is iliofemoral deep vein thrombosis that is associated with embolus to the top of the basilar artery.

Takayasu's disease dramatically affects the blood vessels emanating from the aortic arch and the aorta itself. Subclavian steal is prominent arteriographically, but is rarely clinically significant. Cataracts and facial atrophy are prominent due to loss of nutritive blood supply to the face. The strokes are primarily in the anterior circulation. Claudication of vision occurs with head position and walking due to the tenuous blood supply to the retina. It occurs with rheumatic diseases as reported from Scandinavia.

HERNS disease is a hereditary stroke syndrome associated with endotheliopathy, renal disease neuropathy and stroke. Polyarteritis, polyangiitis and Fabry's disease are other vascular arteritides which are associated with renal disease.

Cerebral autosomal dominant arteriopathy with subcortical infarction and leukoencephalopathy (CADASIL) is a

named disease associated with dementia. Severe migraines are common. Binswanger small vessel microangiopathy also is associated with dementia. Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) are also associated with dementia and migraine. Posterior leukoencephalopathy is characteristic in parietal occipital areas. In a similar syndrome reported in French Canadians, Saguenay-Lac St. John syndrome, the leukoencephalopathy is frontal rather than parieto-occipital. Divry–Van Bogaert's disease is also associated with dementia.

Named Syndromes in Association with Stroke

1. Eales disease
2. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
3. Buerger's disease (thromboangiitis obliterans)
4. Ehlers-Danlos syndrome (type IV)
5. Homocystinuria
6. Moyamoya disease
7. Antiphospholipid antibody syndrome (APL)
8. Sneddon's syndrome
9. Susac syndrome (microangiopathy of the retina, inner ear, and brain)
10. Takayasu's disease
11. Divry–Van Bogaert syndrome
12. Grönblad–Strandberg disease (pseudoxanthoma elasticum) PXE
13. Köhlmeier-Degos disease (malignant atrophic papulosis)
14. Behçet's disease
15. Moschcowitz syndrome (thrombotic thrombocytopenic purpura) TTP
16. Disseminated intravascular coagulation (DIC)
17. Sturge–Weber disease
18. Osler-Weber Rendu
19. Bing-Neel syndrome
20. Kawasaki syndrome
21. Loeffler's syndrome
22. Ménétriér's syndrome
23. Acute posterior multifocal placoid pigment epitheliopathy (APMPPE)
24. Vogt-Koyanagi-Harada syndrome
25. Hereditary endotheliopathy renal neuropathy syndrome (HERNS)
26. Fabry's disease
27. Leigh's syndrome
28. Sanguinary-Lac-St. John syndrome
29. Erdheim-Gesell syndrome (medial cystic necrosis)
30. May-Thurner syndrome
31. Cogan's syndrome
32. Churg-Strauss disease

Eales Disease

General Characteristics

1. Disease of young men
2. Occurs in the second to fourth decades of life
3. Prevalent in the Middle East and India
 - a. In India it has been associated with tuberculosis

4. No systemic symptoms
5. Eye symptomatology is dominant
6. Systemic illnesses that can present with retinopathy and stroke include:
 - a. SLE
 - b. Sarcoidosis
 - c. Ulcerative colitis/regional enteritis
7. A syndrome of retinal neovascularization
8. Human leukocyte antigen (HLA)
 - a. Higher phenotype frequency of human leukocyte antigen
 - b. HLAB5, DR1 and DR4 individuals may be susceptible to retinal vasculitis
9. Association with tuberculosis has been suggested
 - a. Patients may be hypersensitive to tuberculo protein
 - b. Epiretinal membrane samples have been reported as positive for mycobacterium species
 - c. Some patients have been described with meningitis
10. Other conditions with peripheral retinal revascularization without inflammation include:
 - a. Sick cell disease
 - b. Diabetic retinopathy
 - c. Retinopathy of prematurity
 - d. Familial exudative vitreoretinopathy
 - e. Hyperviscosity syndromes
 - f. Idiopathic retinal vasculitis
 - g. Neuroretinitis (IRVAN syndrome)

Clinical Manifestations

1. Ophthalmological features:
 - a. May be asymptomatic
 - b. Retinal periphlebitis
 - c. Retinal revascularization that may cause vitreous hemorrhage
 - d. Retinal capillary ischemia
 - e. Perivenous and periarterial sheathing
 - f. Vitreous hemorrhage
 - g. Macular arteries are less severely affected:
 - i. Relative sparing of central vision
 - h. Uveitis
 - i. Signs and symptoms predominant and present in three stages
 - i. Venous inflammation (vasculitis)
 - ii. Occlusion
 - iii. Retinal neovascularization
2. Cerebrovascular Manifestations
 - a. Focal ischemic infarcts
 - b. Large vessel thrombosis
3. Patients may suffer focal small vessel infarcts or occasional large vessel stroke
4. Retinal vasculitis may also be associated with CNS vasculitis
 - a. Retinal hemorrhages associated with epistaxis
 - b. Young men
 - c. Recurrent monocular vitreous hemorrhage; may involve the second eye

- d. May be associated with:
 - i. Subacute myelopathy
 - ii. Chronic lymphocytic meningitis
 - iii. Middle cerebral artery stroke
5. Meningitis
6. Tuberculosis
 - a. Hypersensitivity to tuberculo protein
 - b. Some epiretinal membranes samples are positive for mycobacterium species
7. Human leukocyte antigen (HLA)

Neuropathology

1. Retinal ischemia
 - a. Retinal and/or optic nerve revascularization that causes
 - i. Vitreous hemorrhage
 - ii. Retinal detachment
 - b. Cerebral vasculitis
 - c. Large vessel stroke

Neuroimaging

1. Cerebral vasculitis
2. Large vessel infarction
3. Intracranial hemorrhage

Laboratory Evaluation

1. Arterial fundoscopic evaluation (fluorescein)

Differential Diagnosis of Eales Retinopathy

1. Sick cell disease
2. Diabetic retinopathy
3. Retinopathy of prematurity
4. Familial exudative vitreoretinopathy
5. Hyperviscosity syndromes
6. Idiopathic retinal vasculitis
7. Neuroretinitis (IRVAN syndrome)
8. Systemic illnesses that can present with retinopathy and stroke include:
 - a. SLE
 - b. Sarcoidosis
 - c. Ulcerative colitis
9. There is discussion that the neurologic features associated with the retinopathy may be due to the underlying condition and may not be specific to Eales disease

CADASIL

Overview

CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is an inherited cerebral small vessel disease whose clinical features include recurrent transient ischemic attacks and strokes, severe migraines, cognitive decline and cerebral microbleeds.

General Characteristics

Genetics

1. Autosomal Dominant inheritance:
 - a. Mutation of the NOTCH 3 gene; chromosome 19

- b. Involved in cell fate determination and development
- c. If associated with APOE- ϵ 2 allele:
 - i. Increased hemorrhage
 - ii. Vasculopathy
- 2. Expressed only in arterial smooth muscle cells
- 3. Mutations are in exon 3 and 4 (70%) which encodes a transmembrane receptor with epidermal growth factor repeats
- 4. Regulates differentiation and maturation of vascular smooth muscle cells

Clinical Manifestations

1. Onset 30 to 50 years of age
2. Migraine with aura starting between 20 to 40 years of age may be the initial presentation
3. Cerebral ischemic events supervene between 4th and 5th decade associated with behavioral changes and cognitive dysfunction
4. Dementia is apparent between age 50 to 60
5. Approximately 50% of patients suffer atypical migraine auras that include basilar hemiplegia or long duration. A few suffer coma
6. 60 to 85% of patients suffer TIAs or strokes. 2/3 of ischemic events are classic lacunar strokes. TIAs and strokes may occur in the absence of classical risk factors
7. May have a gradual or step-wise progression
8. Gait disturbances
9. Seizures and small cortical infarcts are rare
10. 5 to 10% of patients have seizures that may be focal or generalized
11. Apathy is common while aphasia, apraxia or agnosia is rare
12. Dementia is associated with corticospinal tract signs, gait disturbance and urinary incontinence. Pseudobulbar palsy is demonstrated in approximately 50% of patients

Neuropathology

1. In small and medium-sized blood vessels
 - a. Basophilic granular material replaces the smooth muscle cells of the media
 - b. Dense granular osmophilic deposits are seen in the media close to the cell membranes of smooth muscle cells
 - c. The dense granular osmophilic deposits are seen in the media of arteries in internal organs (spleen, liver, and kidney) as well as skin and muscle
2. Leukoaraiosis and multiple small infarcts in deep white matter, basal ganglia, thalamus, pons and cerebellum
3. Granular osmophilic material (GOM)
 - a. Accumulates around the basement membrane of blood vessels
4. Blood vessel changes are noted in the myocardium, spinal cord, skin and muscle
 - a. Foveal telangiectasia changes in the retina
5. Diffuse hemispheric demyelination with sparing of U-fibers, periventricular and centrum semiovale predominance

6. Lacunar infarction is noted in the thalamus and basal ganglia
7. Deep infarcts and dilated Virchow-Robin spaces are frequent
8. Walls of cerebral and leptomeningeal arterioles are thickened
9. Smooth muscle cells are swollen and degenerated

Neuroimaging

MRI

1. MRI reveals widespread T2-weighted signal in white matter with focal hyperintensities in the basal ganglia, thalamus and brainstem
2. Younger patients have a periventricular predominance
3. External capsule and anterior temporal lobe lesions are distinctive
4. Corpus callosal lesions occur. Pontine lesions predominate in the brainstem
5. Lacunar lesions and enlarged Virchow-Robin spaces are prominent
6. Gradient-echo sequences detect microhemorrhages in 30 to 50% of patients
7. Superficial siderosis
8. Spinal cord hemorrhage (rare)
9. Diffuse leukoencephalopathy (posterior predominant)

Differential Diagnosis

1. Vasculitis
2. Hexosaminidase A deficiency
3. Adrenomyeloneuropathy (AMN)
4. Adrenoleukodystrophy (ALD)

CARASIL

General Characteristics

1. More prominent in Asian and Japanese populations
2. Mutations of the HTRA1 gene
 - a. A serine peptidase/protease
 - b. HTRA1 gene mutation on chromosome 10:
 - i. Encodes chaperone and serine proteases
 - ii. Mutant HTRA1 demonstrates decreased protease activity and failure to repress TGF- β signaling (therefore causing the arteriopathy)

Clinical Manifestations

1. Ischemic stroke (ictal events) or stepwise neurologic deterioration
2. Stepwise loss of cognitive function
3. Premature baldness
4. Severe back pain (disk disease/spondylosis)

Neuropathology

1. Intense arteriosclerosis of small penetrating arteries (without granular osmophilic material or amyloid as is seen in CADASIL)

2. Increased expression of the extra domain-A region of fibronectin and versican in the thickened tunica intima; TGF- β 1 in the tunica media
3. Vascular fibrosis and overgrowth of the extracellular matrix
4. Intimal thickening
5. Dense collagen fibers
6. Loss of vascular smooth muscle
7. Hyaline degeneration of the media
8. Putative mechanism
 - a. Non-repression of transforming growth factor β -family signaling
 - b. Increased TGF-beta found in cerebral small vessels along with fibronectin and versican

Neuroimaging

MRI

1. Diffuse white matter changes
2. Multiple lacunar infarcts in the basal ganglia and thalamus

Mitochondrial Encephalomyelopathy with Lactic Acidosis Stroke-Like Episodes (MELAS)

Overview

MELAS is a maternally inherited mitochondrial disorder that may have deficient cerebral blood flow due to nitric oxide deficiency. One of its complications is stroke-like episodes that are not in a vascular distribution. It is a multisystem disorder clinically dependent on heteroplasmy.

1. Multisystem disease affecting organs with high energy demands (heart, CNS, skeletal muscle)
2. Mitochondrial genome:
 - a. Circular DNA within the mitochondrion
 - b. Tissue dependent copy number (heteroplasmy: ratio of mutated vs wild type mitochondria in each cell)
 - c. Maternal transmission
 - d. Encodes:
 - i. Mitochondrial transfer RNA (tRNA)
 - ii. Ribosomal RNA
 - iii. 13/80 proteins in the respiratory chain
 - e. Mitochondria are exposed to free radicals generated by the respiratory chain and have poor repair mechanisms
 - f. Mitochondrial dysfunction causes ATP depletion due to failure of the respiratory chain
 - g. Mutations identified in both tRNA, rRNA and protein encoding genes
 - h. MELAS most often is caused by point mutation in mtDNA m3243 within the tRNA encoding gene tRNA^{Leu(UUR)}

Clinical Manifestations

1. Fever and infection possible triggers of stroke-like episodes
2. Episodic vomiting, migraine headaches and seizures
3. May occur in adolescence

4. Siblings of MELAS patients with the 3243 mutation may present with different phenotype:
 - a. Diabetes and deafness
 - b. Myopathy
5. Clinical associations of MELAS:
 - a. Short stature
 - b. High incidence of diabetes
 - c. Migraine-like headaches
 - d. Sensorineural hearing loss
 - e. Visual dysfunction
 - i. Ophthalmoplegia
 - ii. Pigmentary retinopathy
 - f. Hemiparesis
 - g. Ataxia
 - h. Fatigue with exercise
 - i. Hypertrophic cardiomyopathy
 - j. MERRF (Myoclonic Epilepsy with Ragged Red Fibers)
 - k. Ischemic colitis
 - l. Seizures
 - m. Cognitive impairment
 - n. Nephropathy
 - o. Hypothyroidism
 - p. Hypogonadism
6. Most common presentation of MELAS is migraine headache and seizures with recurrent stroke-like episodes
7. Stroke-like episodes:
 - a. In general do not follow a vascular distribution
 - b. Involve the posterior parietal and occipital lobes
 - c. Rare brain embolization from cardiac involvement (CHF; arrhythmia)
 - d. Episodes most consistent with mitochondrial dysfunction and alterations in calcium homeostasis

Neuropathology

1. Ischemic brain lesions:
 - a. Metabolic dysfunction of mitochondria
 - b. Decreased COX activity (mitochondrial complex III)
 - c. Arteries supplying (ischemic areas) are open
2. Petechial hemorrhages along cortical gyri
3. Magnetic resonance spectroscopy reveals decrease of N-acetyl aspartate and an increase in lactate
4. Mitochondrial cytopathy
5. Mutations in subunits of components of the respiratory chain causes:
 - a. Oxidative stress
 - b. Energy failure in the affected tissues
 - c. Ragged red fibers on muscle biopsy

Neuroimaging

MRI

1. Multifocal lesions
2. Parieto-occipital predominance
3. Cortex and underlying white matter is affected
4. High incidence of basal ganglia calcification
5. Elevated DWI in early studies in acute stroke
 - a. Some later studies demonstrate a decrease in ADC

Laboratory Evaluation

1. Elevated resting lactate and pyruvate levels (blood and CSF)
2. Mitochondrial myopathy
 - a. Most often a proximal myopathy with ragged red fibers (abnormal aggregates of subsarcolemmal mitochondria) on the Gömöri trichrome stain
3. COX deficiency on muscle biopsy
4. Genetic mutation analysis of peripheral blood leukocytes
5. Point mutation A3243G
 - a. Severe occipital infarcts

Differential Diagnosis*Differential Diagnosis from Other Mitochondrial Diseases*

1. MELAS and Alpers' disease
 - a. Primarily cerebrocortical lesions
2. Leigh's syndrome
 - a. Basal ganglia involvement
3. Congenital lactic acidosis with or without pyruvate dehydrogenase deficiency
 - a. Cerebrocortical atrophy
 - b. Agenesis or atrophy of the corpus callosum
4. Associated other mitochondrial syndromes from the A32437G mutation
 - a. Maternal inherited deafness with diabetes
 - b. Progressive external ophthalmoplegia

*Susac's Syndrome (Retinocochleocerebral Syndrome)***Overview**

An autoimmune disease that is characterized by encephalopathy, branch retinal artery occlusion and sensorineural hearing loss.

General Characteristics

1. Clinical triad of encephalopathy, deafness, retinal artery branch occlusion
 - a. Microangiopathy: affects the precapillary arteriole of the brain, retina and inner ear
2. Age varies between 8–58; predominantly females between the age of 20–40
3. Fluctuating course

Clinical Manifestations

1. Headache and behavioral change may be premonitory
2. Diffuse encephalopathy in which decreased auditory and visual perception is common
3. Psychiatric and behavioral alterations can progress to dementia
4. Focal neurologic involvement:
 - a. Cranial Nerves III, VI and VIII
 - b. Hemihypesthesia
 - c. Hemiparesis
 - d. Generalized seizures and myoclonus
5. Retinal involvement:
 - a. Branch retinal artery occlusion (BRAO)

- i. Fluorescein angiography demonstrates multifocal fluorescence
- b. Amputated retinal arteries (branch occlusion)
- c. Thickened arterial walls with “light streaking”
- d. Edema; cherry red macula
6. Auditory and visual loss may be simultaneous
7. Auditory loss:
 - a. Unilateral or bilateral hearing loss
 - b. Cochlear hearing loss
 - i. Loss of low and intermediate frequencies (microinfarction of the apical cochlea)
8. Vertigo and tinnitus may occur from infarction of the vestibular labyrinth
9. Multiple bursts of over 3 years; final stage is 1 to 8 years in a self-limited disease
10. Encephalopathy
 - a. In approximately 25% of patients the process may be preceded by slowly progressive altered mentation

Neuropathology

1. Small vessel disease (arteriolar)
2. Obliteration of small intracranial arteries
3. Ischemic and hemorrhagic infarction
4. Thrombotic mechanisms are more common than embolic
5. Microinfarcts in end arterioles distribution (white and gray matter) as well as the retina and cochlea
6. Hypertrophic astrocytes in white matter surrounding arterioles
7. Non-specific periarteriolar cell infiltrate
8. Disease of the vascular wall with thrombosis
9. Anti-endothelial cell injury

Neuroimaging*MRI*

1. Multiple small hyperintense T2-weighted lesions in supratentorial gray and white matter
2. Lesions may be round or linear
3. Lesions occur in the central corpus callosum
4. Infratentorial lesions of the middle cerebellar peduncle, cerebellum and brainstem
5. Leptomeningeal involvement is seen in 30% of patients
6. Fluctuation of lesions overtime

Fluorescein Retinal Angiography

1. Distal branch retinal occlusions
2. Pathognomonic multifocal fluorescence
3. Plaques (endothelial damage)
 - a. Mid arteriolar segment involvement

Laboratory Evaluation

1. CSF protein may be elevated
2. Factor VIII and vWF antigen are increased in some patients

Differential Diagnosis

1. Cogan's syndrome (interstitial keratitis prominent)

2. Brown-Vialetto-Van Laere syndrome
 - a. Pontobulbar palsy (lower cranial nerves)
 - b. Familial and sporadic forms have been identified
3. MS (hearing loss and arteriolar occlusive retinal disease don't occur)
 - a. Generalized corpus callosum demyelination
 - b. Callosal lesions are Dawson's fingers (rare)
4. Acute disseminated encephalomyelitis (ADEM)
 - a. Monophasic; lesions are the same age
 - b. Unusual for retinal and VIIIth nerve involvement
5. SLE
 - a. Psychosis, seizures and proximal myopathy are characteristic
6. Polyarteritis
 - a. Ocular and auditory involvement is rare
 - b. Systemic involvement (kidney is the most prominent)
 - c. Usual CNS presentation is encephalopathy
7. Wegener's granulomatosis
 - a. Sinus and respiratory tract involvement
 - b. Systemic necrotizing vasculitis
 - c. May have glomerulonephritis
8. Hypersensitivity vasculitis (Henoch-Schönlein purpura)
 - a. Neurologic, retinal, auditory involvement is rare
 - b. Skin and vein involvement is most prominent
9. CADASIL
 - a. Notch 3 gene
 - b. Foveal telangiectasia changes in the retina
 - c. Migraine, small vessel disease, dementia

Rare Diseases in the Differential Diagnosis

1. Usher's syndrome (autosomal recessive)
 - a. Retinitis pigmentosa
 - b. Labyrinthitis
2. Vogt-Koyanagi-Harada syndrome
 - a. Uveo-meningeal syndrome (recurrent meningitis)
 - b. Dementia
 - c. White forelock
 - d. Harada (prominent VIIIth nerve involvement)
 - e. Blindness from diffuse exudative choroiditis and retinal detachment
3. Rocky Mountain Spotted Fever (retinal arterioles)
4. Takayasu's syndrome
 - a. Aortic arch derived vessel involvement
 - b. Ischemia of the retina (positional blindness); claudication of vision (with walking); early cataracts
5. Mitochondrial encephalomyopathies
 - a. Kearns-Sayre syndrome
 - i. Ophthalmoplegia
 - ii. Heart block
 - iii. Loss of consciousness
 - b. MELAS
 - i. Stroke-like episodes that do not respect a vascular territory
 - ii. Manifestations of most mitochondrial diseases include:
 1. Short stature

2. Diabetes
3. Ophthalmoplegia
4. Cardiomyopathy
5. Fatigue
6. Weakness
7. Sensorineural hearing loss
8. Migraines

Acute Posterior Multifocal Placoid Pigment Epitheliopathy (APMPPE)

Overview

APMPPE is a self-limiting chorioretinal inflammatory disease that affects healthy young adults with rapid loss of central vision.

General Characteristics

1. Primarily an ophthalmologic syndrome best evaluated with fluorescein angiography (indocyanine green angiopathy)
2. Associated with:
 - a. Infectious/post-infectious disorders (bacterial and viral)
 - i. Tuberculosis
 - ii. Streptococcus
 - iii. Syphilis
 - iv. Lyme's disease
 - v. Schistosoma mansoni
 - vi. Epstein-Barr Virus (EBV)
 - vii. Adenovirus
 - b. Vaccination
 - i. Swine flu
 - ii. Hepatitis B
 - iii. Meningococcal
3. Inflammatory conditions:
 - a. Lymphadenopathy
 - b. Nephritis
 - c. Wegener's granulomatosis
 - d. Crohn's disease
 - e. Ulcerative colitis
 - f. Thyroiditis
4. Autoimmune disorders
 - a. Post-streptococcal syndrome
 - b. Anticardiolipin antibodies
 - c. Juvenile rheumatoid arthritis
 - d. Grave's disease
5. Paraneoplastic syndrome
 - a. Renal cell cancer

Clinical Manifestations

1. Ophthalmologic syndrome characterized by:
 - a. Multiple cream-colored placoid lesions
 - b. At the posterior pole in the level of the pigment epithelium and choroid
 - i. Demonstrated by indocyanine green fluorescein angiography

- c. Occlusive choroidal vasculitis
 - d. Papillitis
 - e. Optic neuritis
 - f. Entity may be a continuum of Harada's disease; a possible autoimmune cause of uveo-meningeal syndrome
 - g. Inflammatory yellow-white lesions at the level of the retinal pigment epithelium (probable choroidal hypoperfusion)
2. Both eyes are affected simultaneously; ocular involvement may occur seriatim
 3. Visual blurring; scotoma and distortion of vision
 4. Vision usually recovers after several weeks but deficits may be permanent
 5. Fundoscopic examination:
 - a. Pathology is in the retinal pigment epithelium
 - b. Well circumscribed gray-white flat lesions
 6. Stroke
 - a. Arteritis pattern

Neurologic Features

1. Neurological complications (mean age 26.5 years)
2. VIIIth nerve involvement
3. CNS vasculitis
4. Optic neuritis
5. Neuro-otological signs (tinnitus, hearing loss, vertigo)
6. Headache
7. Aseptic meningitis
8. Pseudo tumor cerebri
9. Meningoencephalitis (associated with vasculitis of CNS)
10. MS like episodes

Cerebrovascular Disease Associated with APMPE

1. Similar to primary angitis of CNS
2. Cerebral vein thrombosis
3. Cortical and tentorial strokes in 70% of patients:
 - a. Posterior cerebral and MCA territories
 - b. 40% of patients with deep white matter infarcts
 - c. Striatocapsular infarcts
4. Ischemic and hemorrhagic stroke (rare)
5. Lobar hemorrhage from cortical venous thrombosis (rare)

Neuropathology

1. Vasculitis of the CNS
2. Primary involvement of:
 - a. Retinal pigment epithelium
 - b. Choriocapillary vasculitis
 - c. Partial occlusive vasculitis
 - d. May be a continuum between APMPE and Harada's disease
 - e. Possible uveo-meningeal syndrome similar to:
 - i. Vogt-Koyanagi-Harada disease
 - ii. Behcet's syndrome
 - iii. Sarcoid
 - iv. Wegener's granulomatosis
3. Granulomatous involvement of medium-sized blood vessels

4. Some autopsies have demonstrated granulomas with Langhans cells

Neuroimaging

Arteriography

1. Arteriographic evidence of vasculitis (approximately one third of cases)

Ocular Computed Tomography

1. The outer nuclear layer, external limiting membrane and the inner and outer segment (IS/OS) line are disrupted

Laboratory Evaluation

1. Elevated CSF leukocytes and protein

Differential Points Between APMPE, Eales and Susac's Disease

1. Eales primarily affects retinal arteries (neovascular proliferation and vitreous hemorrhage):
 - a. Young men (20 to 40)
 - b. Stroke is rare
2. Susac's (young women approximately age 30)
 - a. Microangiopathy of the retina, cochlea and brain
 - b. Lesions in the corpus callosum (middle area)
3. APMPE
 - a. Rapid decrease in central vision
 - b. Yellow-white multiple placoid lesions of the retina
 - c. Acute/chronic visual blurring, scotoma or metamorphopsia
 - d. Both eyes are involved simultaneously or less commonly sequentially within a few days
4. Inflammatory conditions that are associated with retinal edema
 - a. Vogt-Koyanagi-Harada disease
 - b. Ocular toxoplasmosis

Takayasu's Disease

Overview

Takayasu's disease is an arteritis of large vessels that involves the aorta and its major branches and the pulmonary arteries.

General Characteristics

1. Most common in Asia; may be seen sporadically in the West
2. Prodrome of fever and night sweats
3. High sedimentation rate; anemia; increased gammaglobulin; and positive C reactive protein
4. Gradual obliteration of:
 - a. Major arterial branches of the arch of the aorta
 - b. Vertebral arteries are relatively spared

Clinical Manifestations

1. Constitutional symptoms, limb claudication, asymmetric blood pressure between the arms, claudication of vision, hypertension and stroke. Usually presents in 3rd decade

Neurological Manifestations

1. Loss of extremity and neck pulses

2. Asymptomatic subclavian steal
3. Intermittent claudication of vision
 - a. Tenuous blood supply to the optic nerve and retina
4. Early onset of cataracts
5. Facial atrophy
6. Headache
7. Dizziness
8. Hypothyroidism
 - a. Increase thyrocervical trunk collaterals destroy the thyroid gland
9. Claudication
 - a. Arm and leg
 - b. Vision (with head position and walking)

Neuropathology

1. Ischemic stroke
 - a. Less frequent than expected from the radiologic evaluation
 - b. Media and adventitia of blood vessels are involved in an inflammatory response
 - c. Late stage fibrosis of affected vessels
 - d. Extensive collateral circulation associated with
 - i. SAH
 - ii. ICH
 - e. Ischemic stroke primarily of the anterior circulation
2. Collateral circulation
 - a. May be associated with subarachnoid and intracranial hemorrhage

Neuroimaging

Arteriographic Evaluation

1. Occlusion, stenosis, ectasia, aneurysm formation at vessel origins of the aortic arch
2. Most common sites of involvement:
 - a. Mid portion of the left common carotid artery
 - b. Left and right subclavian arteries
 - c. Mid portion of the innominate artery

Laboratory Evaluation

1. Biomarkers:
 - a. Pentaxin-3, a protein produced by endothelial cells in response to inflammatory signals
 - b. ESR and CRP are usually increased

Differential Diagnosis of Takayasu's Syndrome

1. Arteriosclerosis
2. Burger's disease
3. Behçet's disease
4. Coarctation of the aorta
5. Aortic dissection
6. Congenital anomalies

Behçet's Disease

Overview

A systemic inflammatory disorder characterized by painful oral and genital ulcers, uveitis, well circumscribed skin lesions, large artery stroke and vasculitis.

General Characteristics

1. Relapsing remitting course
2. Major features:
 - a. Oral ulcers
 - b. Genital ulcers
 - c. Uveitis
3. High incidence in Turkey and Japan
 - a. World-wide distribution
4. Systemic involvement:
 - a. Skin:
 - i. Aphthous mouth ulcers
 - ii. Folliculitis
 - iii. Erythema nodosum
5. Ulcerative lesions of bowel and bladder mucosa
6. Stomach ulcers
7. Synovitis
8. Large joint arthritis
9. Thrombophlebitis
10. Affects young adults
11. Male > female 2:1
12. Neurologic involvement in less than 10%
13. An immune-mediated illness that often responds to TNF- α inhibitors if standard immunosuppression fails

Clinical Manifestations

Clinical manifestations include ocular (uveitis and optic nerve inflammation), large joint arthritis, synovitis, ulcerative lesions of the bowel mucosa, oral and genital ulcers. It may have a relapsing course. Large vessel stroke, dural venous thrombosis, and branch occlusions occur.

1. Pattern of involvement:
 - a. Ocular
 - i. Uveitis
 - ii. Optic nerve inflammation
 - b. Brainstem
 - i. Cranial nerve inflammation
 - c. Cortical:
 - i. Subcortical dementia
 - d. Stroke:
 - i. Large artery stroke
 - ii. Vasculitis
 - iii. Cerebral venous thrombosis in 10%
 1. Hetero or homozygous for Factor V Leiden defect
 - e. Dementia:
 - i. Frontal lobe type
 - ii. Subcortical
 - iii. Rarely accompanied by:
 1. Seizures
 2. Aphasia
 - f. Late stage disease
 - i. Quadriparesis
 - ii. Pseudo bulbar palsy

Neuropathology

1. Branch occlusion > large vessel thrombosis

2. Dural venous sinus thrombosis
3. Primarily ocular manifestations
4. Brainstem syndrome (rhombencephalitis)
5. Spinal cord may be involved
6. Retinal vasculitis
7. Demyelinative and/or ischemic foci in:
 - a. Midbrain (most extensive)
 - b. Basis pontis
 - c. Medulla
 - d. Optic nerve
 - e. Globus pallidus
 - f. Spinal cord
 - g. Hypothalamus

Neuroimaging

MRI

1. Topography of involvement
 - a. Pons > midbrain > basal ganglia > thalamus
2. Small well delineated T2-weighted lesions
 - a. Brainstem lesions
 - i. Not in arterial territories
 - b. Gray and white matter lesions
 - c. 10 mm sharply margined irregular and confluent lesions in affected areas

Laboratory Evaluation

1. Increase in IL-6 and IL-8 vs control subjects
2. HLA-B51
3. Genomic wide association studies reveal associations with ERAP-1, CCR1-CCR3 and KLRC4

Cogan's Syndrome (Typical or Classic)

Overview

A chronic inflammatory disorder, affecting multiple systems, characterized by interstitial keratitis and sensorineural hearing loss; may also be associated with systemic vasculitis (rare).

General Characteristics

1. Occurs in young adults (25 years mean age)
2. Men and women affected equally
3. Autoantigens: There is evidence of inner ear autoimmunity possibly triggered by a viral infection. Putative autoantigens are CD148 and Connexin 26
4. Cerebrovascular complications are large vessel stroke and cavernous sinus thrombosis

Clinical Manifestations

1. Systemic features:
 - a. Headache, fever, weight loss, fatigue
 - i. Arthralgias and myalgias (30%)
 - b. 10% have systemic vasculitis
 - a. Aortic insufficiency (10%)
 - b. Distal coronary arteries may be affected
 - c. Skin

- d. Viscera
- e. Kidneys
- f. CNS
- g. Muscles

2. Neurological manifestations
 - a. Blindness (corneal opacification)
 - b. Vertigo
 - c. Ataxia
 - d. Hearing loss
 - i. Vestibular auditory dysfunction from inflammation of the labyrinth
3. Ophthalmologic features
 - a. Acute interstitial keratitis
 - b. Bilateral interstitial keratitis (nonsuppurative cellular infiltrate of the corneal stroma)
 - c. Keratitis fluctuates
 - d. Patchy corneal involvement and absence of intraocular inflammation
 - e. Retinal hemorrhage and papilledema
 - f. Orbital pseudotumor
 - g. Central artery or vein occlusion
 - h. Presents with:
 - i. Red eyes
 - ii. Photophobia
 - iii. Reduced vision
 - iv. Interstitial keratitis
 - v. Uveitis (rare)
4. Vestibulocochlear manifestations:
 - a. Severe hearing loss in all cases
 - i. Asymmetric and sudden
 - b. Vertigo, tinnitus and ataxia
 - c. Inflammation of the labyrinths
 - d. Acute and often bilateral
 - e. Decreased caloric response
 - f. May be coincidental with visual loss
5. Stroke (pial arteries)

Typical Cogan's Signs and Symptoms

1. Photophobia, lachrymation, eye pain
2. Blurred vision
3. Intermittent symptoms for years
4. Ménière's-like attacks may precede eye pain
5. Total deafness and absence of vestibular function

Neuropathology

1. Cerebral venous sinus thrombosis
2. Vasculitic process affecting vessels of all sizes
3. Microscopic evaluation of the aorta
 - a. Inflammatory changes
 - b. Destruction of the internal elastic membrane
4. Autoantibodies against corneal, inner ear and endothelial antigens may be present
5. Autoantibodies to corneal, inner ear and endothelial antigens
6. Acute interstitial keratitis

7. Rare emboli to large arteries from valvular disease
8. Aortic insufficiency in 10%
9. Skin and visceral involvement
10. Inflammation of the labyrinth
11. Ocular pathology (in both typical and atypical Cogan's):
 - a. Retinal hemorrhage
 - b. Papilledema
 - c. Orbital pseudotumor
 - d. Central artery or vein occlusion

Neuroimaging

For both Typical and Atypical Cogan's syndrome.

MRI

1. Multiple ischemic lesions
2. Angiography (topographic stroke)
3. Signs of vasculitis

Angiography

1. Cerebral venous thrombosis
2. PICA thrombosis
3. Signs of suggestive of vasculitis

CT

1. Occasional intralabyrinthine calcifications

Laboratory Evaluation

Typical and Atypical Cogan's Syndrome

1. Elevated erythrocyte sedimentation rate (ESR), anemia, leukocytosis and thrombocytosis
2. Lumbar puncture (LP) may demonstrate pleocytosis and elevated protein
3. Negative tests for syphilis and autoantibodies that include rheumatoid factor, anti-nuclear antibodies and ds DNA
4. Audiometry, electronystagmography and vestibular function deficits are positive

Atypical Cogan's Syndrome

General Characteristics

1. Vasculitis and systemic manifestations
2. Inflammatory ocular disease exemplified by
 - a. Uveitis
 - b. Scleritis
 - c. Episcleritis
 - d. Retinal vasculitis
 - e. Optic nerve edema without interstitial keratitis
3. There may be vestibular auditory dysfunction that occurs at more than 2 years after onset of eye symptoms

Clinical Manifestations

1. Involvement of the CNS or PNS varies from 5 to 50%
2. Vasculitis
 - a. Occurs in atypical disease
 - b. Aortitis and aortic insufficiency in the classic syndrome
 - c. Neurologic symptoms
 - i. Stroke
 - ii. Encephalopathy

- ii. Seizure
- iii. Myelopathy
- iv. Mononeuritis multiplex
- v. Cavernous sinus thrombosis
- d. Differential diagnosis includes syphilis
3. Cerebrovascular disease
 - a. Cerebral venous sinus thrombosis
 - b. PICA thrombosis
 - c. Ischemic brain (cerebellar) lesions
 - d. Frequency of neurologic involvement about 13%
 - e. Emboli to large arteries from valvular disease (rare)

Neuroimaging

MRI

1. Multiple ischemic brain lesions
2. Soft tissue obliteration of the membranous labyrinth

Angiography

1. Cerebral venous thrombosis
2. PICA thrombosis
3. Signs of suggestive of vasculitis

CT

1. Intralabyrinthine calcifications (rare)

Neuropathology

1. Cerebral venous sinus thrombosis
2. PICA stroke; cerebellar lesions
3. Rare emboli to large arteries from valvular disease
4. Ocular pathology (in both typical and atypical Cogan's):
 - a. Retinal hemorrhage
 - b. Papilledema
 - c. Orbital pseudotumor
 - d. Central artery or vein occlusion

Laboratory Evaluation

Typical and Atypical Cogan's Syndrome

1. Elevated erythrocyte sedimentation rate (ESR), anemia, leukocytosis and thrombocytosis
2. Lumbar puncture (LP) may demonstrate pleocytosis and elevated protein
3. Negative tests for syphilis and autoantibodies that include rheumatoid factor, anti-nuclear antibodies and ds DNA
4. Audiometry, electronystagmography and vestibular function deficits are positive

Buerger's Disease (Thromboangiitis Obliterans)

Overview

A non-atherosclerotic segmental inflammatory disease that most often affects small and medium-sized arteries and veins in the upper and lower extremities. Cigarette smoking is important in etiology.

General Characteristics

1. Cigarette smoking: Possible immune reaction to some component of tobacco that causes an inflammatory small vessel occlusive disease

Clinical Manifestations

1. Migratory thrombophlebitis or vascular insufficiency in the extremities (lower greater than upper)
2. Occasional large vessel stroke
3. Two or more limbs are involved in most patients
4. Systemic characteristics
 - a. Intermittent claudication of the legs
 - i. Involvement of the in-step rather than the calf
 - b. Upper extremity claudication of the arms as the disease progresses
 - c. Claudication particularly prevalent in smokers
 - i. Regresses with cessation of tobacco use

Neurological Manifestations

1. Monoparesis
2. Hemiparesis
3. Visual field deficits
4. Dementia

Neuropathology

1. Immune mechanism: There is evidence for an autoimmune mechanism with antibodies directed against the vascular endothelium due to antigens in tobacco. The antibodies demonstrated are anti-nuclear anti-elastin, anti-collagen I and III and anti-nicotine antibodies. Immunoglobulins are deposited in blood vessels
2. Vasculitis of medium and small vessels
3. Primary involvement in distal extremity vessels
 - a. Severe peripheral vascular disease. Extremity lesions are typically below the knee in the posterior and anterior arteries rather than the distal 1/3 of the aorta or the iliac arteries as in atherosclerosis
4. Rarely affects veins
5. Coronary and renal arteries may be affected
6. Granular cortical atrophy

Neuroimaging

1. Brain vessel topography:
 - a. Watershed zones infarctions between ACA/MCA and MCA/PCA territories
 - b. Possibly two vessel sizes involved:
 - i. Arteries <1 mm
 - ii. Large proximal arteries

*Collagen, Type IV Alpha Disorders***General Characteristics**

1. Heterotrimers composed of collagen type IV alpha (COL4A1) and alpha2 (COL4A2) a major component of all basement membranes
 - a. Mutations are pleiotropic
2. Type IV collagens are encoded by 3 pairs of paralogous genes (collagen type IV alpha (COL4A1 – COL4A6)
3. Mutations in COL A3 cause Alpert syndrome that affects:
 - a. Retina
 - b. Cochlea

c. Kidney

4. Large deletions of COL4A5 and COL4A6 cause diffuse leiomyomatosis
5. COL4A1 and COL4A2 mutations
 - a. Chromosome 13q34; controlled by microRNAs that regulate collagen synthesis

Clinical Manifestations*Neurological Diseases Caused by Mutations in COL4A1 and COL4A3*

1. Porencephaly (arises from germinal matrix hemorrhage)
2. Ocular, cerebral, renal, muscular defects
3. Retinal vascular tortuosity highly penetrant in COL4A1 mutations
4. Hereditary angiopathy with nephropathy, aneurysms and muscle cramps (HANC) is associated

Cerebrovascular Disease Associated with COL4A1 and COLA2 Mutations

1. Intracranial hemorrhage
2. Silent infarcts (small vessel disease)
3. Periventricular leukoencephalopathy with calcification

Neuroimaging*MRI*

1. Dolichoectasia
2. COL2 alpha
 - a. Germinal matrix hemorrhage
 - b. Porencephaly
3. Large vessel dissection

Neuropathology

1. Electron microscopy:
 - a. Focal interruptions or expanded and thickened basement membranes
 - b. Fragmented basement membranes in capillaries

*Ehlers-Danlos Syndrome***Overview**

Ehlers-Danlos syndrome is a hereditary connective tissue disorder whose main characteristics are skin and joint hypermobility, poor wound healing and atrophic scarring.

In classic EDS (type I and type II), approximately 50% of patients have mutations in COL5 A1 or COL5A2 genes that encode the $\alpha 1$ and $\alpha 2$ chain of collagen V. In the EDS vascular type (EDS type IV), molecular genetic testing is used to identify the mutation in the COL3A1 gene with defective type III collagen.

General Characteristics

1. Ehlers–Danlos syndrome (EDS) is a group of connective tissue diseases (approximately 10 subtypes) with overlapping clinical features
 - a. Major types are I, II, or III (approximately 80% of patients)

- b. Subtype IV most important for cerebrovascular complications; incidence is 1 in 50,000–500,000 persons
- c. Decreased synthesis of type III collagen
 - i. All of these patients demonstrate autosomal dominant inheritance
 - ii. COL 3A1 gene (mutations) on chromosome 2
 - 1. Exon skipping and multi-exon deletions of COL 3A1 gene chromosome 2
 - 2. Encodes for alpha-1 chain of type III collagen; produces a pro-collagen that causes it to be thin and friable

Clinical Manifestations

- 1. Hyperelastic skin
- 2. Hyperextensible joints
- 3. Increased scarring after injury
- 4. Platelet dysfunction
- 5. Cardiac defects
- 6. History of sudden death
- 7. Hemorrhage after minor trauma
- 8. Hemorrhage after surgery
- 9. Bowel rupture
- 10. 80% of vascular complications by age 40
- 11. Ten subtypes of the syndrome
 - a. Major types are I, II, or III (approximately 50% of patients)
 - b. Subtype IV most important for cerebrovascular lesions:
 - c. Decreased synthesis of type III collagen
 - i. All of these patients demonstrate AD inheritance
 - ii. COL 3A1 gene (mutations); chromosome 2
 - 1. Codes for alpha-1 chain of type III collagen

Cerebral and Vascular Complications

- 1. Aneurysms (type IV; type I rare)
 - a. Intra- and extracranial aneurysms
 - b. Multiple aneurysms
 - c. Most common aneurysm is of the internal carotid artery
 - i. In the cavernous sinus
 - ii. At the site of emergence from the sinus
- 2. Presentation
 - a. Rupture in the cavernous sinus cavity
 - b. SAH
 - c. Carotid cavernous fistula
 - i. Spontaneous rupture or following minor head trauma
 - ii. Symptoms include:
 - 1. Periorbital swelling
 - 2. Conjunctival erythema with arterioles reaching the iris
 - 3. Pulsatile tinnitus
 - 4. Retinal engorgement
 - 5. Increased ocular pressure
 - 6. Proptosis occurrence

- 3. Arterial dissection:
 - a. Documented in both intra and extracranial vessels
 - b. Dissection of intrathoracic artery can secondarily occlude cervical vessels
 - c. Dissection occurs in intra-abdominal, pelvic, and intrathoracic vessels
 - d. Complications during arteriography are common due to friability of the tissue
 - e. Spontaneous dissections
 - f. During surgery and procedures

Neuropathology

- 1. Fragmentation of the internal elastic membrane
- 2. Fibrosis of the arterial wall
- 3. Microscopic rupture between media and adventia

Neuroimaging

Arteriography/MRA

- 1. Carotid cavernous fistula
- 2. Intra and extracranial aneurysms. Rarely in both carotid and vertebral arteries concomitantly
- 3. Arterial dissection of cerebral as well as thoracic, abdominal, and pelvic vessels
- 4. Intracranial carotid artery is the most common site of aneurysm

Differential Diagnosis

Differential Diagnosis Between Marfan's Syndrome and Ehlers-Danlos Disease

- 1. Marfan's syndrome has fewer cerebrovascular aneurysms
- 2. Aortic arch and pulmonary arteries affected more in Marfan's syndrome
- 3. Carotid-cavernous fistula (both)
 - a. May follow minor head trauma
 - b. Spontaneous occurrence
 - c. May occur concomitantly with intracranial aneurysms
- 4. Arterial Dissections (both)
 - a. Arteries fail to hold sutures (EDS)
 - b. Dissection of both intra and external arteries (EDS)
 - c. Carotid and basilar arteries are thin walled, enlarged and tortuous (EDS > Marfan's)
 - d. Arteriograms are dangerous (EDS)
 - e. More friable tissue (EDS)

Marfan's Syndrome

Overview

Marfan's syndrome is a heritable connective tissue disorder whose cardinal features are cardiovascular, ocular and dolichostenomelia skeletal abnormalities (increased length of limbs with respect to the trunk).

General Characteristics

- 1. A connective tissue disorder that is system wide:
 - a. Skeleton and skin abnormalities
 - b. Cardiovascular system (aortic root dilation)
 - c. Lens dislocation and myopia

- d. Lung involvement (emphysema)
- e. MMASS – myopia, mitral valve prolapse, aortic dilatation, skin and skeletal abnormalities

Genetics

1. Autosomal dominant; sporadic in about 25% of patients
 - a. Chromosome 15: mutation in the FBN1 gene that encodes fibrillin-1
 - b. Possible second locus:
 - i. 3p24-25
 - ii. Possible mutations in genes coding for TGF- α (important for angiogenesis)
 - c. Fibrillin-1
 - i. Major component of the extracellular matrix; the fibrillary structure for elastin deposition
 - d. Diagnosis requires a major criteria in two organ systems and involvement in a third

Clinical Manifestations

Neurological Complications of Marfan's Syndrome

1. Dissection of the ascending aorta, the carotid and vertebral arteries:
 - a. Arch dissection: pain in the face and carotid artery stroke
 - b. Dissection below the subclavian artery – pain straight through to the back with paraplegia
 - c. An excess of cerebral aneurysms but not subarachnoid hemorrhage

General Complications of Marfan's Syndrome

1. Emboli:
 - a. Cardiac arrhythmia
2. Spinal Defects:
 - a. Craniospinal junction
 - i. Greater than 50% of patients have increased atlantoaxial translation (greater than 5 mm with neck flexion; causes odontoid compression of the spinal cord)
 - ii. 36% have basilar impression (greater than 135° angle between the planum sphenoidale and the clivus)
3. Ectasia of the dural sac with irritation of lumbosacral nerve roots and back pain
4. Laryngeal nerve paralysis from aortic compression of the recurrent laryngeal nerve
5. Severe scoliosis
6. Multiple facial anomalies with retrognathia
7. Congenital ectopia lentis (may be the most specific finding)

Neuroimaging

1. Evaluation of the acute aortic syndrome that includes:
 - a. Aortic and cervical cephalic arterial dissection
 - b. Intramural hematoma
 - c. Penetrating atherosclerotic ulcer
2. Embolic stroke of cerebral vessels
3. Atlantoaxial dislocation
4. Enlarged dural sac

CT

1. Findings demonstrate “beak sign” and aortic “cobwebs”

MRI

1. Topographic embolic stroke

Angiography

1. Dissection of the ascending aorta, carotid and vertebral arteries
2. Arterial malformations
3. Tortuosity and dilatation of intracranial cerebral vessels

Neuropathology

1. Defect is primarily in the vessel media with profound diminution of elastic fibers
2. Decreased fibrillin in microfibrillar fibers in the skin
3. Mutation in fibrillin causes a disordered microfibril matrix
4. Release of sequestered latent transforming growth factor β :
 - a. Mediator of vascular remodeling
5. Regional biomechanical dysfunction

Differential Diagnosis

1. Homocystinuria:
 - a. Mental retardation
 - b. Autosomal recessive
2. Congenital contractural arachnodactyly (Beals syndrome):
 - a. Marfanoid features; Autosomal dominant
 - b. Heart defects
 - c. Ocular defects
3. Loeys-Dietz syndrome:
 - a. Transforming growth factor β receptor mutation
 - i. TGBRA gene mutation
 - ii. Arterial tortuosity and aneurysms
 - iii. Hypertelorism
 - iv. Bifid (bifurcated) uvula/cleft palate

Pseudoxanthoma Elasticum (PXE)

Overview

PXE (Grönblad–Strandberg syndrome) is an ectopic mineralization disorder-associated with ocular and cardiovascular manifestations.

General Characteristics

1. Female predominance (2:1)
2. Mutations in the ABCC6 gene on the short arm of chromosome 16 (16p13.1);
 - a. Autosomal dominant and recessive forms
 - b. Autosomal dominant form possibly has more severe vascular disease
3. ABCC6 gene encodes:
 - a. Multi-drug resistance associated protein 6 a trans membrane transporter protein of the ABC (ATP binding cassette) family
 - b. β -Thalassemia patients have high prevalence of PXE

Clinical Manifestations

1. Systemic Signs
 - a. Additional eye signs:
 - i. Choroid retinal atrophy
 - ii. Subretinal edema
 - iii. Pattern dystrophy-like changes
 - iv. Retinal drusen
2. Heart:
 - a. Premature coronary artery disease:
 - i. Sudden death
 - ii. Cardiomyopathy
 - b. Endocardial changes (elastic fiber changes):
 - i. Thickened mitral valves
 - ii. Mitral stenosis; MVP
 - iii. Restrictive cardiomyopathy (calcification of the endocardium)
3. GI tract
 - a. Gastrointestinal hemorrhage:
 - i. Often the presenting symptom
 - ii. Degeneration of small-sized arteries
 - iii. Microaneurysms and angiomatous malformations
4. Skin:
 - a. Linear, round or oval yellow orange elevated lesions (resemble xanthomas)
 - b. Papular lesions in flexure areas
 - c. Face, neck, axilla, inguinal, umbilical topography
 - d. Late stage – lax and redundant skin
 - e. Involvement of skin and mucosa in:
 - i. Lips
 - ii. Mouth
 - iii. Vagina
 - iv. Rectum
 - f. Gastric mucosa
 - g. Endocardium and heart valves
5. Eye involvement
 - a. Classic
 - i. Angioid streaks
 1. Red, brown or gray
 2. Wider than veins
 3. Radiate from the disc
 4. Rupture of Bruch's membrane (a thin membrane separating the blood vessel-rich layer from the pigmented layer of the retina)
 5. "Peau d'orange" (a French term meaning that the retina resembles the skin of an orange)
 6. Chorioretinal scarring and hemorrhage
 - b. Optic nerve infarction
 - i. Involvement of the posterior ciliary arteries
 - ii. Comet bodies

Cerebrovascular Disease in PXE

1. Hypertension
2. Aneurysmal dilation of the aorta
3. Calcification of peripheral arteries with intermittent claudication

4. Occlusive cervicocranial arterial disease; intra and extracranial
5. Subarachnoid hemorrhage
6. Carotid artery:
 - a. Increased thickness; more elastic with increased intimal-medial thickness
 - b. Tortuosity and ectasia
7. Ischemic symptoms develop in the 5th and 6th decades
8. Concomitant pathology of hypertensive cardiovascular disease:
 - a. ICH
 - b. Lacunar infarction
 - c. Microvascular disease (Binswanger)
9. Aneurysm formation and SAH
 - a. Cavernous sinus
 - i. May present with cranial nerve palsy rather than SAH
10. Possibly increased incidence of dissection

Neurologic Manifestations

1. Large artery infarction
2. Hemorrhage from saccular aneurysms hypertension and microaneurysm
3. Cavernous artery aneurysm

Neuropathology

1. Decreased calcium extracellular homeostasis
2. Loss of elastic tissue, fragmentation of the internal elastic membrane; calcifications between the intima and media
3. Dystrophic mineralization and fragmentation of elastic fibers, Large and medium-sized vessels
4. Fibrosis of the arterial wall
5. Microscopic ruptures between media and adventia
6. Carotid artery
 - a. Increased intimal-medial thickness
 - b. Tortuosity and ectasia
7. Concomitant pathology of HCVD:
 - a. ICH
 - b. Lacunar infarction
 - c. Microvascular disease (Binswanger)
8. Aneurysm formation and SAH:
 - a. Cavernous sinus
 - i. May present with cranial nerve palsy rather than SAH
9. Possible increased incidence of dissection

Neuroimaging

1. Occlusive cervicocranial disease that is intra or extracranial
2. Tortuosity and ectasia of cervical arteries
3. Lacunar infarction
4. Hyperintensive changes
5. Aneurysm with SAH
6. Thicker carotid arteries
7. Moyamoya syndrome
8. Binswanger type microvascular disease

Laboratory Evaluation

1. Identified genes for the disease:
 - a. ENPPI
 - b. ABCC6 (PXE)
 - c. NT5E
 - d. SLC20A2
 - e. CD73 deficiency

Differential Diagnosis*Differential Diagnosis of Identified Genes for Arterial Calcification*

1. ENPPI
2. ABCC6 (PXE)
3. NT5E
4. SLC20A2
5. CD73 deficiency

Differential Diagnosis of Angioid Streaks

1. Sickle cell anemia
2. Paget's disease
3. Hypophosphatemia
4. Ehlers-Danlos syndrome
5. Lead poisoning
6. ITP
7. PXE
8. Trauma
9. Pituitary disease
10. Additional eye signs:
 - a. Choroid retinal atrophy
 - b. Subretinal edema
 - c. Pattern dystrophy-like changes
 - d. Retinal drusen

Differential Diagnosis of Arterial Calcification

1. Aging
2. Diabetes mellitus
3. Chronic kidney disease
4. Generalized arterial calcification of infancy
5. PXE
6. Familial idiopathic basal ganglia calcification

Moyamoya Syndrome**Overview**

Moyamoya disease is a progressive intracranial arteriopathy due to unilateral stenosis of the distal portion of the internal carotid artery and the proximal anterior and middle cerebral arteries that cause TIA and strokes.

General Characteristics

1. Prevalence in asymptomatic Japanese population is 50.7/100,000 people
 - a. Patient in Northeast Asia have genetic disease and not syndrome
 - b. Two peak ages:
 - i. Children younger than 14 years
 - ii. Young adults between 25–49 years
 - iii. Japanese female to male ratio is 1.6- to 1.8: 1

Genetics

1. Autosomal dominant with incomplete penetrance
2. Complex chromosome rearrangements at 6p25.3; variant RNF 213c14576G7A
3. Genetic or acquired form
 - a. Genetic form more common in children

Clinical Manifestations*Cerebrovascular Disease in Adults*

1. Recurrent stroke or TIA is a common presentation
 - a. Border zone territorial stroke between MCA/ACA and MCA/PCA
2. Infarctions in the cortex, deep hemispheric white matter or basal ganglia
3. Progressive ischemic frontal lobe syndrome occurs with behavioral changes
4. Brainstem strokes are rare
5. Less frequent: headache and seizures than in children
6. May present with ICH:
 - a. Asymptomatic microhemorrhages
 - b. Recurrent hemorrhages are frequent
 - c. Pathogenesis of hemorrhages can be rupture of collateral blood vessel, small false aneurysm or vascular malformation
 - d. Hemorrhages:
 - i. More frequent in 46–55 year old patients
 - ii. Intracerebral in 60% (BG and thalamus)
 - iii. Intraventricular in 30%
 1. Extension from the thalamus
 2. Direct from the caudate
 - iv. Deep penetrating arteries:
 1. Degenerative changes; hypertrophied arterioles
 2. Develop microaneurysms
 3. Small asymptomatic hemorrhages in the paraventricular white matter and subcortex
 - v. Rare: SAH; high incidence of posterior circulation aneurysm
 1. Small false aneurysms along the ventricular surface and Moyamoya collaterals are a source of SAH
 - vi. A unilateral process is against Moyamoya disease

Neuropathology

1. Bilateral severe stenosis or occlusion of the terminal ICA and proximal ACA and MCA; can affect the PCA; superficial temporal artery and the middle meningeal artery can be affected

Microscopic Evaluation of Large Intracranial Arteries

1. Thickening of the intimal and medial layers
2. Proliferation and degeneration of smooth muscle cells
3. Fragmentation of the internal elastic membrane
4. No inflammatory, calcification or lipid droplets
5. Ethmoidal collaterals involve:
 - a. The frontal basal areas
 - b. The vault where Moyamoya collaterals are a generalized vascular network

6. Collaterals develop from external carotid artery as well as the thalamoperforators, the dorsal branches of the PCA, tectal plexus and posterior choroidal vessels
7. Associated with a greater number of illnesses that include:
 - a. Sickle cell disease
 - b. Neurofibromatosis type I
 - c. Tuberculosis
 - d. Severe atherosclerosis

Neuroimaging

1. There are six angiographic stages from narrowing of the distal ICA (stage I to the cerebral circulation supplied from meningeal pial collaterals of the external carotid)
2. Collaterals from the ethmoidal arteries
3. Intracranial saccular aneurysms: posterior > anterior circulation
 - a. Arise at arterial bifurcations

MRI

1. Infarctions primarily in deep hemispheric nuclei and hemispheric white matter
2. Border zone topography infarctions occur primarily between the ACA/MCA
3. Dilated leptomeningeal and transdural collateral arteries

Sneddon's Syndrome

Overview

Sneddon's syndrome is characterized by livedo reticularis of the skin and pial artery stroke. Approximately 80% of Sneddon's syndrome patients have an antiphospholipid antibody marker.

General Characteristics

1. No definite ethnic predilection; hospital based studies possible incidence of .25% to .5% of stroke patients
2. Hospital derived patients
 - a. 80% are women
 - b. Average age at onset: 40 years
 - c. Possible autosomal dominant genetics in familial patients

Clinical Manifestations

1. Livedo reticularis (mottling, bluish lace-like discoloration with pale center) precedes neurological symptoms although it may occur concurrently or afterwards
2. Topography of the lesions:
 - a. Lower trunk, buttocks, proximal thighs
 - b. Lesions may generalize to upper body
 - c. Exacerbation with cold and concomitantly with exacerbation of neurologic symptoms
 - d. Some patients demonstrate area cyanosis and Raynaud's phenomena

Systemic Signs

1. Hypertension (60–80%)
2. Valvular heart disease

3. Thrombosis of peripheral arteries
4. Pulmonary embolus
5. Retinal and mesenteric artery involvement

Neurological Manifestations

1. Headache and vertigo in >50% of patients
2. TIA in >50%
3. Cognitive dysfunction: dementia in some late stage patients
4. Patients with antiphospholipid antibodies have
 - a. Seizures
 - b. Thrombocytopenia
 - c. Mitral valve disease
5. Rare: tremor with a high incidence of seizure

Cerebrovascular Manifestations

1. Multiple TIA and strokes
 - a. Cortical and subcortical topography in anterior and posterior circulations
 - b. Lacunar and white matter lesions
 - c. Spinal cord is rarely involved
 - d. Case reports of SAH and ICH

Neuropathology

1. Skin biopsy
 - a. Medium-sized arteries of deep dermal or subcutaneous tissue are involved
 - b. Endotheliitis; inflammatory infiltrate
 - c. Fibrin occlusion of small vessels
 - d. Late stage subendothelial occlusion
2. Non-specific subcortical infarction with gliosis; no inflammation or fibrinoid necrosis
3. One autopsy study:
 - a. Cortical infarction of medium-sized arteries; hyperplasia of smooth muscle
4. Some patients have a non-vasculitic small and medium-sized vessel arteriopathy

Coagulation Associated Defects

1. Antiphospholipid, lupus anticoagulant and prothrombin antibodies are frequently found
2. Less frequently seen:
 - a. Platelet aggregation defects
 - b. Antithrombin III deficiency
 - c. Protein Z deficiency in patients that are antiphospholipid negative
 - d. Deficiency of Factor V Leiden in 10% of patients
 - e. Deficiency of Protein S

Neuroimaging

MRI

1. Multiple subcortical and white matter lesions in separate arterial territories
2. Cortical and subcortical atrophy

Angiography

1. Normal in many patients

2. A subset demonstrates distal arterial occlusions with extensive collaterals

Differential Diagnosis Between Sneddon's Syndrome and APL (Antiphospholipid Syndrome)

1. Antiphospholipid antibody titers (APL) approximately equal in both
2. APL Sneddon's patients are older than APL patients
3. Miscarriages more frequent in APL patients
4. Cardiac valve abnormalities more common in APL than Sneddon's syndrome patients (marantic endocarditis)
5. Venous thrombosis more common in APL than Sneddon's syndrome patients
6. Digital artery narrowing and dilation demonstrated angiographically; acrocyanosis (Sneddon's)
7. Early inflammatory skin lesions (Sneddon's)
 - a. Medium-sized arteries between the dermis and subcutis affected
8. May be familial (Sneddon's)
9. May have antiphospholipid antibodies (Sneddon's)
10. Valvular cardiac defects less common in Sneddon's syndrome than APL
11. Neurological manifestations of Sneddon's syndrome
 - a. Multifocal cortical infarcts
 - b. Lesions in the cerebral white matter
 - c. Intranuclear ophthalmoplegia
12. Arteriography
 - a. Branch occlusions of intracranial arteries

Differential Diagnosis of Livedo Reticularis

1. Collagen vascular disease
 - a. SLE
 - b. Rheumatoid arthritis
 - c. PAN
2. Tuberculosis
3. Syphilis
4. Complex regional pain syndrome, types I and II (usually allodynia/hyperalgesia associated)
5. APL syndrome
6. TTP
7. Thrombocythemia
8. DIC
9. Oral contraceptives
10. Neoplasm
11. Cryoglobulinemia (legs)
12. Cholesterol emboli syndrome (legs and toes are blue)
13. Divry-Van Bogaert syndrome

Mencke's Disease

Overview

Menckes disease is an X-linked recessive neurodegenerative disorder in the gene that encodes the copper transporting ATPase (ATP7A). Majority of patients are male.

General Characteristics

1. Mutations in the ATP7A gene on the long arm of the X chromosome (xq12-q13)

2. P-type ATP protein encoded functions to translocate metal cations across cellular membranes and transport copper to those enzymes that require it
3. ATP7A mutations also cause:
 - a. Occipital horn disease
 - b. Distal hereditary motor neuropathy
4. Patients have low copper levels in the brain
5. Signs and symptoms are due to deficiencies of Cu^{2+} dependent enzymes such as ceruloplasmin; superoxide dismutase; dopamine β -hydroxylase (DBH)

Clinical Manifestations

Neurologic Signs and Symptoms

1. Classic presentation:
 - a. Neonatal
 - i. Hypothermia
 - ii. Poor feeding
 - iii. Failure to thrive
 - iv. Seizures
 - b. Scalp hair abnormalities that include:
 - i. Twisted, colorless, friable hair
 - ii. Fractures of the hair shaft at regular intervals
2. Severe tortuosity of blood vessels
3. Long bone-metaphyseal spurring and a diaphyseal periosteal reaction
4. Hydronephrosis; bladder diverticula

Neuropathology

1. Tortuous arteries:
 - a. Irregular lumen
 - b. Split intimal lining
 - c. Non sulfate and sulfate chondroitin are deposited within elastin fibers:
 - i. Poor elastin formation and cross linking
 - ii. Dysfunction of copper dependent lysyl hydroxylase
 - iii. Focal degeneration of gray matter with gliosis
 - iv. EM demonstrates increased mitochondria in Purkinje cells and cortical neurons

Neuroimaging

MRI

1. Vascular tortuosity
2. Cerebral atrophy
3. Infarcts of deep gray matter and the cortex
4. Asymptomatic subdural hematoma

Vogt-Koyanagi-Harada Syndrome

General Characteristics

1. Uveomeningeal process
2. White forelock and eyelashes
3. Alopecia
4. Iridocyclitis
5. Choroiditis
6. HLA-DRB1-040 carrier

Clinical Manifestations

1. Meningeal signs (cause of recurrent meningitis)

2. Adhesive arachnoiditis
3. Papilledema
4. Increased intracranial pressure
5. Dementia
6. Cerebellar signs
7. May remit after 6–12 months

Neuropathology

1. Inflammatory infiltrates composed of CD3+ T-lymphocytes
2. CD68 positive macrophages that contain melanin
3. Granulomatous pan uveitis
4. Antigenic targets for VKH are tyrosine family proteins

Neuroimaging

1. Diffuse pachymeningeal enhancement and thickening

Laboratory Evaluation

1. CSF lymphocytic pleocytosis
2. Elevated protein

Hereditary Endotheliopathy with Retinopathy, Nephropathy and Stroke (HERNS)

General Characteristics

1. Chromosome 3p21; mutation of the TREX1 gene
 - a. Codes for a 3'-5' DNA exonuclease
2. Progressive visual loss in the 3rd to 4th decade
3. Neurologic deficits begin 4 to 10 years after initiation of the disease

Clinical Manifestations

Neurologic Manifestations

1. Central vision loss with decreased visual acuity
2. Premonitory behavioral and psychiatric symptoms (early as the second decade)
3. Stroke-like episodes may be presenting symptoms; may progress over several days
4. Later in the course there are multifocal cortical and sub-cortical signs of small vessel stroke
 - a. Migraine is common
 - b. 50% of patients have renal dysfunction

Ophthalmologic Signs

1. Retinal vasculopathy
 - a. Loss of macular capillaries
 - b. Dilated tortuous telangiectatic vessels; capillary shunts
 - c. Fluorescein angiography
 - i. Juxtafoveolar capillary obliteration with microaneurysm
 - d. Peripheral retina is involved late in the disease's course

Neuropathology

1. Small blood vessels occluded by fibrin thrombi
2. Electron microscopy:
 - a. Multilaminated vascular basement membranes

- b. Kidney, stomach, omentum and skin are concomitantly involved
- c. Generalized vasculopathy with disruption of capillaries and arterioles
- d. Breakdown of the blood-brain barrier
- e. A primary endothelial injury

Neuroimaging

MRI

1. Reveals T2 high intensity lesions in deep white matter
 - a. Overtime, contrast enhancing lesions in the deep frontoparietal area
2. May have space occupying mass lesions

Laboratory Evaluation

1. Fluorescein angiogram of the retina
 - a. Macular capillary dropout
2. Dilated tortuous telangiectasia vessels and capillaries

Hereditary Cerebroretinal Vasculopathy (CRV)

Clinical Manifestations

1. Macular edema, capillary obliteration, microaneurysms and telangiectasia
2. Strokes, visual loss, dementia

Neuropathology

1. Fibrinoid necrosis without inflammation

Hereditary Vascular Retinopathy

1. Migraines, Raynaud's phenomena and visual loss

Divry–Van Bogaert Syndrome (DVBS)

General Characteristics

1. Diffuse meningocerebral angiomas
 - a. Autosomal recessive
 - b. Involves children and adults
2. Infantile form:
 - a. Starts after age 3
 - b. Skin and neurologic lesions
 - i. Skin lesions may be absent but if present resemble those seen in adults
 - c. Neurologic involvement includes seizures, cognitive dysfunction and focal motor deficits
3. Adult onset-form:
 - a. Skin lesions and neurologic dysfunction

Clinical Manifestations

Adult Form

1. Skin lesions present as diffuse symmetrical livedo reticularis
2. May increase at the onset of neurologic signs and symptoms
3. Neurologic signs and symptoms:
 - a. Focal motor deficits (infarctions)
 - b. Seizures
 - c. Dementia
 - d. Cognitive/behavioral abnormalities predominate
 - e. Death occurs approximately 10 to 15 years after onset

Neuropathology

1. Skin biopsy demonstrates increased dermal capillaries with absent “zonulae occludens” between endothelial cells
2. Brain infarcts
3. White matter demyelination
4. Cerebromeningeal angiomatosis
 - a. A large corticomeningeal network
 - b. Vascular congestion and vessel occlusion
 - c. Fibrotic changes of the vascular walls with fatty degeneration and amyloid deposits

Neuroimaging

1. Multifocal cerebral infarctions of both gray and white matter
 - a. Axonal and oligodendrocytes loss
 - b. Astrogliosis (also known as astrocytosis)

Differential Diagnosis of Neurologic Livedo Reticularis

1. Sneddon's syndrome
2. Divry-Van Bogaert syndrome
3. SLE
4. Antiphospholipid antibody syndrome
5. Polyarteritis nodosa
6. Cholesterol embolization syndrome
7. Livedoid vasculopathy

Blue Rubber Bleb Nevus Syndrome**General Characteristics**

1. Blue Rubber Bleb Nevus syndrome (also known as Bean syndrome and formerly called Gascoyen syndrome) is a systemic disorder characterized by cutaneous and visceral cavernous hemangiomas
2. Skin lesions are rubbery and compressible over the trunk and extremities
3. Gastrointestinal angiomas occur most frequently in the small bowel resulting in anemia from bleeding

Clinical Manifestations

1. Brain angiomas (present in childhood)
2. Angiomas may involve the orbit
3. Seizures
4. Progressive neurologic deficits
5. Spinal cord compression

Neuropathology

1. Cutaneous and visceral cavernous hemangiomas
2. Skin lesions
 - a. Rubbery texture and compressible
 - b. Bluish purple
 - c. Present in childhood
 - d. Primarily over the trunk and/or extremities
3. Gastrointestinal angiomas
 - a. Most often in the small intestine
 - b. May bleed throughout life
4. Dilated venous channels

5. Myxoid degeneration of the wall

6. A venous malformation

Neuroimaging**MRI**

1. Multiple angiomatous lesions with contrast enhancement
2. Phleboliths in the orbit

Leigh's Syndrome (Subacute Necrotizing Encephalomyelopathy)**General Characteristics**

1. Genetically heterogeneous
 - a. Affects nuclear or mitochondrial DNA
2. SURF-1 gene
 - a. Milder phenotype
3. Most common biochemical deficit
 - a. COX complex and pyruvate dehydrogenase complex deficits
4. Late onset cases occur

Clinical Manifestations**Juvenile Form**

1. Spastic paraparesis
2. Visual disorder
3. Acute sensorimotor neuropathy, ataxia, deafness and retinitis pigmentosa (NARP)
4. Myopathy and cardiomyopathy
 - a. Respiratory depression and coma
5. Emboli from cardiomyopathy
6. Stroke-like attacks
7. Infantile form diagnosed by developmental delay and elevated serum and CSF lactate

Neuropathology

1. Gray matter degeneration
2. Brainstem and spinal cord necrosis
3. Spongiosis, endothelial proliferation and demyelination

Neuroimaging**MRI**

1. Symmetric hypointense T1/hyperintense on T2-weighted sequences; lesions in the basal ganglia
 - a. Putamen and brainstem
2. Sparing of red nuclei and mammillary bodies (occasionally the mammillary bodies are hemorrhagic)
3. Olivary nucleus hypertrophy
4. Some patients with SURF-1 mutations

Laboratory Evaluation

1. Infantile form diagnosed by developmental delay and elevated serum and CSF lactate

Saguenay-Lac Saint Jean (Cox Deficiency)**Overview**

Saguenay-Lac Saint Jean disease, the French Canadian variant of Leigh's disease, is a nuclear encoded cytochrome c-oxidase deficiency.

General Characteristics

1. Autosomal recessive; the largest known cohort of patients with a genetically homogeneous nuclear encoded congenital lactic acidosis
 - a. A354V mutation in LRPPRC (leucine-rich pentatricopeptide repeat containing)

Clinical Manifestations

1. Developmental delay
2. Facial dysmorphism
3. Fulminant lactic acidotic crises
4. Leigh's syndrome like

Neurological Manifestations

1. Frontal cortical lesions
2. Stroke-like episodes

Neuropathology

1. Decreased cytochrome oxidase in tissues
 - a. Cytochrome oxidase deficiency in the brain and liver
2. Necrotizing encephalopathy involving the thalamus, brainstem and spinal cord
3. Vascular proliferation and gliosis

Laboratory Evaluation

1. High CSF lactate

Differential Diagnosis*Differential Point*

1. MELAS affects parietoccipital areas primarily
2. SLSJ-COX differs from SURF1 Cox deficiency

*Disseminated Intravascular Coagulation (DIC)***Overview**

Disseminated intravascular coagulation (DIC) is a severe coagulopathy whose pathophysiology is multifactorial that involves feedback loops between coagulant, immune and inflammatory pathways. Inciting injury may be infection, trauma obstetrical disasters and trauma. Clinical picture is often dominated by systemic inflammation and sequential organ failure. Cerebral vascular manifestations are large and small vessel stroke, subarachnoid and ICH and subdural hematoma.

General Characteristics

1. Occurs in a setting of:
 - a. Septicemia
 - b. Cancer
 - c. Obstetrical procedures with release of amniotic fluid into the circulation
 - d. Neurosurgical procedures (release thromboplastin)
 - e. Chemotherapy
 - f. Viremia:
 - i. HIV
 - ii. Hepatitis

iii. Varicella

- g. Intravascular hemolysis
 - h. Heat stroke
 - i. Burn patients
 - j. Liver disease
 - k. Prosthetic devices
 - l. Collagen vascular disease
2. Clotting and fibrinolytic system are activated simultaneously
 3. Usually systemic hemorrhage and thrombosis:
 - a. Hypotension
 - b. Fever
 - c. Hypoxia
 - d. Acidosis
 - e. Shock
 - f. Acrocyanosis (distal)
 - g. Bleeding from all punctures sites

Clinical Manifestations

1. May present in coma with a non-focal neurological exam
2. Large vessel occlusion
3. Lethargy; stupor
4. Cranial nerve palsies
5. Seizure
6. SAH
7. Emboli from NBTE
8. Multifocal hemorrhage and infarction

Laboratory Evaluation

1. Peripheral blood smear:
 - a. Schistocytes (fragmented RBC's) in 50% of patients
 - b. Thrombocytopenia $<50,000$ platelets mm^3
 - c. Reticulocytosis
 - d. Slight shift to immature leukocytes
2. Clotting abnormalities:
 - a. Prothrombin time decreased
 - b. Activated partial thromboplastin time (aPTT) decreased
 - c. Exception:
 - i. 25% of DIC patients have a normal PT or fast time due to circulating activated clotting factors or early degradation products
 - ii. 40–50% of patients may have normal or fast aPTT for similar reasons
 - d. Decreased factors II, V, VIII
 - e. Decreased antithrombin III
 - f. Elevated levels of B-peptides 15–42
 - g. D-dimer neoantigen DD-3B6/22 is noted
 - h. Elevated levels of platelet factor IV

Differential Diagnosis of DIC from Multiorgan Thrombotic Illness

1. SLE with or without antiphospholipid syndrome
2. Thrombotic thrombocytopenic purpura hemolytic uremia syndrome (TTP-HUS)

*Sturge-Weber Syndrome***Overview**

Sturge-Weber syndrome, also called encephalotrigeminal angiomas, is a neurocutaneous disorder characterized by vascular lesions in the skin, eye, and brain.

General Characteristics

1. Facial port-wine stain (cutaneous nevus) in VI
2. Ipsilateral parietal-occipital leptomeningeal angioma

Genetics

1. Sporadic
2. Somatic mosaicism
3. Occurs in all ethnic groups; no gender preference

Clinical Manifestations

1. Cutaneous nevus
 - a. Usually involves the forehead and upper eyelid (VI distribution)
 - i. May involve the face bilaterally and extend to the trunk
 - ii. Trunk or V2 or V3 distribution lesions (without V1) rarely have intracranial lesion
 - iii. Rarely patients have intracranial lesion without skin manifestations
2. Bilateral cerebral lesions occur in 15% of patients with unilateral facial nevus
 - a. The extent of the nevus increases the risk of a bilateral intracranial lesion
 - b. Similar cutaneous lesions on the limb with hypertrophy comprise Klippel-Trénaunay-Weber syndrome
3. Ophthalmologic features
 - a. Glaucoma if the nevus is adjacent to the eyes
 - b. Newborns have buphthalmic amblyopia (rare)
 - i. Abnormal anterior chamber angle
4. Seizures and hemiparesis
 - a. Develop acutely during the first or second year; often triggered by a febrile illness
 - b. Early onset and refractoriness of seizures are correlated with cognitive deficits
5. Adult patients with Sturge-Weber syndrome: greater than 50% suffer contralateral motor deficits
6. Intracranial hemorrhage is rare
7. Seizures occur in:
 - a. 72–80% of patient with unilateral lesions and greater than 90% of those with bilateral lesions
 - i. Early seizures are focal (infantile spasm, myoclonic and atonic seizures also occur)
 - ii. Adults have complex partial seizures or focal motor seizures
8. Patients may develop stroke-like episodes without seizures suggestive of TIA
9. Occipital lobe involvement
 - a. Visual field deficits
 - b. Cognitive deficit occurs in approximately 50% of patients; particularly severe if there is bilateral involvement

Neuropathology

1. Parietal and occipital lobe involvement is greater than in the frontal lobe
2. Leptomeninges:
 - a. Thickened
 - b. Angiomatous vessels may obliterate the subarachnoid space
 - c. Tortuous deep draining veins
 - i. Thin walled
 - ii. May extend into the parenchyma
 - iii. Ipsilateral choroid plexus may be involved
 - iv. Hyalinization and subependymal proliferation occurs in some vessels
 - d. Cerebral atrophy adjacent to the angioma
 - i. Neural loss and gliosis which may extend into normal appearing tissue
 - ii. Gyriiform (“train track”) calcification is seen in outer cortical layers; calcium may be seen adjacent to blood vessels
 - e. Chronic venous stasis

Neuroimaging

1. Gyral calcification; bilateral calcification is common
2. Calcification more apparent with age; may be present at birth
3. Cerebral atrophy
4. Accelerated myelination in young patients
5. Hypoperfusion:
 - a. Impaired venous drainage
 - b. Several impaired regions demonstrate arterial perfusion deficits

PET

1. Decreased brain glucose utilization beyond the leptomeningeal lesion

SPECT

1. Decreased cerebral perfusion that may include areas with normal glucose uptake; often deficit is larger than that noted by MRI

Angiography

1. Rare arterial occlusion
2. Decreased number of superficial cortical veins; enlarged and tortuous draining veins
 - a. Failure of opacification of the ipsilateral sagittal sinus due to occluded cortical veins

*Von Hippel-Lindau Syndrome***Overview**

Von Hippel-Lindau disease is a rare, autosomal dominant multisystem disorder associated with hemorrhagic blastomas of the CNS, retinal angiomas as well as cysts and tumors of the viscera. The most common tumors are retinal and CNS hemangioblastomas, clear cell renal carcinoma, pheochromocytoma, pancreatic islet cell tumors and endolymphatic sac tumors.

General Characteristics

1. Autosomal dominant; 95% penetrance by age 60 with incomplete expression
 - a. Von Hippel-Lindau (vHL) suppressor gene on chromosome 3p25-26 is mutated
2. Development of benign and malignant tumors and cysts
 - a. Hemangioblastoma (HB) in the CNS
 - b. Retinal hemangioblastoma (RA)
 - c. Pheochromocytoma (Pheo)
 - d. Clear cell renal carcinomas (RCC)
 - e. Renal cysts
 - f. Pancreatic cystadenoma
 - g. Pancreatic neuroendocrine tumors
3. vHL protein mutations cause:
 - a. Decreased ubiquitination of hypoxia-inducible factor 1 α (HIF1 α)
 - b. Dysfunction of vascular endothelial growth factor in stromal cells
 - c. Upregulation of VEGFR1 and 2 in tumor endothelial cells
 - d. vHL protein regulates extracellular matrix formation and the ability of cells to exit the cell cycle
 - e. Major effect of vHL mutation:
 - i. Causes altered vHL protein and Elongin BC complex

Clinical Criteria for the Diagnosis of vHL Disease

1. Positive family history
2. Development of hemangioblastoma in the CNS, retinoblastomas, renal cell cancer, pheochromocytoma, pancreatic tumors or cysts
3. Patients who develop hemangioblastomas or retinal hemangioblastomas concomitant with renal cell carcinoma and the usual associated tumors
4. 80% of patients have a family history
 - a. Inter- and intrafamilial phenotypic variability
 - b. 20% are sporadic and require two manifestations: included requirements are CNS or retinal hemangioblastoma

Clinical Classification

1. vHL type I
 - a. No pheochromocytoma
2. vHL type II
 - a. Type 2A
 - i. Has pheochromocytoma
 - ii. Associated hemangioblastoma in the CNS
 - iii. No renal cell cancer
 - iv. Low risk of renal cell cancer and neuroendocrine pancreatic tumor
 - b. Type 2B
 - i. Has pheochromocytoma, renal cell cancer and other CNS tumors
 - ii. High risk of renal cell cancer and pancreatic endocrine tumor
 - c. Type 2C
 - i. Has only pheochromocytoma

Clinical Manifestations

1. Isolated hemangioblastoma present in early adulthood (20 to 40 years of age)
 - a. Type 1 (no pheochromocytoma) or type 2A in 70% of vHL patients
 - b. Males 1.5:1 females
 - c. Location:
 - i. Cerebellum (83–95%)
 - ii. Spinal cord (3.2–13%)
 - iii. Medulla (2%)
 - d. Multiple spinal hemangioblastoma occur
 - e. In 40%, hemangioblastoma may be first manifestation of disease
2. Posterior fossa signs and symptoms
3. High hemoglobin occurs from overproduction of erythropoietin from hypoxia inducible factor (HIF)
4. Hemangioblastomas from vHL disease are 5–30% of cerebellar hemangioblastomas and 10% of spinal hemangioblastomas
5. Asymptomatic vHL gene carriers are approximately 4%
6. Intracranial or intramedullary subarachnoid or intraparenchymal hemorrhage is low (less than 5%)
 - a. Tumors size (1.5 to 5 cm); the average size that bleed is 2.7 cm (larger than average HB)
 - b. Size of the tumor is associated with hemorrhage both spontaneous and following surgery
 - c. Subarachnoid hemorrhage occurs in a high percentage of patients that bleed
 - i. Superficial location of medullary HBs
 - ii. Cerebellar hemangioblastoma bleeds occur in the parenchyma
 - iii. Large solid hemangioblastoma have a higher risk of peri- and post-operative hemorrhage
7. Patients with complete deletion mutation of the vHL gene (as opposed to missense or protein-truncating mutations)
 - a. Better visual acuity
 - b. Decreased tumorigenesis incidence of hemangioblastomas
8. Higher levels of vascular endothelial growth factor VEGF, hypoxia-inducible factor (HIF) and ubiquitin have ocular hemangioblastomas

Neuropathology

1. Association with:
 - a. Visceral cysts of the kidney, pancreas and epididymis
 - b. Pheochromocytoma (type II, VHL)
 - c. Pancreatic neuroendocrine tumors
 - d. Endolymphatic carcinoma
 - e. Head and neck paraganglioma
2. Stroma:
 - a. Foamy vacuolated cells
 - b. Tumorlet dells (retinoblastoma) are poorly differentiated, small cells, prominent dark nuclei
3. Epithelial clear cell morphology
4. Increased expression (retinoblastoma) of erythropoietin (Epo); CD133; and the chemokine CXCR4

Neuroimaging

MRI

1. Should be of the entire neuraxis to rule out multiple hemangioma
2. Lesions are well circumscribed and are often associated with a cyst
3. Cystic lesions are hypointense on T1-weighted images and hyperintense on T2-weighted images
4. Minimal or no edema
5. Enhancement of a mural nodule with gadolinium
6. May have vascular flow voids (MRA)
7. Solid HB enhance homogeneously with gadolinium

Differential Diagnosis

Neuroradiologic Differential Diagnosis

1. Pilocytic astrocytoma (children; spreads through the brainstem)
2. Astrocytoma (solid or cystic)
3. Metastasis (usually surrounding edema)
4. AVM (appear similar to large solid hemangioblastoma)

Angiography of vHB

1. May demonstrate a large vascular peduncle
2. Early draining vein (AV shunting)
3. Absence of a cystic component suggests metastatic renal cell carcinoma

Cobb's Syndrome

Overview

Cobb's syndrome (cutaneous meningospinal angiomatosis) is a somatic disorder characterized by vascular abnormalities of the spinal cord with associated skin, muscle and dura involvement at the same metameric level.

General Characteristics

1. Cutaneous nevus
2. Associated vascular lesion at the same dermatologic level
3. Vascular skin, muscle, bone and dural involvement at the same somite

Clinical Manifestations

1. Large AVM may be associated with congestive heart failure
2. Compression, bleeding and deterioration of spinal cord function
3. May just have extradural and paraspinal components

Neuropathology

1. Progressive myelopathy
 - a. Venous congestion of an extradural nidus or fistula
 - b. May cause similar neurologic dysfunction as is seen with dural-based intradural lesions
 - c. Large epidural venous lakes

Neuroimaging

1. Type A – spinal extradural AVF

- a. Diffuse high signal intensity of the spinal cord on T2-weighted MR images
 - b. No mass effect
 - c. Primarily thoracolumbar and lumbar location
2. Type B – lesions
 - a. Normal signal intensity of the cord
 - b. Severe mass effect due to enlarged extradural venous plexus
 - c. Cervical and upper thoracic locations

Hereditary Hemorrhagic Telangiectasia (Osler-Weber-Rendu Disease)

Overview

Hereditary Hemorrhagic Telangiectasia (Osler-Weber-Rendu) is autosomal dominant, characteristic by epistaxis, cutaneous telangiectasia, visual and cerebral malformations. Epistaxis occurs in childhood, pulmonary AVMs at puberty, cutaneous and gastrointestinal telangiectasia in adulthood. Arteriovenous fistulas occur in childhood, small AVMs in adolescents and micro-AVMs in young adults.

General Characteristics

1. Autosomal dominant; high penetrance
2. Incidence of 1 in 5,000–8,000 persons
3. Telangiectasias are found:
 - a. Face
 - b. Nasal mucosa (nose bleeds)
 - c. Conjunctiva (30%)
 - d. Hands > legs and trunk
 - e. Anterior tongue
 - f. Retina (10%)
4. Telangiectasia – enlarge and multiply
5. Telangiectasia occur in internal organs
 - a. Lungs
 - b. GI tract
 - c. Genitourinary tract

International Diagnostic Criteria

1. Epistaxis
 - a. Spontaneous
 - b. Recurrent
2. Multiple telangiectosis
 - a. Lips, oral cavity, fingers, nose
3. Visceral lesions
 - a. Gastro-intestinal telangiectosis
 - b. Pulmonary arteriovenous malformation; hepatic, cerebral and spinal AVM
4. Family history of first degree relative involvement
5. Clinical manifestations develop with age
6. Epistaxis in childhood, pulmonary AVM from puberty, microcutaneous and gastrointestinal telangiectosis in adulthood
7. Approximately 2/3 of patients have some sign of HHT by 16 and 90% by 40 years of age
8. Neurologic symptoms occur in approximately 10–20% of patients

Genetics

1. Autosomal dominant; 2 genes described:
 - a. Endoglin – chromosome 9q24(CD105)
 - b. Activin – chromosome 12q HTT2
 - i. Proteins expressed are found in vascular endothelial cells
2. No definite relationship between the type of mutation and the phenotype of the disease
3. Protein levels from the mutated genes suggest haploinsufficiency
4. Endoglin and Activin receptor-like kinase 1(ALK1) involved in:
 - a. Transforming growth factor signaling pathway
 - b. Cell development
 - c. Vascular remodeling by control of the production of the extracellular matrix
 - d. Endoglin and ALK1 influence angiogenesis by binding with transforming growth factor β proteins
5. Some patients have HTT-juvenile polyposis overlap syndrome
6. HTT3 subgroup:
 - a. Chromosome 5 locus; SMAD-4
 - b. Prominent pulmonary involvement

Clinical Manifestations

1. Nasal and mucocutaneous telangiectosis
 - a. Epistaxis from nasal mucosa is the first complaint in about 50% of patients
 - i. Common in childhood
 - ii. Recurrent in 50 to 80% of patients
2. Skin telangiectasia
 - a. Later in life
 - b. Located on the face, lips, tongue, palate and finger tips
 - c. Size and number increase with age
3. Gastrointestinal telangiectasia
 - a. Recurrent hemorrhages occur in about 30% of patients usually starting in the fifth to sixth decade
 - b. Telangiectasia more prominent in stomach and duodenum than colon
 - i. Rarely AVM or aneurysms
 - c. Rare liver AVMs
 - i. Multiple AVMs may cause portal hypertension and biliary disease
 - ii. Cardiac failure from right to left shunt
 - iii. Hepatic encephalopathy (rare)

Pulmonary AVM (PAVM)

1. Occurs in 5–20% of the 5HTT 3 subgroups
2. About 70% of all PAVMs occur in 5HTT patients
3. Location is primarily in the lower lobes
 - a. Enlarge with age and become symptomatic during the third or fourth decade
4. Associated with:
 - a. Decreased arterial oxygen saturation (right to left shunt)

- b. Fatigue, dyspnea and cyanosis
 - c. Hemoptysis and hemothorax
 - d. Polycythemia
 - e. Clubbing and cyanosis
 - f. Platypnea-orthodeoxia (improved breathing with supine position; hypoxemia in sitting position)
5. Differential diagnosis of pathologic arteriovenous defects:
 - a. Patent ductus arteriosus
 - b. PFO
 - c. Right to left congenital heart defect
 - d. PAVM

Neurologic Features of PAVM

1. Occur at all ages; peak incidence is in 3rd–4th decade
2. Primary mechanisms:
 - a. PAVM (60%)
 - b. Brain vascular malformations (28%)
 - c. Spinal cord malformations (8%)
 - d. Hepatic encephalopathy (3%)
3. Neurologic complications from PAVM
 - a. Bland emboli to cerebral circulation
 - b. Septic emboli associated with SBE that cause cerebral abscess, meningitis and mycotic aneurysms
 - c. Cerebral abscess most frequently a septic complication:
 - i. Usually solitary
 - ii. Supratentorial (MCA territory most frequent)
 - iii. Incidence 3–5%; much higher if there is a recurrence
 - d. Embolic patterns:
 - i. Paradoxical from peripheral sources such as DVT
 - ii. In a large ectatic PAVM a clot may develop in the wall of the malformation
 - iii. MCA territory most often affected (40 to 50% of CBF)
 - iv. Rarely CNS embolism is the initial symptom
 - v. Overall risk of emboli is related to the number of PAVMs
 1. Single PAVM infarction occurs in about 30%
 2. 60% of them are multiple PAVMs
 - vi. Other mechanisms of cerebral ischemia:
 1. Hyperviscosity from polycythemia
 2. An embolism

Differential Diagnosis of PAVM

1. Hepatopulmonary syndrome
2. Mitral stenosis
3. Trauma
4. Actinomycosis
5. Schistosomiasis
6. Metastatic thyroid cancer
7. Fanconi syndrome
8. Surgery in congenital heart case
9. Bronchiectasis
10. Venous atresia

Hemorrhagic CNS Complications

1. About 30% of HTT patients suffer hemorrhages from cerebral or spinal vascular malformation
2. Prevalence of cerebrovascular malformations by MRI is about 20%
 - a. Large malformations bleed at a rate of 1.4–2% per year
3. Symptoms from malformations also occur due to
 - a. Thrombosis of the venous pouch
 - b. Venous ischemia
 - c. Rarely SAH from AVF or arterial aneurysm
4. Spinal malformations (AVFs):
 - a. Often large
 - b. High risk of hemorrhage
 - i. Progressive para or tetraparesis the usual premonitory sign

Neuropathology

1. Telangiectosis is the most prominent lesion:
 - a. Focal dilatations of post-capillary venules
 - b. Some perivascular lymphocytic infiltration
 - c. Enlargement of telangiectasias associated with excessive layers of smooth muscle without elastic fibers
 - d. Connecting arterioles dilate and connect to venules by-passing a capillary bed
2. Associated arteriovenous malformation and arteriovenous fistula
 - a. Most often responsible for neurologic sequelae
 - b. Largest arteriovenous malformations occurs in the lungs, liver and CNS
 - c. Rare aneurysm
 - d. Multiple types of malformations may occur concomitantly
3. Three different malformations occur:
 - a. Large fistula
 - i. Direct arteriovenous shunt
 - ii. No nidus
 - iii. Ectatic draining vein
 - b. Small AVMs (1–3 cm)
 - i. Nidus
 - c. Micro-AVMs
 - i. Nidus smaller than 1 cm
4. Malformations most often are near the surface of the CNS
5. Venules are the initial component of the pathologic process
6. PAVM may enlarge during pregnancy (increased hemorrhagic risk)

Neuroimaging

1. Cerebral and spinal AVM's (16%)
2. No evidence of different features of AVMs among different genetic groups
3. Multiple brain AVMs (23%)
4. AVMs are of small size and tend to be cortical
5. Associated arteriovenous malformation and arteriovenous fistula
 - a. Most often responsible for neurologic sequelae

- b. Largest arteriovenous malformations occurs in the lungs, liver and CNS
- c. Rare aneurysm
- d. Multiple types of malformations may occur concomitantly

*Bing-Neel Syndrome**General Characteristics*

1. Increased blood viscosity with decreased or slowed cerebral laminar flow
2. Hematocrit greater than 67
3. Hemoglobin at 18–22 grams/ml
4. Bleeding from the gums
5. Dilated tortuous retinal veins
 - a. Box car phenomena (pressure on the globe with clumping of RBC's in the central retinal veins)
6. Petechiae of the lower extremities
7. Associated with:
 - a. IgM > IgG monoclonal gammopathy
 - b. Waldenström's macroglobulinemia

Neurological Manifestations

1. Encephalopathy
 - a. Poor cerebral perfusion
 - b. Cerebral small vessel ischemia

*Köhlmeier-Degos Disease**Overview*

Köhlmeier-Degos disease (Malignant Atrophic Papulosis) is a thrombo-obliterative vasculopathy characterized by papular skin lesions with a central porcelain-white atrophy and a surrounding telangiectatic rim. Clinical manifestations include skin lesions and multiple limited infarcts of the intestine, CNS, lungs (pleuritic and/or pericarditis) and the eyes. The benign form only affects the skin.

General Characteristics

1. Two distinct forms
 - a. Systemic form with G.I and CNS involvement
 - b. Cutaneous benign variant
2. Most common in Caucasians
3. Age of onset 3 weeks to 67 years

*Clinical Manifestations**Systemic Signs*

1. Any organ can be involved from multifocal infarctions
2. Cutaneous signs usually precede visceral involvement
3. Multiple lesions
4. Involve the trunk and upper limbs (skin lesions)
5. Red macules that evolve to a porcelain white necrotic scaly center with an erythematous border
6. Differential diagnosis includes
 - a. SLE
 - b. Dermatomyositis
 - c. Atrophic blanche
 - d. Allergic necrotizing vasculitis

Gastrointestinal Tract

1. Microvascular infarction of the intestines with perforation and peritonitis
2. Abdominal symptoms often start after the appearance of skin lesions
3. Lesions also occur in the esophagus, duodenum, stomach, colon and rectum

Major Organ Involvement

1. Infarctions of the heart, pericardium, kidneys, bladder, lungs, liver and pancreas occur – often asymptomatic

Neurological Signs

1. CNS involvement occurs in about 20% of patients
2. May precede the skin lesions by years (mean is 2 years)

CNS Signs

1. Cranial nerve deficits
2. Cognitive decline
3. Ophthalmoplegia
4. Focal motor and sensory deficits
5. Multifocal infarction and hemorrhage
6. SAH (rare)
7. Demyelinating peripheral neuropathy (rare)
8. Polyradiculopathy (rare)

Neuropathology

1. Non-inflammatory occlusive endarteriopathy
 - a. Primarily of arterioles
 - b. Endothelial proliferation with superimposed thrombosis
 - c. Media is spared
2. Leptomeningeal, cranial nerve, spinal root and posterior lateral spinal cord infarction occurs
3. Extracutaneous organs demonstrate a fibromucinous occlusive arteriopathy
4. Evidence of high expression of interferon α (a type 1 interferon-inducible protein)
5. Endothelial tubuloreticular inclusions
6. MXA tissue expression with C5b-9 deposition
7. A distinct vascular injury
 - a. Dysregulated interferon α response
 - b. Membranolytic attack complex deposition

*Neuroimaging**Angiography*

1. Occlusions and beading of arteries
2. Distal branches of intracranial vessels are affected

MRI

1. Infarction and intraparenchymal hemorrhages in different territories

*Erdheim-Gsell Disease**Overview*

Erdheim-Gsell disease, also known as medial cystic necrosis, is defined by non-inflammatory smooth muscle cell loss, frag-

mentation of elastic fibers, and accumulation of basophilic ground substance within cell-depleted areas of the medial layers of the vessel wall.

General Characteristics

1. Associated with bicuspid aortic valve and aortic root dilatation
2. Cystic medial necrosis prevalent in congenital heart disease with dilated aortic root
3. Transcriptional regulator NOTCH 1 gene on chromosome 9q3y.3 linked to non-syndromic associated bicuspid aortic valves
4. Possible spontaneous arterial dissection

Neuropathology

1. Necrosis of smooth muscle of the lamina media

*May-Thurner Disease**Overview*

May-Thurner syndrome comprises left lower extremity swelling secondary to left iliac vein compression. This anatomic abnormality can predispose patients to increased risk of paradoxical embolism and stroke.

General Characteristics

1. The left iliac vein compresses the right iliac artery at the level of the fifth lumbar vertebrae
2. Left lower extremity edema pain, varicosities and deep venous thrombosis
3. Source of paradoxical emboli is from right to left cardiac shunt
4. Typically presents in the second to fourth decades of life; more common in women than men (3:1)

Clinical Manifestations

1. Possible paradoxical embolism to the basilar apex
2. Possible increased risk of paradoxical emboli
3. Deep vein thrombosis

Neuropathology

1. Compression of the left common iliac vein
 - a. Risk factor for lower-extremity deep vein thrombosis

Neuroimaging

1. Stenosis of the left common iliac vein
2. Normal LCIV diameter in 6.5 mm
3. 4 mm in those with DVT (LCIV)
4. The odds of left DVT increased by a factor of 1.68 for each millimeter decrease in LCIV

*Progeria**General Characteristics*

1. Characterized by premature aging
2. Childhood form: Hutchinson-Gilford progeria syndrome
3. Adult Progeria: Werner's syndrome

4. Several progeria-like syndromes have been defined genetically and clinically
5. Genetics of progeria and progeroid syndromes
 - a. Progeria is caused by mutation of the LMNA gene on chromosome 1q
 - i. Encodes lamins A and C (filamentous structural protein of the nuclear lamina)
 - ii. Exon II mutation responsible for 80% of progeria patients
 1. The mutation causes the accumulation of progerin (farnesylated prelamin protein A) that interferes with nuclear membrane function
 2. Most often paternally imprinted
 3. Also autosomal recessive, germline and somatic mosaicism mutations cause a phenotypic spectrum of disease
 - iii. Werner syndrome gene
 1. Short arms of chromosome 8
 2. Encodes a DNA helicase
 - iv. Incidence is about 1 in 4 million persons

Clinical Manifestations

1. Some patients have scleroderma-like abdominal skin at birth
2. Poor weight gain prominent veins over the scalp, alopecia by adolescence
3. Facial dysmorphism
4. Deficient subcutaneous fat and lax skin
5. Delayed or absent sexual maturation
6. Bone and joint destruction
7. Premature vascular disease
8. Most patients succumb in the second decade; some survive to middle age

Neurological Manifestations

1. Atherosclerotic stroke of both anterior and posterior circulations
2. Cerebral aneurysms

Neuropathology

Cerebrovascular Disease

1. Occlusive infarctions of the cervical carotid and vertebral arteries
2. Perforating artery disease
3. Intracranial large artery disease
4. WMH from arteriole and capillary involvement

Neuroimaging

MRI

1. MRI demonstrates infarctions of:
 - a. Pial vessels
 - b. Arterioles
 - c. Watershed territories
 - d. Lacunar
 - e. Large arteries
 - f. Silent infarcts in 60% of patients

Angiography

- a. Calcified cervical and internal carotid arteries
- b. Stenosis of intra/extracranial vessels
- c. Distal stenosis VA stenosis

Werner's Syndrome (Adult Onset Progeria)

General Characteristics

1. Autosomal recessive; DNA Rec Q helicase/exonuclease (WRN)
2. Encodes a DNA helicase (chromosome 8p 12)
 - a. Induces wide range of premature aging phenotypes
 - b. Abnormal pattern of tumors
 - c. Mutation causes dysfunction of telomeres
 - d. Dysfunction of telomeres activates the TP53 gene which:
 - i. Suppresses cell growth and shortens cellular life span
 - ii. Decrease mitochondrial biogenesis
 - iii. Increases reactive oxygen species that causes multiple aging phenotypes
 - iv. Telomere dysfunction is correlated with tumorigenesis

Clinical Manifestations

1. Premature hair graying and hair loss
 - a. Alopecia starts age 2–3 years
2. Dysmorphic features:
 - a. Receding mandible
 - b. Beaked nose
3. Dermal atrophy:
 - a. Atrophic hyperkeratotic skin over the hands and feet
 - b. Scleroderma-like skin
4. Atrophic appendicular muscle
5. Loss of subcutaneous fat
6. Cardiovascular disease
7. Cancer predilection
8. Progeria, xeroderma pigmentosum and Cockayne's syndrome (as well as Werner syndrome):
 - a. Segmental progeria
 - b. Demonstrates some, but not all aspects of aging
9. Absence of a growth spurt at puberty
10. Type II diabetes mellitus
11. Voice changes (hoarse/high pitched)
12. Colorectal, skin, thyroid, pancreatic and soft tissue sarcoma have an increased risk
13. Hypogonadism
14. Posterior cortical, bilateral cataracts
15. Liver dysfunction
16. Appear 20–30 years older than stated age
17. Osteoporosis
18. Clavicular hypoplasia, acro-osteolysis of distal phalanges
19. Macular degeneration

Cardiovascular Manifestations

1. Accelerated atherosclerosis

- a. Calcification of the aorta and great vessels
- b. Calcification of the mitral and aortic valve

Neuropathology

1. Dramatically accelerated cardiovascular disease similar to CVD of aging (atherosclerotic disease):
 - a. Affects the cervical carotid and vertebral arteries
 - b. Intracranial large artery disease
 - c. Perforating artery disease of the basal ganglia and white matter
2. Vessels exhibit prominent adventitial fibrosis
3. Progerin found in blood vessels at higher rate than controls
4. Down-regulation of mitochondrial oxidative phosphorylation

Cardiovascular Pathology

1. Increased arterial wall density as measured by carotid duplex in the intima-media and adventia
2. Generalized atherosclerotic lesions with stenosis and plaque formation in coronary and cerebral arteries
3. Valvular heart calcification
 - a. Calcification of the aorta and great vessels
 - b. Calcification of mitral and aortic valves
4. Pulmonary arterial lesions
5. Strokes in all topographical distributions; silent infarcts
6. Cardiac death more common than stroke related death

Cerebrovascular Pathology

1. Intracranial steno-occlusive arterial lesions
2. Basal cistern collateral vessels

Related Syndromes

1. Mandibuloacral dysplasia
2. Wiedemann-Rautenstrauch syndrome

Neuroimaging

Arteriography

1. Intracranial steno occlusive arterial lesions
2. Basal cistern collateral vessels

MRI

1. Infarction by MRI in 60% of patients (approximately 50% were silent)

Binswanger's Disease

General Characteristics

1. A small vessel vascular dementia caused by extensive white matter damage

Clinical Manifestations

1. Loss of memory and executive function that presents in the 5th and 6th decade

Neuropathology

1. Irregular loss of axons and myelin associated with widespread gliosis

2. Arterioles of the subcortical white matter are more involved than capillaries

Neuroimaging

1. Severe leukoaraiosis with occipital predominance
2. Increase diffusion in the periventricular and deep white matter

Wyburn-Mason Syndrome

General Characteristics

1. Wyburn-Mason syndrome (Bonnet-Dechaume-Blanc syndrome) is a phakomatosis associated with congenital retinal orbital and brainstem arteriovenous malformations; rarely facial vascular malformations

Clinical Manifestations

1. Retinal AVM: rare loss of visual acuity from orbital cranial AVM
2. Primarily midbrain AVM with focal findings after hemorrhage

Thrombotic Thrombocytopenic Purpura

Overview

Thrombotic Thrombocytopenic Purpura (Moschowitz's disease) is a thrombotic microangiopathy causing damage to many organs including the kidneys, heart and brain. Most cases of TTP arise from inhibition of the enzyme ADAMTS13, a metalloprotease responsible for cleaving large multimers of von Willebrand factor (vWF) into smaller units.

General Characteristics

1. Incidence of 3.8–6.5 patients per million individuals
2. Incidence associated with ADAMTS-13 (von Willebrand cleaving protease) deficiency in approximately 1/7 patients per million individuals
3. Sex ratio of 3:1 females to males
 - a. Possible increased incidence in those of Afro-Caribbean origin

Clinical Manifestations

1. Onset is usually between the ages of 20–40 years
2. Three presentations:
 - a. A single episode with recovery with no recurrence
 - b. Intermittent episodes with rare relapses and normal hematologic evaluation between attacks
 - c. Chronic relapsing form with continuing hematologic abnormalities
 - d. Intermittent and persistent forms predominate in childhood
3. The classic form presents with:
 - a. Microangiopathic hemolytic anemia
 - b. Thrombocytopenia
 - c. Neurologic signs and symptoms
 - d. Fever
 - e. Renal alterations
 - f. Occurs in 20 to 40% of patients

Neurologic Manifestations

1. One third of patients do not have neurologic signs and symptoms at onset. Almost all have neurologic impairment during the course of the illness
2. Neurologic manifestations include:
 - a. Headache
 - b. Dizziness
 - c. Behavioral changes
 - d. Altered level of consciousness
 - e. Focal and generalized seizures
 - f. Focal cortical neurologic signs
 - g. Fluctuating neurological signs
3. Systemic manifestations include:
 - a. Hematuria and oliguria that may progress to renal failure
 - b. Purpura, petechiae and ecchymosis occur in approximately 1/3 of patients
 - c. Retinal hemorrhages
 - d. Epistaxis
 - e. Gingival, vaginal and gastrointestinal bleeding
4. Atypical presentation:
 - a. Acute abdominal pain
 - b. Pancreatic involvement
 - c. Peripheral digit ischemia

Neuropathology

1. Thrombosis of the microvessels of both gray and white matter
 - a. Cortical and subcortical infarction
2. Branch occlusions of the MCAs and PCAs; rarely the entire MCA artery is infarcted
3. Rarely ischemia is restricted to the brainstem or cerebellum
4. Rare supratentorial or brainstem hemorrhages are seen
5. ADAMTS-13
 - a. A metalloprotease and:
 - i. Disintegrin with a thrombospondin type I motif
 - ii. Deficient in the plasma with acute and relapsing TTP
 - iii. A failure of proteolysis of hyper adhesive and ultra large von Willebrand factor multimers in terminal arterioles and capillaries that cause:
 1. Adhesion and aggregation of platelets under high-flow, high-shear stress
 2. Platelet clumping and microvascular thrombosis in arterioles and capillaries but spare veins
6. Two types of TTP
 - a. Autoimmune type from antibodies that inhibit ADAMTS-13
 - b. Hereditary form from mutations of ADAMTS-13; chromosome 9q34
7. Most TTP adult patients:
 - a. Present with severe (<5% of ADAMTS-13 activity in the plasma) or moderate deficiency
 - i. These abnormalities have been seen in association with neutralizing IgG and IgM antibodies

8. Secondary TTP may occur with:

- a. Drugs
- b. Pregnancy
- c. Organ transplantation
- d. Infections
- e. Autoimmune diseases
- f. Cancer

*Neuroimaging**MRI*

1. Cerebral edema predominately in white matter more than gray
2. PRES appearance when lesions are predominate in the posterior parietal and occipital lobes
3. Increased or normal signal in ADC maps
4. Increased signal with t2-weighted and FLAIR sequences (in affected cortical and subcortical areas)
5. Large and small infarctions throughout the brain
6. Rarely petechial brainstem or supratentorial hemorrhages are noted

Laboratory Evaluation

1. Coomb-negative hemolytic anemia
2. Severe thrombocytopenia
 - a. Platelet count <20,000 mm³
3. Red blood cell fragmentation on peripheral blood smear
 - a. Anisocytes
 - b. Poikilocytes
 - c. Schistocytes
4. Increased lactic dehydrogenase levels in the serum
5. In approximately 50% of TTP patients creatinine and blood urea nitrogen are elevated
6. Gingival biopsy:
 - a. Hyaline thrombi in 50% of patients

*Kawasaki Disease**Overview*

Kawasaki disease is a self-limited, necrotizing pan vasculitis that affects all vessels but primarily the coronary arteries.

Clinical Manifestations

1. Systemic panvasculitis of medium-sized blood vessels
2. Cerebrovascular disease includes ischemic stroke, Moyamoya disease and subdural hemorrhage
3. Coronary artery but no cerebral aneurysms

Systemic Manifestations

1. Fever, conjunctivitis erythematous lesions of the palms and soles, painful swelling of extremities and acute cervical adenopathy. Coronary artery aneurysms are noted

*Sweet's Syndrome**Overview*

Sweet's syndrome is an acute febrile neutrophil dermatosis. It is characterized by tender red inflammatory nodules and occurs with infection, malignancy, connective tissue disease and drug exposure.

General Characteristics

1. Etiology:
 - a. Idiopathic
 - b. Para-inflammatory
 - c. Drug exposure related
 - d. Pregnancy related
2. Granulocytic growth factor appears pivotal
3. Mucosal Sweet's syndrome suggests an underlying malignancy
4. Cerebrovascular manifestations are rare and include vasculitis-like small vessel involvement. Cytokines have an etiologic role

Vasculopathy**Overview**

The term vasculopathy as used for this section denotes an abnormality of the vascular wall that predisposes to occlusion, emboli, hemorrhage or compression of neighboring structures. They most frequently occur in younger patients and are a significant component of the differential diagnosis of stroke in the young. The following is a description of the major vasculopathies and their differential diagnosis.

Differential Diagnosis of Vasculopathy

1. Antiphospholipid syndrome
2. Recanalization of atherosclerotic emboli
3. Fibromuscular dysplasia
4. Thrombotic thrombocytopenia purpura
5. Sarcoid
6. Neurofibromatosis 1
7. Tuberous sclerosis
8. SLE
9. X-RT (irradiation treatment)
10. Pseudoxanthomata elastica (PXE)
11. Marfan's disease
12. Medial cystic necrosis
13. Cerebral arterial ectasia and dolichoectasia
14. Congophilic amyloid angiography
15. PHACES
16. VZV
17. Sickle Cell disease

Cerebral Amyloid Angiopathy (Congophilic Angiopathy)**General Characteristics**

1. Increase of E2/E4 alleles
2. Amyloid AB 39–43 amino acids
 - a. Usual vascular amyloid 39–40 aa
3. Younger at first hemorrhage
4. Rare association with isolated cerebral angiitis

Genetics

1. Groups Affected:

- a. Hereditary cerebral amyloidosis (Dutch); Icelandic
- b. Chromosome 21 p11
- c. APP gene (amyloid precursor protein) gene
- d. Clinical manifestations:
 - i. Ocular vessels involved
 - ii. Leptomeningeal deposits of amyloid
 - iii. Lobar hemorrhages
- e. Icelandic
 - i. Cystatin C gene (chromosome 21 p11)

Clinical Manifestations

1. Cerebral hemorrhages
 - a. Multiple
 - b. Superficial
 - c. Subcortical lobar
 - d. Recurrent
2. Rare TIA
3. Multiple infarcts
4. SAH
5. Leukoencephalopathy
 - a. Concomitant multiple infarcts
 - b. Clinically similar to Binswanger microangiopathy
6. Dementing illness from:
 - a. Concomitant multiple infarcts
 - b. Alzheimer's pathology

Imaging Evaluation

1. Gradient ECHO MRI
 - a. Demonstrates old hemorrhages (residual hemosiderin)

Recanalization of Embolus with Thrombus

1. Embolus:
 - a. Fragments and moves distally
 - b. Movement occurs most often in the first 48 hours
2. Recanalization of a thrombosed intracranial artery:
 - a. Evident by 14–21 days
 - b. Irregular vascular wall of the affected vessel

System Lupus Erythematosus**General Features**

1. Cardiac:
 - a. Luminal narrowing from:
 - i. Sub-endothelia accumulation of immunoglobulins and complement components
 - ii. Activated platelets
 1. Express adhesion molecules that interact with endothelial cells and leukocytes
 - iii. Small arteries and arterioles are primarily affected
 - b. Chilblain Lupus:
 - i. Cutaneous lupus; bluish-red infiltrate in acral body locations
 - ii. Affects middle aged women primarily
 - iii. Mutation in the TREX 1 gene that encodes:
 1. 3–5 repair exonuclease 1

- iv. 20% develop systemic SLE
- v. Associated cerebral vasculopathy with ischemic stroke

Sickle Cell Disease (SCD)

General Features

1. SCD in adults
 - a. Thrombin antithrombin complexes (TAT) and D-dimer are correlated with a history of stroke and retinopathy
 - b. Chronic vasculopathy in adults is correlated with:
 - i. Stroke
 - ii. Silent infarcts
 - iii. Ischemic lesions in white matter and basal ganglia
 - c. Lung vasculopathy associated
 - d. Significant increase of thrombin generation and fibrin degradation products
2. Transcranial Doppler Evaluation
 - a. <170 cm/sec decreased risk
 - b. >200 cm/sec increased risk of stroke
3. Remodeling of the arterial wall leading to stenosis and occlusion of primarily small > large vessels

Varicella Zoster Viruses (VZV)

General Features

1. Early VZV infected arteries contain
 - a. CD4+ and CD8+ T-cells
 - b. Macrophages
 - c. Rare: B-cells and neutrophils
2. Perivascular inflammatory cells underlie areas of thickened intima (suggestive that soluble factors are released)
 - a. Infection is initiated in the adventitia
 - b. Hypertrophic intima is composed of cells expressing smooth muscle actin
 - c. Decreased smooth muscle cells
3. Late VZV Infection:
 - a. Viral antigens, but not leukocytes (no inflammation) in the media
4. Ischemic Strokes are predominant with approximately 18% being multifocal
 - a. Usually in the carotid artery 2 weeks following the rash in V₁
 - b. Some hemorrhagic multifocal strokes

Posterior Fossa Malformations, Hemangiomas, Arterial Malformations, Cardiac Defects, Eye Abnormalities and Sternal Cleft Syndrome (PHACES Syndrome)

General Features

1. A significant number of children with a facial hemangioma have PHACES syndrome
2. Posterior fossa malformations
3. Facial hemangiomas
4. Arterial cerebrovascular malformations
5. Cardiovascular anomalies

6. Eye abnormalities
7. Sternal clefting or supraumbilical raphe
8. Rare that all features occur in one patient
9. Abnormal neural crest migration is the putative cause
10. Female to male predilection of 9:1
11. A childhood disease but does occur in adults
 - a. ischemic stroke usually occurs prior to one year of age

Neuropathology

Cerebrovascular Features

1. Dysplasia of large cerebral arteries
2. Arterial stenosis or occlusion with or without Moyamoya collaterals
3. Absence or moderate to severe hypoplasia of the large cerebral arteries
4. Persistence of embryonic arteries and arrest of normal vasculature development
5. Vascular abnormalities often are ipsilateral to the cutaneous hemangiomas; may be bilateral

Categories of Arterial Anomalies

1. Dysplasia
2. Narrowing
3. Aberrant course or origin
4. Persistence of embryonic anastomosis
5. Progressive vasculopathy
 - a. Putatively related to the proliferative phase of hemangioma evolution

Imaging Evaluation

1. Agenesis of cervical carotid arteries
2. Persistent embryological vessels
3. Arterial stenosis
4. Dolichoectasia of intracranial arteries

Erdheim-Gesell Disease (Medial Cystic Necrosis)

General Characteristics

1. Medial cystic necrosis

Clinical Features

1. Spontaneous arterial dissection

Pathology

1. Necrosis of smooth muscle of the lamina media

Fibromuscular Dysplasia (FMD)

General Characteristics

1. Affects systemic arteries:
 - a. Renal arteries are affected with consequent hypertension
2. May involve the entire arterial wall
3. Incidence of 6% in selected arteriograms
4. Most common in middle aged women
5. Bilateral ICA involved in 86% of patients

6. Spares the carotid bifurcation:
 - a. Most common in the pharyngeal carotid artery
 - b. Spares the in the intracranial carotid artery
7. 20% of patients have concomitant extracranial vertebral artery involvement (ECVA)
8. The media is most often involved
 - a. Constricting bands (MRA; arteriogram)
 - b. Proliferation of smooth muscle cells that alternate with media thinning and disruption of the elastic membrane
 - c. Hypertrophy of fibrous tissue leads to focal stenosis
 - d. Band-like diaphragms within enlarged carotid bulb (mega bulbs)
 - i. Embolic source
 - e. Affects medium-sized muscular intracranial arteries
9. Associations:
 - a. Aneurysms of intracranial arteries
 - b. Arterial dissections

Clinical Features

Neurological Manifestations of FMD

1. TIA
2. Embolus
3. Stroke
4. Dissection
5. Horner's syndrome
6. Headache
7. Syncope
8. Intracranial hemorrhage
 - a. Renal hypertension
9. Neurological complications of dissection
10. Stroke recurrence is rare
11. Internal carotid involvement
 - a. Periorbital pain

Neurofibromatosis Type I

General Characteristics

1. Vasculopathy in the setting of other general manifestations of the disease
2. May also overlap with tuberous sclerosis that also demonstrates arteriopathy
3. Dilated vascular wall
4. Rarely causes stroke

X-Ray Therapy (X-RT)

General Characteristics

1. Occurs following >3000 rads delivered to the arterial wall
2. Carotid artery involvement most frequent after the irradiation of:
 - i. Pharyngeal tumors
 - ii. Hodgkin's and other lymphomas
 - iii. Little soft tissue mass to protect the artery in the neck
3. Characteristics of bifurcation atherosclerosis
4. Arterial calcification

Clinical Features

1. TIA in the carotid and MCA territory
2. Stroke in similar distributions from
 - a. Embolic
 - b. Thrombotic
 - c. Distal field ischemia

Pathology

1. Long segments of arteries are involved; frequently calcify
2. Dose dependent endothelial apoptosis
3. Vascular rarefaction
4. Disruption of the BBB
5. Thickening of vascular basement membranes

Tuberous Sclerosis Complex (TSC)

General Features

1. Arteriopathy is usually asymptomatic
2. May overlap syndromically with NF Type I
 - a. Gaps in the internal elastic membrane
 - b. Decrease in the muscularis layer
 - c. Fibrotic arterial segments
 - d. Elastic tumor degeneration

Clinical Features

Cerebrovascular Manifestations

1. Ischemic changes in territory of the affected vessels
2. Emboli from thrombi in ectatic aneurysms
3. SAH (rare) from ruptured aneurysms
4. Dolichoectasia

Cerebral Arterial Ectasia

General Characteristics

1. May be seen in children
2. Often involves several arteries
3. Familial tendencies noted:
 - a. One family with alpha-glucosidase deficiency
4. If severe the condition is known as dolichoectasia
5. Most frequent location:
 - a. Posterior fossa
 - b. Basilar and vertebral artery
 - c. Middle cerebral artery
 - d. Both anterior and posterior circulations may be involved concomitantly

Clinical Features

1. Spasticity (ventral pontine compression)
2. Dysarthria (XIIth nerve compression)
3. Hydrocephalus (pressure on the IIIrd ventricle); obliterates the prepontine cistern
4. Ischemia in the distribution of the affected arteries:
 - a. Emboli from thrombi in ectatic aneurysms
 - b. Plaque or clot obstruction in penetrating arteries
 - c. Rare rupture of aneurysms with SAH
 - d. Distortion and elongation of arteries cause reduced blood flow

Pathology

1. Gaps in the internal elastic lamina
2. Decrease in the muscularis layer
3. Fibrotic arterial segments
4. Elastic tissue degeneration and increase in the vasa vasorum

Imaging Evaluation

1. CT, MRA > MRI are diagnostic
 - a. Reveals dilated, enlarged tortuous vessels
2. Transcranial Doppler Evaluation:
 - a. Reduced mean-flow velocities
 - b. Preserved peak-flow velocities
 - c. Reduced antegrade flow
 - i. To and fro movement within the dilated vessel

Familial Occipital Calcification*General Characteristics*

1. Late onset of dementia
2. Patchy leukoencephalopathy
3. Intracerebral hemorrhages
4. Bilateral occipital calcifications
5. External carotid artery dysplasia

Clinical Features

1. Late onset dementia
2. Intracerebral hemorrhage
3. Probable AD inheritance
4. Ischemic stroke

Pathology

1. Skin biopsy:
 - a. Multilayered round shaped calcifications in the basal lamina of capillaries
 - b. Capillary vasculopathy

Imaging Evaluation

1. Fine tram tracking bilateral occipital calcifications
2. Severe leukoencephalopathy
3. Bilateral external carotid dysplasia

Oculo Meningeal Amyloid*General Features*

1. Primary uveal veil (vitreous)
2. SAH with secondary vasospasm and stroke
3. Thickened dura
4. Acquired factor V deficiency

Vasoconstriction Syndromes and Stroke**Migraine/Pre-Eclampsia/Eclampsia/RVCS***Overview*

Migraine headache and vasoconstriction following subarachnoid hemorrhage are the two most common causes of cere-

bral artery vasoconstriction and consequent stroke. During migraine headache there may be demonstrated arteriographic vasoconstriction, a reduced cerebral blood flow and increased velocity measurement by TCD. 18F-2-deoxy-D-glucose (18FDG) PET studies have also demonstrated a spreading posterior to anterior oligemia often preceding change in blood vessel diameter. This spreading cortical depression of metabolic activity with consequent lessened production of H^+ from decreased production of lactic acid may also cause vasoconstriction. The DRASIC receptor (along with other vasoactive agents) on cerebral blood vessels interacts with H^+ to dilate the vessel. This autoregulation with a match between the local cerebral metabolic rates for glucose (LCMRglu) and the local cerebral blood flow (LCBF) may determine the caliber of cerebral blood vessels during migraine attacks. The locus coeruleus (norepinephrine) may contract proximal cerebral blood vessels whereas out flow from the superior nucleus salivatorius may dilate cerebral blood vessels during a migraine attack. The relationship between spreading depression and cerebral blood flow has not been fully elucidated. Migraine has been associated with severe intense vasoconstriction with infarction. Vasoconstriction in migraine may be associated with ICH and arterial dissection.

Reversible cerebral segmental vasoconstriction usually affects young women following delivery, but may also occur during menopause. It may occur after carotid endarterectomy and involves large, medium and small vessels. There are focal regions of vasodilation and vasoconstriction.

Vasoconstriction following subarachnoid hemorrhage is a major cause of death and morbidity from this event. It is most often seen at 4–7 days following the bleed and is correlated with the amount of blood surrounding the affected vessels. Mechanisms and characteristics will be discussed in the section on subarachnoid hemorrhage from aneurysms. Pre-eclampsia and eclampsia are major etiologies of cerebral vasospasm.

Migraine and Stroke*General Characteristics*

1. Higher prevalence of stroke occurs in migraineurs particularly those with aura (3 times the risk) and young women
2. Definition of a migraine stroke:
 - a. Occurs in a patient with migraine and aura
 - b. The aura persists for more than one hour
 - c. Neuroimaging reveals a deficit concomitant with the clinical symptoms and signs

Migraine and Associated Medical Conditions

1. Inherited disorders:
 - a. CADASIL
 - b. MELAS
 - c. Channelopathies
2. Connective tissue disorders
 - a. SLE is prominent

3. Dissection of the carotid and vertebral arteries (migraine may also predispose to dissection)
4. Arteriovenous malformations
5. Rare in cavernous hemangioma
6. Glioma
7. Patent foramen ovale
8. Mitral valve prolapse
9. Drugs of abuse (cocaine and sympathomimetic)
10. Antiphospholipid syndrome
11. Prosthetic heart valves

Clinical Manifestations

1. Transient global amnesia (TGA):
 - a. Higher prevalence of TGA in migraineurs
 - b. Migraine may occur with the amnesic event
2. Bartleson syndrome:
 - a. Occurs primarily in young men
 - b. Severe headache with focal neurologic signs
 - c. Clustered attacks similar to migrainous aura
 - d. Maybe associated with fever
 - e. Episodes may last for 6 to 12 weeks
 - f. CSF lymphocytic pleocytosis (greater than 100 lymphocytes/mm³ with an elevated protein; no autoimmune markers; no glucose depression or infectious etiology)
 - g. MRI is usually normal but infarctions have been seen

Late Stroke-Like Migraine After Radiation Therapy (SMART)

1. May occur several years after XRT:
 - a. Therapy usually was prolonged
 - b. The whole brain was irradiated
2. The migraine is prolonged and often preceded by auras
3. MRI demonstrates diffuse cortical enhancement
4. No correlation with radiation dose, tumor type or chemotherapy

Intracranial Hemorrhage After Migraine

1. Severe prolonged migraine
2. Reperfusion hemorrhage in formerly ischemic areas

Neuropathology

1. Silent brain infarction:
 - a. Increased prevalence of silent infarcts in migraineurs
 - b. Putative mechanism is spreading depression
 - c. Women with migraines have a higher prevalence of silent deep white matter lesions that may be small infarcts
2. Migraine is associated with edema of vascular walls:
 - a. Susceptibility for arterial dissection (putative)
3. Cortical spreading depression:
 - a. Pivotal mechanism for aura
 - b. Causes vasoconstriction, decreased cerebral blood flow and activation of the endothelium
 - c. Endothelial activation:
 - i. Initiates the clotting cascade
 - ii. Platelet aggregation
4. Bilateral hypoperfusion may occur during a migraine without aura

Neuroimaging

MRI

1. White matter abnormalities (WMA):
 - a. Higher incidence of WMAs are seen in migraineurs with subclinical hyperthyroidism and hypothyroidism and elevated homocysteine levels
 - b. Infarct-like lesions (ILLs):
 - i. Preferentially localized in the cerebellum and deep gray matter
2. Volumetric changes in gray matter and white matter:
 - a. Sites of volume loss include:
 - i. Bilateral insula
 - ii. Frontal, prefrontal, temporal, parietal and occipital cortices
 - iii. Anterior cingulate gyrus
 - iv. Basal ganglia
 - v. Cerebellum
 - b. Sites of volume gain:
 - i. Dorsolateral pons
 - ii. PAG

Differential Diagnosis

Differential Points Between Migraine and Ischemic Stroke

Migraine

1. Several modalities are involved sequentially in migraine
 - a. Vision, parietal, sensory, motor, speech
 - i. Several modalities are involved concomitantly in stroke
 - ii. Negative symptoms predominate in stroke
2. Symptoms tend to be positive in migraine:
 - a. Scintillating scotoma
 - b. Paresthesia
 - c. Teichopsia
 - d. Brightness in a visual field (VF)
3. Positive symptoms followed by negative symptoms occur in migraine
4. Headache follows neurologic symptoms by 10 to 15 minutes in migraine
 - a. Rarely headache precedes symptoms
5. Average attack lasts 20 minutes in migraine (neurologic manifestations)
6. Migraine occurs more often in women than men
7. Attacks last over the lifetime of the patient
 - a. Acephalgic form of migraine occurs more frequently in older patients
8. May not have atheromatous risk factors in migraine

Ischemic Symptoms

1. Several modalities are involved concomitantly (motor/sensory/speech)
2. Negative symptoms predominate
3. Headache concomitant with the deficit
4. Small white platelet fibrin emboli cause deficits for less than 2 minutes; large emboli (red; primarily of cardiac origin) cause a deficit for greater than 5 minutes
5. Occurs more in men than women
6. Clear atherosclerotic risk factors

Reversible Cerebrovascular Constriction Syndrome*General Characteristics*

1. A collective term for transient non-inflammatory, non-atherosclerotic segmental constriction of cerebral arteries
2. Transient condition (relatively good prognosis)
3. Angiographic mimic of vasculitis
4. Presentation usually is severe headache, delirium, seizure or cerebral ischemia and/or hemorrhage
5. Possible mechanism is alteration in vascular tone

Clinical Manifestations

1. Affect women more than men; peak incidence is between 20–50 years; children also affected
2. Sudden severe headache ('thunderclap'):
 - a. Reaches maximally intensity instantly
 - b. Occipital or diffuse
 - c. Severe and throbbing
 - d. May also be accompanied by nausea, vomiting and photophobia
 - e. May persist or recur for days or weeks then gradually decrease
 - f. May occur spontaneously or be precipitated by exercise or valsalva maneuvers
 - g. May have migraine and depression history; may develop migraine after the headache onset
3. Precipitants:
 - a. Pregnancy and the puerperium
 - b. Sympathomimetic drugs/drugs of abuse
 - c. Blood products
 - d. Head trauma
 - e. Neurosurgical procedures
 - f. Emotional episodes
 - g. Immunosuppressants
 - h. Chemotherapeutic agents
4. Blood pressure may be normal or mildly elevated
5. Cerebral vascular manifestations:
 - a. Focal neurologic deficits depending upon the ischemic territory and affected artery
 - b. Brain hemorrhage (ICH)
 - c. Sulcal subarachnoid hemorrhage
 - d. Focal or generalized seizures from the ischemic cortex
 - e. Neurological deficits:
 - i. Occur during the first few days
 - ii. In parieto-occipital lobes
 - iii. Borderline arterial territories
 - iv. Visual dysfunction is frequent:
 1. Bálint's syndrome
 2. Cortical blindness (Anton's syndrome)
 3. Scotoma and flashing lights
6. Other signs and symptoms reported are:
 - a. Apraxia
 - b. Dysarthria
 - c. Aphasia
 - d. Ataxia

- e. Hemiparesis
7. Severe attacks rarely cause death
8. Benign CSF analysis

Neuropathology

1. Disturbance in the control of cerebrovascular tone
2. Migrainous vasospasms
3. Abnormalities of catecholamines, nitric oxide, endothelium, serotonin and calcium metabolism
4. Hormonal changes during pregnancy
5. Medium-sized cerebral arteries are involved and demonstrate segmental narrowing and vasodilatation
6. Putative mechanism of cerebral hemorrhage:
 - a. Ischemia – reperfusion
 - b. Rupture of cortical vessels due to sudden hypertension and dysfunctional autoregulation
7. Rarely the extracranial carotid can be occluded from vasoconstriction
8. Rare unruptured cerebral aneurysms (most probably incidental)
9. Complete or near complete reversibility of the vasoconstriction by 3 months

*Neuroimaging***MRI and CT**

1. Approximately 1/3 of patients have negative CT and MRI evaluations in the face of segmental narrowing by arteriography (opposite of cerebral vasculitis)
2. MRI and CT evaluations:
 - a. Bi-hemispheric symmetric infarcts in arterial border zone territories
 - b. Ischemic lesions are often crescentic or horseshoe shaped
 - c. Wedge shaped lesions with severe ischemia
 - d. FLAIR images on MRI reveal:
 - i. Dot-shaped or linear hyperintensities on the cortical surface
3. One third of patients suffer ICH:
 - a. Cortical sulcal SAH
 - b. ICH often in hypertensive areas
4. ICH's tend to occur early and infarcts in the second week after onset of the headache

Angiography

1. Demonstrates segmental cerebral artery vasoconstriction; the diagnosis is confirmed with:
 - a. Reversibility of the angiographic abnormalities within 12 weeks after onset
 - b. Autopsy rules out:
 - i. Vasculitis
 - ii. Intracranial atherosclerosis
 - iii. Aneurysmal subarachnoid hemorrhage

Transcranial Doppler

1. Blood flow through the brain: velocities almost always elevated at onset

*Laboratory Evaluation***CSF**

1. Has been found to be normal in 80% of patients
2. 95% of patients had cell counts of $<10/\text{mm}^3$; protein levels $<80 \text{ mg/dl}$

Blood

1. Useful blood test to rule out alternate diagnosis include:
 - a. ESR, rheumatoid factor, anti-nuclear and anti-neutrophil cytoplasmic antibody titers
 - b. 5-hydroxyindoleacetic acid levels
 - c. Serum calcium and parathyroid levels
 - i. Hypercalcemia may cause cerebral vasoconstriction

Urine

1. Vanillylmandelic acid to rule out pheochromocytoma

*Differential Diagnosis***Differential Diagnosis of Thunderclap Headache**

1. SAH (depressed consciousness/neck stiffness)
2. Embolus (focal signs)
3. ICH (focal signs, vomiting)
4. Arterial dissection (neck/occipital pain for vertebral artery; face pain and Horner's syndrome for the carotid)
5. Viral meningitis (stiff neck; consciousness preserved)
6. Spontaneous intracranial hypotension (exacerbated by standing)
7. Pituitary apoplexy (pain infrabrow area; cranial nerve III and VI involvement)
8. Cerebral venous thrombosis (seizures in one leg; papilledema)
9. Migraine (past history, phono and photophobia, nausea)

Differential Diagnosis of Reversible Cerebral Vasoconstriction Syndrome

1. Migraine
2. Intracranial atherosclerosis
3. Infectious arteritis
4. Fibromuscular dysplasia
5. Autoimmune vasculitis
6. Subarachnoid hemorrhage (vasoconstriction in 4–11 days)

Differential of RCVS from Primary Angiitis of the CNS (PACNS)

1. Headache and neurologic signs and symptoms may be similar
2. PACNS:
 - a. Headache:
 - i. Dull; insidious progression
 - b. Cognitive deficits
 - c. Multifocal infarction of gray and white matter
 - d. Abnormal CSF

Differential Diagnosis of RCVS from Posterior Reversible Encephalopathy Syndrome (PRES)

1. Associated conditions of eclampsia, immunosuppressant drugs, hypertensive encephalopathy and porphyria (RCVS)

2. Headache in PRES not as explosive as noted in RCVS
3. Visual symptoms often prominent in PRES
4. Gray and white lesions on MRI; rarely are the lesions in the frontal and parietal lobe, cerebellum or the brainstem in PRES
5. Negative angiographic pattern in PRES

Eclampsia*General Characteristics*

1. New onset of hypertension ($>140/90 \text{ mmHg}$) and proteinuria >20 weeks of gestation
2. Eclampsia:
 - a. Life threatening; severe proteinuria and hypertension complicated by:
 - i. Generalized seizure
 - ii. Depressed consciousness
 - iii. Visual dysfunction to blindness
 - iv. Occurs in a pre-eclamptic patient
3. Severe pre-eclampsia and eclampsia may be complicated by:
 - a. HELLP syndrome that includes:
 - i. Hemolysis
 - ii. Elevated liver enzymes
 - iii. Low platelet count
 - iv. Occurs in about 20% of severely pre-eclamptic women
 - v. Poor prognosis for the pregnancy
 - b. HELLP syndrome associated with:
 - i. DIC
 - ii. Abruptio placentae
 - iii. Acute renal failure
 - iv. Hepatic failure
 - v. Pulmonary edema
 - vi. Cerebral edema
 - vii. Stroke
 - c. Develops in the 3rd trimester or 48 hours after delivery; delayed post-partum eclampsia has similar symptoms but occurs >48 hours (usually within 1 week)
 - d. Incidence of pre-eclampsia in the US is approximately 5–10% of pregnancies; mortality is 2–5/100 patients
 - e. Occurs more frequently in women with chronic hypertension, renal disease, diabetes and antiphospholipid antibodies

Risk Factors

1. First pregnancy
2. Pre-eclampsia in past pregnancies
3. Family history of pre-eclampsia
4. Malnutrition
5. Women older than 35
6. BMI greater than 35
7. Elevated C-reactive protein
8. Elevated homocysteine
9. African-American ethnicity
10. Multiple pregnancies

Putative Genes

1. ACVR2A
2. STOX 1

Putative Biomarkers

1. Neutrophil gelatinase associated lipocalin (NGAL)

Clinical Manifestations

1. Most patients with pre-eclampsia are asymptomatic

Neurologic Symptoms of Pre-Eclampsia

1. Headache
2. Photophobia
3. Depressed consciousness
4. Scotoma
5. Eclampsia is diagnosed after progression that includes:
 - a. Pulmonary edema, kidney and liver failure, abruptio placentae, DIC, HELLP syndrome, elevated uric acid, decreased platelets and thrombin III
 - b. Seizures, stroke, posterior reversible leukoencephalopathy (PRES)

Cerebral Vasculature Disease and Severe Pre-Eclampsia/Eclampsia (SPE/E)**General Characteristics**

1. The most common cause of stroke in pregnancy is eclampsia:
2. In severe pre-eclampsia/eclampsia (SPE/E):
 - a. 24–47% of patients have ischemic stroke
 - b. ICH occur in 14–47% of patients
 - c. Brain hemorrhage is the major cause of morbidity and mortality in SPE/E

Clinical Manifestations

1. Headache
2. Agitation and cognitive dysfunction
3. Visual hallucination to cortical blindness
4. Bálint's syndrome
5. Gerstmann's syndrome (rare)
6. Hemianopia (rare)
7. Motor signs and ataxia (not severe)
8. Encephalopathy similar to hypertensive crisis
9. Most often reversible with treatment

Visual Symptoms with SPE/E

1. Cortical blindness (Anton's syndrome):
 - a. Normal pupillary reaction to light
 - b. Confabulation of vision; patient is blind but confabulates that he can see objects
 - c. Failure to follow optico-kinetic stimuli
 - d. May have slight peripheral visual spared so that he can walk in a room without hitting furniture
 - e. May be euphoric
2. Visual complaints occur concordantly with headache, nausea and seizures

3. Rarely Bálint's syndrome occurs:

- a. Optic apraxia with under reaching
- b. Poor visual scanning
- c. Inability to voluntarily break fixation

4. Simultagnosia

- a. Inability to integrate parts of an object into a whole; patient can see eyes, mouth and nose but can't integrate the parts to see a face

5. Alexia

6. Homonymous hemianopsia

7. Most patients have complete visual recovery

8. Peripheral visual loss can occur from choroidal infarction with serous retinal detachment and optic nerve ischemia and infarction

Neuropathology

1. Capillary leak syndrome (endothelial damage of cerebral blood vessels) causing vasogenic edema
2. Small hemorrhage and microinfarction (0.3–1. Mm):
 - a. Scattered throughout the cerebral cortex asymmetrically
 - b. Arterial border zone proclivity
 - c. Occipital > parietal > frontal lobes; rarely the cerebellum is involved
3. Subcortical hemorrhages:
 - a. 2–6 mm in size
 - b. Deep white matter, basal ganglia and brainstem topology
4. Large intraparenchymal hemorrhages in hypertensive distribution
5. Congested capillaries with surrounding hemorrhage
6. Small cerebral blood vessels may demonstrate:
 - a. Fibrinoid necrosis
 - b. Occlusive fibrin thrombi

General Placental Pathology

1. Placental pathology is causative of eclampsia
 - a. Removal of the placenta cures the disease
2. Cytotrophoblasts invade maternal spiral arterioles
 - a. Transforms these resistance vessels to larger conducting vessels
 - b. Cytotrophoblasts differentiate from an epithelial to an endothelial phenotype (pseudo-vasculogenesis)
 - c. The process requires growth factors and cytokines
 - d. Failure of the epithelia to endothelial phenotypic switch allows spiral arterioles to remain as resistance vessels and causes:
 - i. Defective uteroplacental circulation and decreased placental perfusion
 - ii. The placenta becomes hypoxic within the intervillous space that leads to oxidative stress, apoptosis, endothelial dysfunction and an inflammatory response
 - e. Angiogenic factors direct the regulation of placental vascular development. They include:

- i. Soluble Fms-like tyrosine kinase-1 (sFlt-1)
- ii. VEGF-1 and 2 (vascular endothelial growth factors)
- iii. Placental growth factor (PlGF)
- f. The disruption of the interplay of these factors leads to loss of the endothelial control of vascular development that causes:
 - i. Hypertension
 - ii. Increased vascular permeability
 - iii. Disturbed endothelial expression of coagulation factors and coagulopathy
- g. Placenta may also be the source of circulating inflammatory cytokines that are systemically deleterious

Putative Mechanisms

1. Hypertension with a decrease of cerebral autoregulation primarily in the occipital lobe (less sympathetic innervation to posterior cerebral arteries)
 - a. May also occur in other cortical lobes and the brainstem

Laboratory Evaluation

Biomarkers

1. Angiogenic factors for the development of the placental vascular system
 - a. VEGF and PlGF:
 - i. Decrease of VEGF seen in pre-eclamptic patients due to an increase of its soluble receptor – receptor Flt-1 (VEGFR-1)
 1. Neutralizes both VEGFs and PlGF
 - b. A rise in Flt-1
 - c. Endoglin:
 - i. Transmembrane glycoprotein
 - ii. Co-receptor for transforming growth factors which regulate angiogenesis and vascular tone
 - iii. S-endoglin (sEng) is an anti-angiogenic factor:
 1. Blocks binding of TGFβ1 to its receptor
 2. Decreases nitric oxide vasodilatation and capillary formation by endothelial cells
 3. sEng increases with pre-eclampsia
 - d. Placental protein 13 (PP-13):
 - i. Important in placenta implantation and remodeling of maternal arteries
 - ii. Increases with pre-eclampsia
 - e. Neutrophil gelatinase associated lipocalin (NGAL)
 - i. Upregulated in damaged epithelial cells, during inflammation, renal disease, CV disease
 - ii. Best and earliest marker of kidney disease

Neuroimaging

CT

1. Scan particularly useful in discriminating hemorrhage from ischemia or encephalopathy
2. White matter hypo densities that are often symmetric in:
 - a. Cerebral cortex
 - b. Subcortical white matter

- c. Supratentorial deep gray nuclei
3. In patients with acute encephalopathy syndrome hemorrhages are predominately in the parietal and occipital lobes but spare:
 - a. Paramedian areas
 - b. Calcarine cortex
 - c. Peristriate areas

MRI

1. Abnormal in 48–100% of patients and include:
 - a. Confluent or punctate lesions on T2-weighted sequences in:
 - i. Centrum semiovale
 - ii. Deep white matter of the posterior parietal and occipital lobes
 - iii. Gray-white junction
 - iv. External capsule
 - v. Basal ganglia
 - vi. Cerebellum (rare)
 - b. Occipital lobe is the predominant site but frontal, parietal and temporal lobes may be involved solely
 - c. Eclamptic patients demonstrate curvilinear lesions at the gray-white junction
 - d. MRI evaluation in pre-eclampsia patients:
 - i. May be present in white matter only
 - ii. Predominantly frontal and parietal areas rather than the gray-white junction
 - iii. No curvilinear topography of lesions
 - iv. PRES may be seen with eclampsia

Angiography

1. Vasoconstriction generally involves large arteries and circumferential branch arteries:
 - a. Constriction is usually multifocal but can be diffuse
 - b. Vasoconstricted segments can alternate with areas of vasodilation
 - c. Angiographic abnormalities are usually reversible

Transcranial Doppler Evaluation

1. Elevated blood flow velocity and lower average pulsatility index in eclampsia but not in pre-eclampsia

FDG-PET Evaluation

1. Decreased glucose metabolism in areas that demonstrated T2-signal abnormalities

Differential Diagnosis of Eclampsia

1. Dural sinus thrombosis:
 - a. More common in puerperium than during pregnancy
 - b. Not hypertensive
 - c. More focal neurologic exam
2. Reversible cerebral vasoconstriction syndrome:
 - a. Sudden severe ‘thunderclap’ headache
 - b. Seizures
 - c. Focal (not severe) neurologic deficits

- d. Angiographic multifocal vasoconstriction
- e. Less white matter involvement than SPE/E
- f. Not hypertensive
- 3. Cocaine
- 4. Sympathomimetic drugs
- 5. Benign cerebral vasculitis
- 6. Migraine
- 7. Post-partum angiopathy
- 8. Subarachnoid hemorrhage (aneurysm or malformation rupture)
- 9. Embolic stroke
- 10. Long chain-3-hydroxyacyl-coenzyme A dehydrogenase deficiency
- 11. SLE
- 12. Budd-Chiari syndrome
- 13. Hypertensive encephalopathy
- 14. Vasculitis

Vascular Wall and Vasculopathy

Diseases of the Arterial Wall

Overview

Dilatative arteriopathy comprises a group of hereditary and acquired pathologies that cause cerebral arteries to enlarge, dilate and develop tortuosity. The most severely affected vessels are the intracranial vertebral and basilar arteries although the carotid and middle cerebral arteries may also be involved. The most prominent genetic diseases that demonstrate the process of dolichoectasia are Marfan's syndrome, Ehlers-Danlos disease, fibromuscular dysplasia and Gesell-Erdheim disease. A far more common pathology with arterial wall involvement leading to cerebral vascular disease is congophilic angiopathy. Dissection of the arterial wall occurs with connective tissue disease and with prolonged hypertension and is primarily an arterial wall disease. These diseases are a prominent cause of both large and small vessel disease in both young and elderly patients.

Congophilic Angiopathy (CAA)

Overview

Cerebral amyloid angiopathy (CAA) is a heterogeneous group of biochemical and genetic disorders that demonstrate amyloid fibrils in the walls of small to medium-sized arterial blood vessels. In some conditions amyloid fibrils are found in capillaries of the CNS parenchyma and the leptomeninges.

Amyloid is composed of insoluble 8 to 10 nm wide fibrils formed from aggregation and polymerization of soluble circulating proteins. They are converted from a random-coil secondary structure into β -sheet conformations. Once these protofibrillar intermediate structures exceed a critical level high-ordered amyloid fibrils form. Amyloid is formed by proteolytic modifications of a larger precursor protein (amyloid

precursor protein (APP)) by β and γ secretases or processing by furin of mutated β R12 precursor protein. In this instance ABri or ADan amyloid proteins are produced that cause British (FBD) or familial Danish dementia (FDD).

Mechanisms that destabilize the secondary structure of soluble native proteins include:

1. Genetic modifications
2. Post-translational modifications
3. Low pH
4. Presence of metal ions

Other mechanisms that cause toxic misfolded proteins to form from naturally soluble proteins are:

1. Missense mutations in the coding region of genes that can change the rate of conversion of a native protein to a fibrillary conformer
2. "Pathologic chaperons" that co-deposit with different parenchymal or cerebrovascular amyloids

Clinical Manifestations

1. Amyloid deposition in blood vessel walls has been associated with:
 - a. Cognitive decline
 - b. Microhemorrhages (lobar primarily)
 - c. Alteration of cerebral microvascular tone and reactivity
 - d. CAA-related ischemia
 - e. CAA-angiitis

Neuropathology

1. Vessels affected by CAA
 - a. Cortical small and medium-sized arteries and arterioles
 - b. Veins
2. Predilection sites of CAA due to A β deposition are the occipital, parietal frontal and temporal lobes; medial temporal and hippocampal structures are spared
3. Cerebrovascular amyloid deposition is sequential:
 - a. It first appears around smooth muscle cells in the subluminal side of the tunica media and adventitia
 - b. Progresses through the intimal layers and replaces the smooth muscle
 - c. Degenerative changes follow with fibrous thickening of the vessel wall, microaneurysm formation and fibrinoid necrosis
 - d. Blood breakdown products accumulate around the affected vessels
 - e. A perivascular inflammatory response from the deposition of A β that includes:
 - i. Activated microglia and astrocytes
 - ii. Activation of the complement cascade
 - f. CAA-associated angiitis (from the perivascular inflammatory response) is associated with:
 - i. Adventitial and perivascular inflammation of lymphocytes and histiocytes
 - ii. Multinucleated giant cells
 - iii. A β phagocytosis
 - g. Microhemorrhages are seen with or without lobar hemorrhages due to weakening of the vessel wall from

the loss of smooth muscle and degenerative changes.

ApoE2 allele increases hemorrhage risk

- h. Cerebral infarctions and focal or diffuse white matter ischemic changes
 - i. $A\beta$ deposited in blood vessel walls:
 - j. Heterogeneous at both N and C termini
 - k. $A\beta$ 40 is usually predominant
 - l. $A\beta$ 42 is predominant in capillaries

Neuroimaging

MRI

1. Cerebral microhemorrhages
2. Cortical lobar hemorrhages
3. Small vessel infarctions
4. Diffuse leukoaraiosis of hemispheric white matter
5. Gradient ECHO (for microhemorrhage)
6. Superficial cortical siderosis

Dilatative Arteriopathy (Dolichoectasia)

General Characteristics

1. Dolichoectasia refers to enlarged, tortuous and dilated arteries
2. The dilatative process may form fusiform aneurysms
3. Dilatative arteriopathy preferentially involves the intracranial vertebral and basilar arteries although it does involve the carotid and middle cerebral arteries

Associated General Risk Factors

1. Older age
2. Male sex
3. Hypertension
 - a. Left ventricle hypertrophy
 - b. Dilated and pulsatile brachial arteries with prominent aortic notch pulsations
4. History of myocardial infarction
5. Increased diameter of the thoracic aorta

Clinical Manifestations

1. Distortion of brain structure by tortuous elongated arteries (particularly in the medulla and pons)
2. Stretching of cranial nerves upon their exit from the brainstem that causes:
 - a. "Tic douloureux" – Vth cranial nerve
 - b. Hemifacial spasm – VIIth cranial nerve
 - c. Vertigo/tinnitus – VIIIth cranial nerve
 - d. Torticollis – XIth cranial nerve
3. Hydrocephalus:
 - a. Compression of the IIIrd ventricle
4. Ataxia and motor weakness from compression of:
 - a. The brainstem
 - b. Middle cerebellar peduncle
 - c. Pontine tracts
 - d. Pyramidal tract
 - i. Tic douloureux

Neuropathology

1. Distortion of the orifices of arterial branches

2. Decreased blood flow of penetrating branches
 - a. Decreased blood flow velocities
 - b. Reduced antegrade flow
 - c. Increased contact factor-endothelial contact time that increases thrombus formation and emboli

3. Fusiform aneurysms

Histology

1. Intimal thickening
2. Deficiencies in the muscularis and internal elastic lamina
3. Areas of fibrosis
4. Elastic tissues degeneration
5. Increase in the vasa vasorum

Dolichoectasia in Specific Diseases

1. Marfan's syndrome (young patients)
2. Ehlers-Danlos syndrome
3. AIDS (children)
4. Fabry's disease
5. Sickle cell disease (children and adults)

Small Vessel Disease Features of Dolichoectasia

1. Lacunar infarction
2. Leukoaraiosis
3. Dilated Virchow-Robin spaces around penetrating arterioles ("état criblé")

Arterial Disease

1. Arterial media disease may be associated with up-regulation of metalloproteinases
2. Penetrating arterial disease and dilatative arteriopathy demonstrate:
 - a. Disease of the arterial wall rather than intimal endothelium
3. Penetrating arterial vessel pathology includes:
 - a. Increased amount of fibrinoid material and lipids
 - b. Abnormal connective tissue elements within the arterial wall affect matrix metalloproteinases which may alter the vascular permeability of the BBB

Neuroimaging

MRI

1. Enlarged, tortuous and dilated arteries most prominently affecting the vertebrobasilar system
2. Fusiform basilar artery aneurysms
3. Lacunar infarction, leukoaraiosis and enlarged Virchow-Robin spaces
4. Increased white matter hyperintensities

Fibromuscular Dysplasia

General Characteristics

1. Probably multitietologic; HLA association
2. May affect any cerebral somatic artery
3. Primarily affects medium-sized muscular arteries at specific sites:
 - a. Distal 2/3 of renal arteries

- b. Distal extracranial vertebral artery (adjacent to C2 vertebrae)
- c. Distal carotid artery with rare involvement of:
 - i. Cavernous carotid
 - ii. Arteries of the Circle of Willis

Clinical Manifestations

1. Most commonly affects Caucasian women in the 4th to 6th decades
2. Occurs in infants and children with involvement of:
 - a. Renal arteries that causes severe hypertension
 - b. Splanchnic arteries
 - c. Cervical-cranial vessels
3. Incidence of less than 1% of routine cerebral arteriograms
4. Associated with intracranial aneurysms and dissections
5. ICH from associated HCVD due to renal artery involvement (including dissection)
6. Spontaneous cervical and intracranial artery dissection
7. Male presentation described:
 - a. Abdominal pain
 - b. Systemic signs
 - c. Hypertension
8. Associated dissection of the coronary arteries occur
9. Subarachnoid hemorrhage from rupture of thin walled blood vessels
10. Arterial dissection with appropriate territorial infarction
11. A relatively benign condition
 - a. Few recurrent cerebrovascular episodes

Neuropathology

1. Fragmentation of the arterial media with rings of fibrous and muscular hyperplasia cause:
 - a. Saccular dilations of the artery
 - b. Arterial wall involvement:
 - i. Adventitial form:
 1. Narrowing of the vascular lumen by fibrous tissue hypertrophy that surrounds the artery
 - ii. Intimal form:
 1. An increase of the fibrous components of the intima
 - a. Concentric narrowing of the lumen
 - b. About 5% of patients
 - c. Children and adolescents are the most commonly affected
 - iii. Medial form:
 1. Most common form
 2. Constricting bands of fibrous dysplastic tissue and proliferating muscle cells in the media
 3. Alternating with areas of medial thinning (disruption of the elastic membrane)
 - a. Leads to luminal dilatation
 - b. "String of beads" arteriographic pattern

Neuroimaging

1. Bilateral ICA involvement is frequent
 - a. Pharyngeal component of the artery

- i. Level of C2 and spares the bifurcation and intracranial carotid artery
- ii. 20% of patients have concomitant involvement of the vertebral arteries
- b. Rare: intracranial FMD
- c. "String of beads" arterial lesions may be concurrent with tertiary constrictions and aneurysmal dilatation
- d. Shelf-like segmental stenosis from fibrous septa and webs
- e. Enlarged carotid bulbs

Aortic Medial Wall Abnormalities [Gsell-Erdheim]

General Characteristics

1. Ascending aorta may dilate in congenital heart disease
2. Aortic dilatation is well recognized in:
 - a. Marfan syndrome
 - b. Turner syndrome
 - c. Bicuspid aortic valve
 - d. Coarctation of the aorta
3. Congenital heart disease (CHD) and aortic medial abnormalities occur with:
 - a. Single ventricle
 - b. Persistent truncus arteriosus
 - c. Transposition of the great arteries
 - d. Hypoplastic left heart syndrome
 - e. Tetralogy of Fallot
4. The CHDs with aortic dilatation are associated with:
 - a. Decreased elasticity and stiffness of the aorta and cause
 - i. Increased afterload and ventricular hypertrophy

Clinical Manifestations

1. Aortic dissection
2. Coronary artery dissection
3. Carotid artery aneurysm
4. Giant aneurysm of the ascending aorta

Neuropathology

1. Cystic medial necrosis
2. Elastin fragmentation
3. Fibrosis
4. Media necrosis

Mechanisms of Structural Alteration of the Ascending Aorta Media

1. Systemic hypertension
 - a. Abnormalities of medial elastin and collagen
2. Aging
 - a. Parallel aortic elastic fibers fragment
 - b. Decrease of smooth muscle cells
3. Pregnancy
 - a. Elastic fiber fragmentation
 - b. Hypertrophy/hyperplasia of smooth muscle cells
4. Chromosome abnormalities
 - a. Marfan's syndrome
 - i. Defect of fibrillin-1; increased elastin

5. Gene abnormalities
 - a. Fibrillin-1 defect (15q 21.1)
 - b. Deletion of TGF-B receptor
 - c. ALK 5 (activin receptor-like kinase 5)
6. Medial smooth muscle apoptosis
7. Metalloproteinase and elastin up-regulation
8. Hemodynamic abnormality (increased aortic flow)
9. Intrinsic abnormalities of the aortic wall in congenital heart diseases

Neuroimaging

Arteriography

1. Coronary artery dissection
2. Enlargement of the aortic root
3. Aortic artery dissection

Radiation Induced Arterial Disease

General Characteristics

1. Delayed radiation-related strokes most often reported following X-RT for:
 - a. Leukemia
 - b. Hodgkin's disease
 - c. Brain tremors
2. Risk of stroke
 - a. Leukemia survivors: about 6%
 - b. Brain tumor: 29%
 - c. Hodgkin's disease: 83/100,000 patients
 - d. Increased in a dose-dependent manner
3. Major pathology in vascular injury; dependent upon:
 - a. Dose of irradiation
 - b. Location of irradiated nervous tissue – those areas with more surrounding tissue receive less dose
 - c. Order of vessel vulnerability:
 - i. Capillaries and sinusoids (most sensitive)
 - ii. Arterioles and small vessels
 - iii. Medium-sized vessels
 - iv. Large arteries (least sensitive)
 - d. Typical lesions are not in the usual areas for atherosclerosis
 - i. Often not at bifurcations
 - ii. Long arterial segments are involved

Neuropathology

1. Denudation of the endothelial layer
2. Infiltration of foam cells, histiocytes and fibroblasts
3. Collagen formation in the subendothelium
4. Myointimal proliferation and fibrosis
5. Calcification and adventitial fibrosis
6. Fragmentation of the internal and external elastic membranes; inflammatory changes
7. A proliferative small vessel endarteritis

Clinical Manifestations

1. Chronic dementing illness

- a. All systems may be involved (Parkinsonism, ataxia, corticospinal deficits, subcortical apraxia and cognitive slowing)
2. Moyamoya disease of basal arteries
 - a. Children and young adults are the most affected
 - b. Prevalent with NF1 and higher doses of X-RT
3. Focal brain infarcts and strokes
4. Spinal cord
 - a. Sulcal artery infarction with Brown-Séquard syndrome
 - b. Upper extremity parathesias (C5–C6)
 - c. Spastic paraparesis
 - d. Transient ischemia
 - e. Stroke
 - f. Intracranial vascular occlusive disease
5. Delayed symptoms
 - a. Months to years after X-RT
 - b. Mass lesions in the brain or spinal cord
 - c. Fibrinoid degeneration of blood vessels, coagulative necrosis and gliosis
6. Delayed dementia with focal signs
 - a. Brain atrophy and leukoencephalopathy
 - b. Diffuse loss of white matter
 - i. Some patients demonstrate enhancement of focal lesion

Neuroimaging

1. Acute radionecrosis presenting as a mass (MR spectroscopy demonstrates no lactic acid peak which distinguishes it from recurrent glioma)
2. Generalized atrophy and leukoencephalopathy
3. Long segment stenosis of extracranial vessels with calcification

Arterial Dissections

Cerebral Artery Dissections

Overview

1. Cervico-cephalic arterial dissection (CAD)
 - a. A heterogeneous group of arteriopathies that have an intramural hemorrhage
 - b. Affects extracranial arterial segments (88%)
 - i. ICA (58–75%)
 - ii. Vertebral artery (19–30%)
 - iii. Multiple arteries (16–28%)
 - c. Intracranial dissections occur in 12%
 - i. VA > carotid branches > basilar artery branches
2. There are 3 forms of dissection:
 - a. Stenotic (45–66%)
 - b. Occlusive (21–42%)
 - c. Aneurysmal (12–49%)
 - d. Combined stenosis and dissecting aneurysms
3. Multiple vessel dissections women > men
4. Dissections cause 2.5%* of all strokes (primarily by artery-to-artery embolism)
 - a. 10–20% of strokes in those <40 years

*Carotid Artery Dissection***General Characteristics**

1. Location
 - a. Pharyngeal portion
2. Above the bifurcation
 - a. Artery is mobile in this section
 - b. Involves redundant portion of the artery

Clinical Manifestations

1. Ipsilateral headache:
 - a. >65% of patients
 - b. Facial pain 34–53%; periorbital pain above the brow; periauricular pain
 - c. Neck pain (frequently along the sternocleidomastoid muscle)
 - d. In approximately 20% of patients all of these pains are concurrent
 - e. Rare bilateral, occipital or hemicranial pain
 - f. Pain may be progressive and develop later in the course of the illness
 - g. Throbbing, constrictive or pulsatile; rare thunder-clap headache
 - h. Pain as the only symptom occurs in 5% of patients
2. Pulsatile tinnitus in stenotic lesions (<20%); rare carotid bruit

Clinical Signs

1. Horner's syndrome (ischemia of the superior cervical ganglion (SCG) or of ocular sympathetic fibers that surround the carotid artery)
 - a. May occur at onset or later concurrently with stroke
2. Cranial palsies:
 - a. Involvement of branches of the meningeohypophyseal trunk from the cavernous portion of the carotid; cranial nerves III and IV most often involved
 - b. XII most commonly involved with compression by the carotid sheath. Accessory and vagal nerves may be involved; possible compression of the ascending pharyngeal artery
 - c. Dysgeusia (compression of the chorda tympani)
 - d. Compression and stretch of the nerves in the neck; ischemia of the peripheral vascular cranial nerve supply or compromise of the cranial nerves' vasa vasorum (small blood vessels that supply the nerves)
3. Ipsilateral partial Horner's syndrome:
 - a. Ptosis (not severe)
 - b. Meiosis (occasionally a dilated pupil is seen from iris ischemia)
 - c. Apparent enophthalmos (sympathetic denervation of Mueller's muscle and the sympathetic fibers in the tarsal plates)
 - d. Facial sweating intact (these sympathetic fibers follow the external carotid)
4. Pharyngeal carotid segment aneurysm:
 - a. Horner's syndrome (complete)

- b. Dysgeusia
- c. Tongue atrophy
 - i. Compression of the hypoglossal nerve in the carotid sheath
5. TIA affecting the ipsilateral eye and hemisphere (MCA territory)
 - a. If extremely frequent, they may be termed 'carotid al-legro'
 - b. Occurs in 15–29% of patients

Cerebral Ischemia

1. 82% of ischemic strokes occur within the first week:
 - a. 2/3 of ischemic strokes have a preceding TIA or amaurosis fugax
 - b. Artery-to-artery embolus rather than distal field ischemia is the major mechanism
 - c. Territorial infarct in the MCA distribution:
 - i. Rarely concomitant border zone infarction
 - ii. Concomitant ACA infarction 4% and PCA infarction in 2%
 - iii. Watershed infarction 3–15%

Ocular Ischemia

1. Amaurosis fugax occurs in approximately 30% of patients
2. Monocular scintillating scotoma or flashing lights
3. Retinal infarction is rare
4. Ischemic optic neuropathy:
 - a. Dissection reaches the carotid sinus
 - b. Often followed by a stroke; may be delayed for days to weeks
 - c. Symptoms caused by emboli or a distal cause of ischemia (hemodynamic) of the retina, choroid or optic nerve
 - d. Rare anterior or posterior ischemic optic neuropathy from severe stenosis or occlusion (slightly dilated, poorly reactive pupil from ciliary ganglion or iris ischemia)

Persistent Neck Pain

1. Suggests extension of the dissection
2. Vertebral and carotid dissection can occur concomitantly
 - a. Suggests underlying collagen defect
3. Asymptomatic internal carotid dissection
 - a. May occur simultaneously with symptomatic vertebral artery dissection
 - b. Concomitant contralateral ICAD

*Vertebral Artery Dissection***General Characteristics**

1. Precipitating factors:
 - a. Neck trauma (often rotational at C1–C2)
 - b. Chiropractic manipulation
 - i. Patients frequently go to the chiropractor because of neck pain
 - ii. Further manipulation extends the dissection

- c. Maintenance of the neck in a fixed posture
 - i. Prolonged surgical procedures
 - ii. Following intubation and resuscitation
- d. Cervical fractures (C2 – transcervical canal compromise)

Clinical Manifestations

1. Posterior headache or neck pain occurs in 88% of patients (innervated by C2–C4; posterior auricular nerve)
 - a. Ipsilateral to the dissection: occasionally the pain is bilateral, frontal or generalized
 - b. Steady or pulsatile quality
 - c. Headache and neck pain may be the only symptom
 - d. Intracranial extension or primary intracranial VAD may be associated with:
 - i. SAH (sudden onset; great intensity)
 1. Rare spinal SAH with severe neck and back pain
2. C5–C6 root irritation (rare)
3. Rarely causes brainstem compression

Cerebral Vascular Features of VAD

1. Primarily posterior circulation signs and symptoms (ischemic)
2. Wallenberg syndrome is most common
3. Less frequent territorial involvement:
 - a. Medial medullary arteries (brainstem)
 - b. Cerebellar arteries
 - c. Pontine
 - d. Thalamic
 - e. PCA
4. Stroke (ischemic infarction) occurs in approximately 60% of patients
 - a. 10–15% with preceding TIA
 - b. 10% no preceding TIA
 - c. Stroke from first TIA is rapid
 - d. Rarely spinal cord ischemia occurs from involvement of the anterior spinal arteries (paralysis; infarction of the medullary pyramids) or severe proprioceptive deficits from infarction of posterior column nuclei

Risk Factors for ICA and VA Dissection

1. Trauma:
 - a. Head and neck
 - i. Severe hyperextension and rotation:
 1. Traction in ICA from crossing transverse process C2–C3
 2. Severe neck flexion:
 - a) Entrapment of ICA between angle of the mandible and upper cervical spine
 - b. Elongated styloid process compression of the ICA during neck rotation
 - c. Traumatic VAD occurs with extreme neck rotation:
 - i. Injured at V3 segment (C2/C1 > C3/C2)
 - ii. Compressed by muscle and fascial bands at arterial junction V1 and V2

- iii. Osteophytes in the transcervical canal (V2 segment)
- d. Minimal trauma:
 - i. Coughing
 - ii. Sleep
 - iii. Posture
 - iv. Sexual activity
2. Genetic causes of arterial wall pathology:
 - a. Marfan's syndrome
 - b. Ehlers–Danlos type IV
 - c. Osteogenesis imperfecta
 - d. COL A1/A2 gene mutations
 - e. Fibromuscular dysplasia (FMD)
 - f. Pseudoxanthoma elasticum (PXE)
 - g. Adult polycystic kidney disease
 - h. Cystic medial necrosis
3. Congenital arterial anomalies:
 - a. Coils, kinks, loops of a redundant ICA
 - b. Dilated aortic root diameter > 34 mm
 - c. Mitral and bicuspid aortic valve (BAV) associations
4. Associated arterial manifestations of dissection:
 - a. Multivessel dissections that include the renal and visceral arteries
 - b. Higher incidence of intracranial aneurysms with ICAD
 - c. Familial ICAD and lentiginosis
 - d. CAD and cerebral aneurysms
5. Infection
 - a. Induces a proinflammatory state
6. Migraine headache

Neuropathology

1. Subintimal dissection
 - a. Blood between the tunica intima and media
 - i. Primarily associated with stenosis
 - b. Subadventitial dissection
 - i. Blood is between the tunica media and adventitia
 - ii. Associated with pseudoaneurysms and local symptoms

Neuroimaging

Arteriography

1. Elongated, irregular tapered stenosis
2. Dissecting aneurysm
3. Occlusion
4. Intimal flap

Intracranial Dissection

General Characteristics

1. Intracranial dissections cause:
 - a. Infarction
 - b. SAH
 - c. Mass effect
2. Anterior circulation
 - a. Supraclinoid carotid affected and may dissect into the intracranial MCA

3. Posterior intracranial extension affects
 - a. Intracranial vertebral artery
 - b. Basilar artery
4. Media and adventitial dissections are associated with:
 - a. SAH (may be recurrent)
5. Aneurysmal mass from dissection may cause:
 - a. Compression of cranial nerves and brain parenchyma
6. Chronic dissections:
 - a. Lesions are of different ages
 - b. Multifocal sites
 - c. Abnormal arterial media and internal elastic membrane
 - d. Most frequent with fibromuscular dysplasia
7. Recanalization:
 - a. Occurs if some lamina are patent

Neuroimaging

Neuroimaging of Arterial Dissections

1. Newer MRI and MRA sequences detail wall and luminal irregularities as well as some flow characteristics

Neuroimaging of ICA

MRI/MRA

1. Irregular and elongated tapered stenosis ('string sign')
2. Reconstitution at the skull base
3. Pseudoaneurysms
4. Tortuosity
5. Intimal flap
6. Slow ICA – MCA flow
7. Lesions usually initiated 1–2 cm above the bifurcation
8. "Flame Sign" at the site of occlusion
9. Distal branch occlusion (if embolization has occurred)
10. Occlusion and pseudoaneurysm more frequent with traumatic dissections

Neuroimaging of Vertebral Artery Dissection

MRI/MRA

1. Elongated, irregular tapered stenosis
2. Dissecting aneurysm
3. Occlusion
4. Intimal flap

Neuroimaging of Basilar Artery Dissection

MRI/MRA

1. Elongated stenosis with occlusion
2. Double lumen
3. Dissecting aneurysm

Neuroimaging of MCA and PCA Dissection

MRI/MRA

1. Non-specific stenotic segment with luminal irregularity that may be associated with dilatation
2. Differential diagnosis
 - a. Vasculitis
 - b. Meningeal infection
 - c. Inflammation

Aortic Dissections

General Characteristics

1. Divided into 2 types:
 - a. Type A – involves the ascending aorta
 - b. Type B – dissection initiated beyond the aortic arch
2. Origins of dissection:
 - a. 2/3 are in the ascending aorta
 - b. 10% are in the transverse portion of the aortic arch
 - c. 20% are in the proximal descending aorta beyond the origin of the left subclavian artery
 - d. Distal descending aorta dissection occurs in 5% of patients
3. Length of dissections is variable
 - a. May extend a few centimeters
 - b. May be extremely long from the ascending aorta to the iliac arteries
4. Cleavage plane:
 - a. Media of the artery
 - b. Follows the curvature of the ascending aorta and arch; partial circumference of the artery
 - c. False lumen occurs by an intimal tear
 - i. Located near the proximal end of the dissection
5. Arterial occlusion
 - a. Ascending aorta dissection
 - i. Brain and arm large arteries are occluded
 - ii. Dissection may extend into the proximal cervical arteries
 - iii. Dissection may extend into the aortic valve and obstruct coronary ostia
6. Medical manifestations
 - a. Acute aortic insufficiency
 - b. Myocardial infarction
 - c. Rupture into the chest (shock)
 - d. Pericardium (tamponade)
 - e. Obstruction of the vena cava
7. Aortic dissection 2–3 times more frequent in men than women

Clinical Manifestations

1. Pain
 - a. Can be in the chest, abdomen, back, face, head and neck
 - b. Rarely painless
 - c. Pain in the face suggests arch and proximal carotid artery
 - d. Pain straight through to the back suggests dissection below the subclavian artery
2. Hypertension
 - a. Classic aortic hypertensive dissection occurs in an obese middle aged plethoric, hyperhidrotic male
 - i. Most present with hypertension
 - ii. Approximately 25% of patients present with hypotension and a few in frank shock
3. Pulse/bruit
 - a. Loss of pulse in common carotid, left subclavian and femoral arteries

- b. Occasionally heard over the carotid and in the supra-clavicular fossa

Neurologic Manifestations

1. Stupor and coma
 - a. Cerebral infarction
 - b. Systemic hypotension
2. Focal or multifocal infarction
 - a. Occlusion of brachiocephalic arteries
3. Flaccid Paraparesis
 - a. Spinal cord infarction (blocked artery of Adamkiewicz)
4. Ischemic peripheral neuropathy
 - a. Blockage of arterial supply to the limbs

Neuropathology

1. Marfan's syndrome
 - a. Defect is primarily in the vessel media with profound diminution of elastic fibers
 - b. Decreased fibrillin in microfibrillar fibers in the skin
 - c. Mutation in Fibrillin causes a disordered microfibril matrix
 - d. Release of sequestered latent transforming growth factor β :
 - i. Mediator of vascular remodeling
 - e. Regional biomechanical dysfunction
2. Gesell-Erdheim syndrome
3. Hypertension
4. Atherosclerosis

Neuroimaging

1. Evaluation of the acute aortic syndrome that includes:
 - a. Aortic and cervical cephalic arterial dissection
 - b. Intramural hematoma
 - c. Penetrating atherosclerotic ulcer
2. Embolic stroke (all causes)
3. Atlantoaxial dislocation (Marfan's syndrome)
4. Enlarged dural sac (Marfan's syndrome)

CT

1. Findings demonstrate "beak sign" and aortic "cobwebs" (FMD)

Recanalization of Thrombosed Vessels

General Characteristics

1. The initial occlusion is the most dangerous time for stroke
 - a. Approximately 60% of strokes occur in the hemisphere ipsilateral to the occlusion (carotid artery)

Clinical Manifestations

1. Transient hypotension may result from low flow state that causes watershed infarction
2. Embolism occurs from:
 - a. The distal component of the occluded artery
 - b. Stump syndrome

- i. A proximally patent area and a patent extracranial carotid artery with retrograde flow
- c. Trans hemispheric migration of clot through the circle of Willis

Neuropathology

1. Spontaneous recanalization of a thrombosed intracranial artery:
 - a. Evident by 14–21 days
 - b. Irregular vascular wall of the affected vessel
 - c. Emboli:
 - i. Fragments and moves distally
 - ii. Movement occurs most often in the first 48 hours

Neuroimaging

MRI

1. In the case of embolic occlusion, the presence of a hyperdense MCA sign and a hypointense signal on T2-GRE imaging diagnoses a red thrombus
2. DWI sequences determine the infarcted core

CT

1. Dense MCA or vessel sign

MRA and DSA Angiography

1. Used to determine the topography of the arterial wall

Systemic Lupus Erythematosus

General Characteristics

1. Stroke occurs in approximately 3.5% of SLE patients under the age of 45 years old
2. Risk of recurrent strokes is increased
3. Major systemic features of SLE include:
 - a. Skin (malar rash and discoid lesions)
 - b. Arthritis
 - c. Serositis
 - d. Renal
 - e. Hematologic
 - f. Immunologic markers
4. A complex disease characterized by autoantibodies and multisystem involvement
5. A central role for β cells in pathogenesis as evidenced by early breakdown of tolerance
6. Autoantibodies pathogenic role in autoimmunity include:
 - a. Immune complex mediated type III hypersensitivity reactions
 - b. Type II antibody-dependent cytotoxicity
 - c. Innate immune cell production of inflammatory cytokines
7. A role for toll-like receptors in the link between the innate and adaptive immune systems in SLE immunopathogenesis
8. Associated neurologic manifestations
 - a. Psychosis

- b. Proximal myopathy
- c. Mononeuritis multiplex
- d. Migraine headaches
- e. Sensorimotor neuropathy
- f. Chorea
- g. Seizures
- h. Stroke (pial arteries; multifocal)
- i. Retinal findings:
 - i. Cytoid bodies
 - ii. Increased nicking of arterioles

Clinical Manifestations

1. Stroke
 - a. Embolic stroke (Libman-Sacks endocarditis)
 - b. Coagulopathy
 - i. Lupus anticoagulant
 - ii. Anticardiolipin antibody
 - c. Non-inflammatory vasculopathy
 - d. Small deep infarcts
 - i. Associated HCV
 - e. Intracranial branch artery occlusion
 - f. Cortical and subcortical infarcts (arteritis)
 - g. Large Vessel Stroke (Atherosclerosis)
 - i. In approximately 86% of patients the disease is active at stroke occurrence
 - ii. Stroke occurs after 4–5 years of disease
 - iii. Headache is common at onset
 - iv. Often associated with low protein S activity
 - v. Antiphospholipid antibody associated with Libman-Sacks endocarditis
 - vi. Global depression of left ventricular function
 1. Cardiac small vessel arteritis
 2. Poor ejection fraction and embolus
 3. Thrombogenic cytokines
 - h. Unusual Vascular Manifestations:
 - i. Vertebrobasilar territory infarction at presentation
 - ii. Vascular monocular or binocular optic neuropathy
 - iii. Posterior ischemic optic neuritis

General Neurologic Manifestations

1. Seizures
2. Psychiatric
3. Proximal myopathy
4. Peripheral neuropathy (mononeuritis multiplex)

Cerebrovascular Manifestations

1. Microinfarcts and hemorrhages
 - a. May be asymptomatic
 - b. Noted at autopsy
2. Minimal evidence to support vasculitis as a cause of stroke
 - a. Vasculitis does occur in the kidney and skin
 - b. Vasculopathy is well documented in the cerebral circulation
3. Cardiac emboli
 - a. Libman-Sacks endocarditis

- i. Non-endothelium covered verrucous deposition of hyalinized blood and platelet thrombi on cardiac valves
- ii. Mitral valve is most commonly affected with Libman-Sacks endocarditis
- iii. SBE may occur
- iv. Cardiac valvular lesions are associated anticardiolipin antibodies

Hypercoagulable State

1. Lupus anticoagulant and anticardiolipin antibody associated with:
 - a. Spontaneous abortions
 - b. Venous thrombosis
 - c. Stroke
2. Lupus anticoagulant may have higher risk of stroke than anticardiolipin antibodies:
 - a. Anti- β_2 glycoprotein I antibodies patients may have a high risk of stroke
 - i. Facilitate the binding of antiphospholipid antibodies to phospholipids
3. Deficits on endothelial function and fibrinolytic pathways occur with SLE
 - a. Decreased endogenous tissue plasminogen activator (tPA)
4. Accelerated atherosclerosis
 - a. Steroid induced atherogenic lipid profile
 - b. Increased low-density lipoprotein immune complexes

Neuropathology

1. Vasculopathy
 - a. Perivascular inflammatory infiltrates and hemorrhages
 - b. Proliferation of blood vessels
 - i. Vascular occlusions with recanalization
 - c. Small arteries and arterioles primarily affected
2. Widespread microinfarcts in the cerebral cortex and brainstem
 - a. Destructive and proliferative changes in arterioles and capillaries
 - b. Attachment of immune complexes to the vessel walls in mechanism of vascular injury
 - c. Thrombocytopenia
 - d. Platelet abnormalities
 - e. Thrombotic thrombocytopenic like syndrome:
 - i. Platelet thrombi in arteries and capillaries
 - ii. Subendothelial hyalin deposits
 - iii. Arterial microaneurysm

Neuroimaging

1. Decreased fractional anisotropy in frontal white matter
2. Voxel based morphometry and diffusion tensor imaging demonstrate deficits in both white and gray matter
3. Microinfarcts in the cerebral cortex
 - a. Destructive and proliferative changes in arterioles and capillaries

- b. Attachment of immune complexes to the vessel wall
- c. No cellular infiltration
- 4. ICH from hypertension
- 5. Cerebral emboli with topographic localization from Libman-Sacks endocarditis
- 6. TTP in the terminal phase

MRI

- 1. 3 Tesla
 - a. Multifocal with matter hyperintensities
 - b. Embolic stroke of major arteries
- 2. 7 Tesla
 - a. Microvascular lesions detected with ultrahigh field MRI
 - b. Minute punctate/linear hyperintense lesions in cortical and subcortical locations

Laboratory Evaluation

- 1. Antibodies to double-stranded DNA (anti-ds DNA)
- 2. Positive anti-nuclear antibodies
- 3. Increased ESR and C-reactive protein; increased alarmin expression
- 4. Antiphospholipid antibodies
- 5. CSF
 - a. May be normal
 - b. Mild lymphocytic pleocytosis
 - c. Slight increase in protein

Sickle Cell Disease

General Characteristics

- 1. Autosomal recessive inheritance
 - a. β globulin gene substitution in codon 6 that forms abnormal hemoglobin (HbSS) disease
 - b. HbSS constitutes 60–70% of the hemoglobinopathies
 - c. Hemoglobin is a heterotetramer with 2α and 2β chains
 - d. Substitution of glutamine to valine in codon 6 of the β globin gene
- 2. Risk factors for ischemic stroke in children
 - a. Overt or silent stroke (MRI)
 - b. Increased cerebral blood flow
 - c. Aplastic crises
 - d. Nocturnal hypoxemia
 - e. Acute chest syndrome
 - f. Seizures
 - g. SEM globin gene haplotype
- 3. Risk factors for ischemic stroke in adults
 - a. Increased homocysteine
 - b. Prior TIA
 - c. Atrial fibrillation
 - d. Hyperlipidemia
 - e. Diabetes mellitus
- 4. HbS > HbC for risk of ischemic stroke; HbA has little or no risk of ischemic stroke

Clinical Manifestations

- 1. Risk of ischemic stroke is higher in homozygous SS disease than SC disease

- 2. HbS disease < 30–50% of total hemoglobin decreases risk of ischemic stroke
- 3. Sickle cell disease in children
 - a. Ischemic brain disease often manifest by:
 - i. Silent brain infarction
 - ii. Microvascular infarction with cognitive decline
 - b. Increased risk of ischemic stroke may be associated with:
 - i. History of seizure
 - ii. Leukocyte count > 11.8 grams/L
 - iii. Low pain event rate
 - c. Significant risk of ischemic stroke occurs with:
 - i. Elevated flow rate by transcranial Doppler

Rarer Cerebrovascular Manifestations

- 1. Primarily in children
 - a. Subdural hematoma
 - b. Subarachnoid hemorrhage
 - c. Moyamoya syndrome
 - d. ICH

Clinical Manifestations of Chronic Vasculopathy in Adults

- 1. Large and small vessel stroke
- 2. Silent infarcts

Clinical Manifestations

- 1. HbS disease
 - a. Scleral telangiectasia
 - b. Arachnodactyly
 - c. Auto-splenectomy
 - d. Pneumococcal peritonitis
 - e. Meningitis
 - f. Bone marrow infarction
 - g. Severe joint and abdominal pain
 - h. Acute chest syndrome
 - i. Numb chin syndrome

Neurological Complications

- 1. Occlusive disease of large intracranial arteries and small penetrating vessels
- 2. Silent infarcts
 - a. About 20% in children
 - b. Cognitive impairment without overt ischemic stroke in children
- 3. Dilated and ectatic arteries
- 4. Moyamoya collateral patterns (MCA or terminal carotid occlusion)
- 5. SAH (rare)

SSA Disease

- 1. Stroke propensity

SC Disease

- 1. “Sea fan” macular sign (abnormal collection of blood vessels)
- 2. Propensity of strokes during pregnancy
- 3. Aseptic necrosis of the hip

Neuropathology

1. Large infarcts and/or hemorrhages in the cerebral hemispheres
2. Thrombosis of major branches of the Circle of Willis
3. Arterial occlusive disease in the terminal portions of the internal carotid arteries as well as their proximal segments
4. Microinfarcts
 - a. Diffuse gliotic scars in the deep white matter and cerebral gray
5. Vaso-occlusive disease
 - a. Thrombin and antithrombin complexes (TAT) and D-dimer are correlated with both stroke and retinopathy
6. Other pathologic mechanisms include:
 - a. Platelet activation from endothelial injury
 - b. Sickled erythrocyte adhesion to endothelium
 - c. Decreased erythrocyte deformability
 - d. Remodeling of the arterial wall leading to stenosis and occlusion
 - i. Small vessels affect more than large vessels
7. Thickened arterial walls from intimal and subintimal proliferation
8. Rare thrombosis of veins and cerebral sinuses
9. Deoxygenated HbS interaction with other HbS molecules leads to RBC polymerization
 - a. Decreased RBC deformability
 - b. Vaso-occlusion of vessels and the vaso-vasorum
10. Sickled cells
 - a. Adhere to the endothelium
 - b. Activate inflammatory cells and clotting factors that form the nidus for thrombosis
 - c. Initiate small vessel sludging
 - d. Deficiency of endothelial nitric oxide which decreases compensatory vaso dilation

*Neuroimaging***MRI**

1. Infarction and ischemic lesions (children) involve both cortex and deep white matter
2. Silent lesions most often seen in deep white matter

Transcranial Cranial Doppler

1. <170 cm/sec decreases risk of ischemic stroke
2. >200 cm/sec increases risk of ischemic stroke
 - a. Velocities above 200 cm/second may occur in large vessels

MRI/MRA

1. Silent infarction
2. Cortical and subcortical infarction
3. Border zone infarction
4. Moyamoya syndrome

Varicella Zoster Virus*General Characteristics*

1. Stroke most often occurs after Vth cranial nerve infection (first division of the Vth cranial nerve)

2. Annual incidence of 1010/100,000 people aged 80–90 years of age
3. Immunocompetent host CNS involvement occurs in 1.5 to 4% of patients
 - a. Higher incidence in immunocompromised patients
4. Thoracic dermatomes are most commonly involved: severely painful with dynamic mechcanoallodynia

Clinical Manifestations

1. Middle cerebral artery stroke may occur 10 to 14 days after the skin lesions appear

Neurological Complications

1. Cranial neuropathy
2. Post herpetic neuralgia
3. Encephalomyelitis
4. Optic neuritis
5. Leukoencephalopathy
6. Ventriculitis
7. Transverse myelitis

Cerebrovascular Manifestations

1. Delayed brain infarction following infection
2. Contralateral hemiplegia from ipsilateral MCA involvement
3. Days to 6–8 weeks following onset of the rash
4. Concomitant encephalitis
5. Rash may occur in V₂ or V₃ as well as V₁ distributions
6. Rare involvement of OCA or the vertebrobasilar territory

*Neuropathology***Early VZV Infection**

1. Infected arteries contain:
 - a. CD4+ and CD8+ T-cells
 - b. Macrophages
 - c. Rare B-cells and neutrophils
2. Perivascular inflammatory cells underlie areas of thickened intima (suggestive that soluble factors are released)
 - a. Infection is initiated in the adventitia
 - b. Hypertrophic intima is composed of cells expressing smooth muscle actin
 - c. Decreased smooth muscle cells

Late VZV Arterial Infection

1. Viral antigens, but not leukocytes (no inflammation) are seen in the media
2. Ischemic strokes are predominant with approximately 18% being multifocal
3. Some multifocal strokes are hemorrhagic
4. Productive virus in infected cerebral arteries (both large and small)
5. Occasional signs of arteritis
6. Concomitant VZV infiltration into the parenchyma (frontal and temporal lobe)
7. Rare SAH
8. Basilar meningitis (rare)

*Neuroimaging***MRI**

1. Middle cerebral artery stroke (stem artery involvement)
2. Hemorrhagic multifocal strokes

MRA

1. Signs of angiitis; small arteries more than large arteries
2. Stenosis of proximal MCA and basilar artery
 - a. Induce large infarction
3. Occlusion of the supraclinoid ICA
 - a. May be preceded by TIA
 - b. Usual clinical onset is that of an abrupt stroke
4. Stenosis of intracranial large conducting vessels
5. Small artery involvement is less common
6. Multiple superficial and deep infarcts

Laboratory Evaluation

1. VZV specific IgG antibodies in CSF
2. Detection of VZV DNA by PCR

Posterior Fossa Malformations, Hemangiomas, Arterial Malformations, Cardiac Defects, Eye Abnormalities and Sternal Cleft Syndrome (PHACES Syndrome)*General Characteristics*

1. Occurs in a significant number of children with a facial hemangioma have PHACES syndrome
2. Female to male predilection of 9:1
3. A childhood disease but does occur in adults
4. Arterial cerebrovascular malformations
5. Abnormal neural crest migration is the putative cause

Clinical Manifestations

1. Posterior fossa malformations
2. Facial hemangiomas
3. Cardiovascular anomalies
4. Eye abnormalities
5. Sternal clefting or supraumbilical raphe lesion
6. Ischemic stroke usually occurs prior to one year of age
7. Rare that all features occur in one patient

Neuropathology

1. Abnormal neural crest migration is the putative cause

Cerebrovascular Manifestations

1. Dysplasia of large cerebral arteries
2. Arterial stenosis or occlusion with or without Moyamoya collaterals
3. Absence or moderate to severe hypoplasia of the large cerebral arteries
4. Persistence of embryonic arteries and arrest of normal vasculature development
5. Vascular abnormalities often are Ipsilateral to the cutaneous hemangiomas; may be bilateral

Categories of Arterial Anomalies

1. Dysplasia

2. Narrowing
3. Aberrant course or origin
4. Persistence of embryonic anastomosis
5. Progressive vasculopathy
 - a. Putatively related to the proliferative phase of hemangioma evolution

Neuroimaging

1. Agenesis of cervical carotid arteries
2. Persistent embryological vessels
3. Arterial stenosis
4. Dolichoectasia of intracranial arteries

Neurofibromatosis, Type I*General Characteristics*

1. NF1 is the most prevalent autosomal dominant disease in humans
 - a. Mutation in the NF1 gene located on chromosome 17q11.2
2. Mutation of gene on chromosome 17
 - a. Protein encoded is neurofibromin; a GTPase-activating enzyme
3. Incidence ranges from 1:2500 to 1:3000 live births

Clinical Manifestations

1. General Neurologic Complications
 - a. Seizures
 - b. Learning disabilities
 - c. Attention deficit disorder
2. Intracranial lesions include:
 - a. Optic gliomas
 - b. Sphenoid wing dysplasia or absence (unilateral pulsatile exophthalmos)
3. NF1 vasculopathy includes:
 - a. Arterial system is most commonly affected
 - b. Occlusion of vessels
 - c. Pseudoaneurysm formation
 - d. Aneurysm
 - e. Ectasia
 - f. Fistula
 - g. Moyamoya syndrome
4. Café-au-lait spots (greater than 6) Lisch nodules (iris) neurofibromas
5. Increased incidence of glial malignant tumors: myelogenous leukemia, pheochromocytoma (benign)
6. Peripheral nerve sheath tumors, malignant peripheral nerve sheath tumors
7. Vasculopathy
8. Optic nerve glioma
9. Learning disabilities
10. Attention deficit disorder
11. Sphenoid wing dysplasia
12. Pseudoarthrosis of the tibia

Neuropathology

1. Most commonly affects arteries. The process does affect veins and vessels of all sizes

2. The carotid artery is most commonly affected followed by the middle and posterior cerebral artery
3. Occlusion of the lumen and hyperplasia of the intima
 - a. Dysfunction of neurofibromin that causes excessive proliferation of vascular smooth muscle cells
 - b. Neurofibromin putatively helps with the maintenance of the endothelial cell layer
4. Moyamoya syndrome in patients with NF1 often involves anterior circulation territories
 - a. Progresses to bilateral disease in 10% of patients
5. NF1 vasculopathy affects arterial and venous blood vessels of all sizes
6. Two major vascular pathologies in NF1
 - a. Occlusive intimal form that affects small arteries
 - b. Aneurysmal form with replacement of the muscular wall with fibrohyaline thickening in arterioles of .1–1 mm
7. Arterial lesions caused by:
 - a. Proliferation of Schwann cells within arteries and proliferation of smooth muscle
 - b. Secondary fibrosis
 - c. Other arteries affected include:
 - i. The abdominal aorta
 - ii. The mesenteric arteries
 - iii. Visceral arteries
 - iv. Muscular arteries
 - d. May also present with multiple arterial aneurysms and venous thrombosis
8. Vascular anomalies:
 - a. Intra- and extracranial arterial connections
 - b. Often present with concomitant intravascular occlusive disease
 - c. Large and medium-sized arteries are affected in any territory
 - d. Possible dysfunction of neurofibromin in blood vessel endothelial and smooth muscle cells
 - e. Recurrent strokes occur in the same or different territories
 - i. Internal carotid artery > MCA > PCA are affected
 - f. Both intra- and extracranial vessels can accrue stenotic lesions
 - g. Hemispheric territorial infarction is most common
 - h. Lacunar infarction and ocular ischemia (retinal) and global occur
9. Aneurysm
 - a. Occurs in the vertebral or other large neck arteries that can present as:
 - i. Large neck mass
 - ii. Brachial plexus lesion
 - iii. Medullary compression syndrome
 - b. Intracranial saccular and fusiform aneurysms occur at:
 - i. Circle of Willis
 - ii. Distally (posterior choroidal artery)
 - iii. Fusiform aneurysm of the intrapetrosal carotid artery cause:
 1. Spheroid wing dysplasia or VIth nerve palsy

- c. The form of the disease associated with cerebral aneurysms is the intimal aneurysmal form
- d. Moyamoya disease
 - i. Slowly progressive distal carotid stenosis
- e. Arteriovenous malformations
- f. Renal artery stenosis with hypertension

Neuroimaging

MRI/MRA

1. “Unidentified bright objects” throughout the hemispheres
 - a. Multiple small foci noted in T2-weighted sequences

MRA/DSA

1. Demonstrates occlusion of the terminal branches of the internal carotid arteries

Angiography

1. Occlusive arterial disease
 - a. Focal concentric stenosis
 - b. Long segment irregular narrowing
 - c. Hypoplasia without luminal narrowing
 - d. Does not occur at bifurcations (as opposed to atherosclerosis)
2. Arteriovenous fistula particularly of the vertebral arteries is associated with:
 - a. Stenosis and pseudo-aneurysmal dilatation of the feeding vessel
3. Moyamoya changes (lenticulostriate collaterals) from gradual bilateral carotid occlusion
 - a. Extensive leptomeningeal collaterals from the external carotid to the Circle of Willis due to proximal occlusions of major intracranial vessels

Tuberous Sclerosis Complex

General Characteristics

1. Tuberous sclerosis complex (TSC)
 - a. Autosomal dominant
 - b. Cardiac rhabdomyomas that cause emboli
 - c. 80% are new mutations
 - d. Abnormalities of cerebral arteries and aorta also occur
2. Characterized by the development of hamartomas in several organs that include:
 - a. Renal angiomyolipomas
 - b. Cardiac rhabdomyoma
 - c. Subependymal giant cell astrocytoma

Clinical Manifestations

1. Epilepsy
2. Mental retardation
3. Autism
4. Arteriopathy is usually asymptomatic

Cerebrovascular Manifestations

1. Ischemia in territories of the affected vessels
2. Emboli from thrombi in ectatic aneurysms
3. SAH from ruptured aneurysms
4. Dolichoectasia

Neuropathology

1. Tubers throughout the brain
2. Subependymal giant cell astrocytoma
3. Peripheral and central aneurysms (rare)
4. Dolichoectasia

Neuroimaging

1. Multiple tubers throughout the brain
2. Subependymal giant cell astrocytoma of the IIIrd ventricle
3. Poor white-gray matter junction demarcation in many cortical gyri

Familial Occipital Calcification*General Characteristics*

1. Probable autosomal dominant inheritance
2. Late onset of dementia
3. Patchy leukoencephalopathy
4. Intracerebral hemorrhages
5. Bilateral occipital calcifications
6. External carotid artery dysplasia

Clinical Manifestations

1. Late onset dementia
2. Intracranial hemorrhage
3. Ischemic stroke

Neuropathology

1. Skin biopsy:
 - a. Multilayered round shaped calcifications in the basal lamina of capillaries
 - b. Capillary vasculopathy

*Neuroimaging***MRI**

1. Fine tram tracking bilateral occipital calcifications
2. Severe leukoencephalopathy
3. Bilateral external carotid dysplasia

Emboli and Valvular Disease**Cerebral Emboli****Overview of Cerebral Emboli**

The overwhelming source of embolic material that blocks the cerebral circulation comes from artery-to-artery (burst plaque cholesterol, lipid and fibrous debris) or larger red fibrin clots from the heart. The specific setting and medical history are pivotal in determining the source and mechanism of the event. The neurological deficit occurs suddenly, usually during activities of daily living. As noted earlier thrombotic infarction often occurs in the early morning (4–6 AM from acidosis with platelet activation, REM sleep induced cardiac arrhythmias, circadian induced hypotension). The deficit often progresses over several days. Intracranial

hemorrhage from hypertension occurs during wakefulness. Headache, nausea and neurologic deficit progresses and does not clear. SAH causes severe headache that reaches maximum intensity instantly often with minimal neurologic deficit (IIIrd cranial nerve with P-Com aneurysm, behavioral change and leg weakness with an A-Com aneurysm and mild to moderate hemiparesis with an MCA aneurysm). Headache and seizures do occur with cerebral emboli in about 10% of patients but are non-specific. The deficits from emboli start to clear early. This occurs from break-up of the clot, the development of the collateral circulation and early recanalization of the artery. The development and use of both thrombolysis and mechanical thrombectomy have opened a new chapter in the diagnosis and treatment of cerebral embolization. In general, thrombolysis is most effective with distal embolization and mechanical thrombectomy with larger proximal vessel occlusion. Age, the severity of the initial deficit (NIHSS > 14), the time from ictus to treatment, hyperglycemia and comorbidities determine success. The degree of recanalization of the affected vessel and the time to treatment (cerebral parenchymal ischemic time) determine the clinical outcome. Multiple protective devices are being utilized and tested to decrease cerebral emboli from aneurysmal coiling, treatment of vascular malformations and stenting procedures. Rarely fat emboli occur from long bone fracture in the young to hip replacement in the elderly. The problem may be fat coming out of solution triggered by a small amount of fat that enters the circulation from the trauma. Chest petechia, fat globules in the retina and urine are diagnostic. The pO₂ is often low at presentation due to concomitant pulmonary involvement. A late stage encephalopathy may occur. Air emboli occur from cardiac, neurosurgical, ENT and obstetrical procedures (primarily from the patient in the sitting position or severely dilated pelvic veins) and cause severe arterial spasm. Rarely nitrogen bubbles (diving), food particles (esophageal atrial fistula) and calcium block the cerebral circulation.

Other unusual sources of artery-to-artery emboli are from:

1. Giant aneurysm (tip of the basilar to PCA)
2. AVM (usually embolic material during treatment)
3. The intimal flap of dissections
4. Carotid allegro (multiple episodes of amaurosis fugax) or neurologic symptoms and signs from a burst carotid plaque

Simultaneous ACA and MCA involvement is characteristic of a carotid siphon localization for embolic material. Broca's and Wernicke's aphasia without hemiparesis can occur in this instance from simultaneous involvement of branches of the superior and inferior MCA.

Cardioembolic stroke is:

1. The mechanism for approximately 25% of cerebral emboli
2. Its incidence increases with age and in patients greater than 85 years old, may be as high as 36%
3. Basic mechanisms are due to any of the following:
 - a. An enlarged left atrium, atrial appendage or ventricle
 - b. Valvular emboli

c. Paradoxical embolism

d. Low ejection fraction

Cardiac emboli are:

1. Large, red (fibrin platelet clots) and tend to cause large strokes
2. The risk of early recurrence is between 1–10%
3. The underlying potential source of cardiac embolism in the absence of significant arterial disease is pivotal for diagnosis. It becomes more difficult when arterial disease and a cardiac cause coexist (atrial fibrillation and concomitant ulcerated carotid plaque)

The clinical features of an embolus are:

1. Sudden onset with maximum deficit at ictus (less than 5 minutes is present in 47–74% of patients)
2. Sudden neurological deficit occurs in approximately 80% of patients while less than 50% in thrombotic stroke and less than 40% in lacunar strokes
3. In a small number of patients (5–12%) there is a spectacular shrinking deficit syndrome on MRI (distal migration and breakup of the clot and recanalization of the affected vessel)
4. Wernicke's aphasia (inferior division of the MCA temporoparietal occipital branch) or global aphasia (stem MCA) without hemiparesis is a common clinical features

Posterior circulation emboli typically cause:

1. Visual field deficits (often superior quadrants)
2. Complete or partial Wallenberg syndrome
3. Top of the basilar syndrome (occlusion of the top of the basilar artery)
4. Multilevel infarcts (brain stem, midbrain, thalamic, parietal and occipital lobe) from tumbling emboli that fragment
5. PCA infarction

In general, visual field deficits, neglect, and a posterior aphasia, (particularly Wernicke's) are more common in cardioembolic than in thrombotic disease.

Perhaps more common but non-specific clinical features of cardioembolism are seizures (irritation of the cortex), headache and onset with activity. Onset of a neurologic deficit with a Valsalva maneuver (coughing, lifting and strain causing an increase of right atrial pressure) are suggestive. Lacunar syndromes occur from emboli but are rare (3–5%).

Hemorrhagic transformation and early recanalization of the occluded vessel suggest cardiac emboli.

Hemorrhagic transformation:

1. Occurs in approximately 70% of cardioembolic stroke
2. Are primarily petechial or multifocal
3. Hemorrhagic transformation may be predicted from:
 - a. A depressed level of consciousness
 - b. Total vessel occlusion
 - c. NIH Stroke Scale score greater than 14
 - d. Stem MCA occlusion
 - e. Greater than one third of MCA territory ischemia by CT
 - f. Decreased collateral perfusion

The most common etiologies of cardiac embolism are:

1. Atrial fibrillation
2. Recent myocardial infarction
3. Mechanical prosthetic valves (mitral > aortic)
4. Dilated cardiomyopathy (ejection fraction < 30%)
5. Infective and marantic endocarditis
6. Atrial myxoma

Less common causes of cardiac emboli are:

1. Patent foramen ovale (PFO) with or without atrial septal defect
2. Atrial or ventricular septal defects
3. Calcific aortic stenosis
4. Mitral annular calcification
5. Complex aortic arch atheromatosis

Early and late embolic recurrences are common and are associated with a higher mortality.

The recurrence occurs (in less than 15%) within two weeks, possible risk factors for recurrence are:

1. Alcohol abuse
2. Hypertension with valvular heart disease and atrial fibrillation
3. Nausea and vomiting
4. Previous cerebral infarct
5. In hospitalized patients, recurrent embolization is associated with:
 - a. Tachyarrhythmias
 - b. Congestive heart failure
 - c. Acute myocardial infarction

Clinical Manifestations of Cerebral Emboli

1. An abrupt onset of a neurological deficit, aphasia (particularly Wernicke's without hemiparesis) in a setting of atrial fibrillation, low ejection fraction, prosthetic heart valve or SBE
2. MCA > PCA > ACA are the most frequent arterial territories affected
 - a. Large fibrin/platelet clots are associated with major deficits
 - i. Rare lacunar territory stroke
 - ii. Early resolution of the deficit

Preceding Symptoms and Signs of Cerebral Emboli

1. Approximately 10% of patients have prodromal symptoms prior to the presenting ictus:
 - a. Stuttering focal deficits due to:
 - i. Distal movement of prior embolus
 - ii. Development of the collateral circulation
 - iii. Recanalization
 - b. Cerebral infarction from cardiac emboli may be preceded by transient ischemic attacks, that are longer than artery-to-artery (cholesterol, platelet, plaque debris) emboli
 - i. Cardiogenic emboli cause deficits that last minutes to hours
 - ii. Artery-to-artery emboli cause a 2 minute deficit (particularly retinal emboli with amaurosis fugax);

the larger the embolus, the longer the deficit (in general)

2. Anterior circulation pattern:
 - a. Focal motor, sensory deficits with or without aphasia
 - b. Muteness:
 - i. Stem MCA (global aphasia)
 - ii. ACA (supplementary motor area; causes an acute apraxia of speech)
 - c. Seizures occur in approximately 10% of patients (along with headache are not specific for emboli)
 - d. About 10% of patients lose consciousness at ictus

Neuropathology of Cerebral Emboli

1. Atheromatous plaque located in the internal carotid artery at the origin from the common carotid:
 - a. In the cervical component of the vertebral arteries and at the junction that forms the basilar artery
 - b. At the stem or bifurcation of the MCA
 - c. Proximal posterior cerebral arteries (perimesencephalic portion)
 - d. Proximal anterior cerebral arteries
 - e. Rare for plaque to develop:
 - i. After the first major branching from the Circle of Willis
 - ii. In the ophthalmic and cerebellar arteries
2. Alternate sites of embolic material
 - a. Thrombus from the heart
 - b. From the distal end of a thrombus within the lumen of an occluded or severely stenotic vessel
 - c. Thrombotic material from involved heart valves
 - d. Subacute Bacterial Endocarditis
3. Non-bacterial thrombotic emboli
4. Clots from prosthetic heart valves
5. Rare embolic material:
 - a. Fat
 - b. Air
 - c. Tumor cells
 - d. Fibrocartilage
 - e. Amniotic fluid
 - f. Calcium particles
6. Atheromatous plaque from the aorta
7. Hemorrhagic infarction is suggestive of embolism

Neuroimaging of Cerebral Emboli

MRI of Cerebral Emboli

1. Wedge shaped deficit (involving the cortex)
2. Multiple deficits in different vascular territories (need to rule out intracranial atherosclerosis)
3. Evidence of prior deficits
4. Rule out mimics (metastasis, subdural hematoma, conophilic angiopathy)

Cardiac Emboli

Vertebrobasilar Signs and Symptoms of Cardiac Emboli

1. Partial Wallenberg syndrome

2. Diplopia (particularly IIIrd > VIth cranial nerve, interpeduncular artery to the midbrain rather than a branch artery from the basilar artery)
3. Ataxia
4. Vertigo
5. Crossed or bilateral sensory or motor deficits
6. Rarely depressed levels of consciousness at onset
7. Top of the basilar syndrome

Neuropathology of Cardiac Emboli

1. Clots breakup an infarction can be seen in the medulla, thalamus and parietal or occipital cortex

Neuroimaging of Cardiac Emboli

MRI of Cardiac Emboli

1. Bilateral cerebellar deficits
2. Multilevel deficits (brainstem, midbrain, thalamus, cortex)

MRA/DSA of Cardiac Emboli

1. Sharp, tapering cut off in the affected artery

Angiography of Cardiac Emboli

1. Abrupt tapering of an artery
2. Rarely long segment may be vasoconstricted

Myocardial Infarction and Ischemic Heart Disease as a Source of Emboli

General Characteristics of Myocardial Infarction and Ischemic Heart Disease as a Source of Emboli

1. Arterial emboli occur in 2–4% of patients after myocardial infarction

Clinical Manifestations of Myocardial Infarction and Ischemic Heart Disease as a Source of Emboli

1. Time of occurrence:
 - a. 10% in the first week
 - b. 35% in the second week
 - c. 15% in the third week
 - d. 5% in the 3rd month
 - e. Newer studies suggest the first 5 days are the major time of risk
2. Mural thrombi occur with higher incidence in:
 - a. Large infarctions
 - b. Transmural infarction involving the intraventricular septum
 - c. Associated congestive heart failure
 - d. Anterior > posterior wall infarction
 - e. Severe apical wall dyskinesia
 - f. 75% of major anterior transmural infarctions have dyskinesias

Neuroimaging of Myocardial Infarction and Ischemic Heart Disease as a Source of Emboli

Echocardiography of Myocardial Infarction and Ischemic Heart Disease as a Source of Emboli

1. Most mural thrombi identified by TEE (transthoracic echocardiography) can be seen in 3–5 days

- a. Embolize at 4 days
- b. Rare embolization after 4 to 6 weeks
2. Echocardiographic correlates of ventricular dysfunction are:
 - a. Spontaneous ECHO contrast ("smoke")
 - i. Swirling haze within cardiac chambers
 - ii. Interaction of plasma protein, erythrocytes and shear rate
 - b. Determinants of "smoke":
 - i. Slow intracardiac flow
 - ii. Hematocrit
 - iii. Fibrinogen level

Neuropathology of Myocardial Infarction and Ischemic Heart Disease as a Source of Emboli

1. Thrombi within cardiac chambers are due to:
 - a. Stasis of blood that initiates:
 - i. Activation of factor XII and the endothelium of the cardiac surface
 - b. Endothelial cardiac wall injury causes:
 - i. Loss of the endothelium
 - ii. Change of negative to positive charge on the cardiac endothelial surface and exposed collagen
 - iii. Platelet aggregation at the site of charge change
 - c. Prothrombotic state is initiated by:
 - i. Low shear rate of circulating RBC within the cardiac chambers

Left Ventricular Thrombi

General Characteristics of Left Ventricular Thrombi

1. Occur in 20–40% of patients with anterior wall myocardial infarction
2. Form in the apical wall of the left ventricle

Clinical Manifestations of Left Ventricular Thrombi

1. Long duration (>1 hour) of neurologic deficits

Neuropathology of Left Ventricular Thrombi

1. Superior branch of the MCA territory
2. Large cerebral artery occlusions may occur in two arterial circulations
3. Mechanisms include:
 - a. Low ejection fraction
 - b. Left ventricular aneurysm
 - c. Dyskinesia from decreased contractility
4. Concomitant with antiphospholipid syndrome
5. Axillary vein I.V. access

Mural Thrombi in Ventricular Aneurysms

Neuropathology of Mural Thrombi in Ventricular Aneurysms

1. 7.6% of patients develop intraventricular aneurysms after an myocardial infarction (MI)
2. Mural thrombi occur in 50% of ventricular aneurysms
3. Clinical emboli occur in 1–3% of patients per year
4. Usually occur within 4–6 weeks after myocardial infarction

Impaired Left Ventricular Contraction

Clinical Manifestations of Impaired Left Ventricular Contraction

1. Risk of stroke is 4.6%
2. Ejection fraction of less than 28% is the highest risk
3. Asymptomatic or unexpected cardiac ventricular thrombi occur in
 - a. A patient with stroke is noted to have cardiac thrombi without known coronary artery disease
 - b. Known cardiac thrombi may regress

Arrhythmia and Cerebral Emboli

Clinical Manifestations of Arrhythmia and Cerebral Emboli

1. Most common arrhythmias associated with stroke:
 - a. Chronic atrial fibrillation
 - b. Intermittent atrial fibrillation
 - c. Sick sinus syndrome
2. The majority of cardiogenic emboli are cerebral

Cardiac Arrhythmia – Atrial Fibrillation (AF)

General Characteristics of Atrial Fibrillation

1. 2–5% of the population > 60 have atrial fibrillation
2. 35% of patients with untreated atrial fibrillation will have an ischemic stroke over their life time
3. Approximately 4% of atrial fibrillation patients suffer a stroke each year
4. Atrial fibrillation with no associated risk factors <2% of stroke per year
5. Atrial fibrillation with known risk factors:
 - a. Approximately 6% strokes per year
 - b. Atrial fibrillation and stroke; 75% have had an ischemic event secondary to Atrial fibrillation
 - c. Atrial fibrillation plus rheumatic heart disease (RHD)
 - i. 17 fold increase of stroke risk
 - d. Atrial fibrillation without rheumatic heart disease
 - i. 5.6 fold increase of stroke risk
 - e. Atrial fibrillation increases risk of stroke with age
 - f. Atrial fibrillation increases the risk of silent infarction
 - g. 25% of stroke patients >70 years of age have non-valvular atrial fibrillation (NVAf)
 - h. Non-valvular atrial fibrillation (NVAf) – 3× greater risk of stroke related death
 - i. Left atrial enlargement and decreased function causes increased risk of cardiac emboli
 - j. Embolus rate highest after the onset of dysrhythmia
 - k. 12% of patients' cardioverted for AF suffer an embolus within the first few days of the procedure
6. Causes of atrial fibrillation:
 - a. 10–30% of AF no identifiable cardiovascular disease
 - b. Identified causes include:
 - i. Dilated left atrium in mitral stenosis
 - ii. Thyrotoxicosis
 - iii. Pericarditis
 - iv. Ischemic cardiac disease
 - v. Hypertension
 - vi. Alcohol abuse

Neuropathology of Atrial Fibrillation

1. Origin of embolic material:
 - a. Left atrium or the left atrial appendage
 - i. 15–50% of valvular atrial fibrillation (VAF) have thrombi in the left atrium
 - ii. Autopsy evidence of arterial emboli in 40% of non-valvular atrial fibrillation (NVAF)
 - b. Valvular disease with atrial fibrillation
 - i. 9–29% have left atrial thrombi
2. Stasis of blood in the AF heart are associated with:
 - a. Increased concentration of fibrinogen D-dimer
 - b. von Willebrand disease

Clinical Manifestations of Atrial Fibrillation

1. Acute Wernicke's aphasia as sole clinical finding:
 - a. Embolus to the temporal-parietal occipital branch of the inferior division of the MCA
2. Highest risk for embolization:
 - a. Evidence of rheumatic heart disease
 - b. Onset of atrial fibrillation within the preceding 3 months
 - c. An enlarged left atrium

Recurrent Embolism in Non-Valvular Atrial Fibrillation (NVAF)

1. 50% of patients with cerebral embolism from atrial fibrillation suffer a second embolic stroke
2. Recurrence is greatest during the first days to weeks (15–20% of patients); some evidence that the greatest risk is at 12–24 hours

Cardiac Arrhythmia – Paroxysmal Atrial Fibrillation*General Characteristics of Paroxysmal Atrial Fibrillation*

1. Cerebral emboli occur during a paroxysm of atrial fibrillation
2. Thrombi form during the arrhythmia
3. Cerebral rather than peripheral arteries are affected
4. 2% may occur at the time of cardioversion
5. Chronic and recurrent atrial fibrillation carry the same risk
6. Paroxysmal atrial fibrillation is being uncovered in an even larger proportion of cryptogenic stroke patients with prolonged monitoring

Neuropathology of Paroxysmal Atrial Fibrillation

1. Occlusion of large arteries
 - a. MCA territory
 - b. Top of the basilar artery
 - c. Inferior division of the MCA
 - d. Multiple circulations
 - e. In young patients with minimal atherosclerotic plaque

Cardiac Arrhythmia – Sick Sinus Syndrome*General Characteristics of Sick Sinus Syndrome*

1. Chaotic atrial activity
2. 29.9% of men and 1.5% of women over 75 years of age may suffer the syndrome
 - a. 14–18% of patients suffer cerebral emboli

Clinical Manifestations of Sick Sinus Syndrome

1. Associated arrhythmias:
 - a. Atrial fibrillation or atrial flutter with slow rate of response (70 beats per minute)
 - b. Sinoatrial arrest
 - c. Atrial tachycardia
 - d. Sinus bradycardia
2. The sinoatrial disease at greatest risk for embolism is the brady-tachy syndrome
 - a. Emboli are more common with prolonged atrial asystole
 - b. Tachyarrhythmias > bradyarrhythmias are more likely to embolize

Neuroimaging of Sick Sinus Syndrome

1. Changing p wave contour
2. Bradycardia with:
 - a. Multiple recurrent ectopic beats
 - b. Runs of atrial and nodal tachycardia
3. Similar to large emboli as seen with AF
 - a. Multiple vascular territory involvement

Neuropathology of Sick Sinus Syndrome

1. Loss of function mutations in Na(v)1.5 cause sodium channelopathies, Brugada syndrome, dilated cardiomyopathy and sick sinus syndrome
2. The cardiac sodium current causes the rapid depolarization of cardiac cells and their consequent contraction
3. Mutations in the gene SCN5A is a congenital cause of sick sinus syndrome
4. Autoimmune, infiltrating entities (such as carcinoma and amyloid) may also destroy the sinoatrial node

Rare Causes of Emboli from Genetic Arrhythmias*General Characteristics of Rare Causes of Emboli from Genetic Arrhythmias*

1. Long QT syndrome
 - a. Jervell and Lang-Nielsen
 - i. Autosomal recessive
 - ii. Sensorineural hearing loss
 - iii. Syncope
 - iv. Sudden death
 - b. Romano-Ward
 - i. Autosomal dominant
 - ii. No sensorineural hearing loss
 - iii. Defective slowly activating rectifier K⁺ current is dysfunctional
 - iv. Generates a normal T wave and QT interval

Rheumatic Heart Disease*General Characteristics of Rheumatic Heart Disease*

1. Majority of RHD patients with cerebral emboli have mitral stenosis (10–20%)
2. Mitral insufficiency (MI) and aortic valve disease are the second most common cause of cerebral emboli in RHD

Clinical Manifestations of Rheumatic Heart Disease

1. 50–75% of RHD patients have AF or other arrhythmias at the time of an embolus
2. Majority of RHD patients with mitral stenosis have a normal sinus rhythm
 - a. AF greatly increase stroke risk
3. Systemic emboli occur in 10–49% of patients with RHD with valve disease

Neuropathology of Rheumatic Heart Disease

1. Mitral stenosis:
 - a. Thrombi form in the left atrium
 - b. Rarely on the valve

*Neuroimaging of Rheumatic Heart Disease***MRI of Rheumatic Heart Disease**

1. Patterns of large vessel obstruction
2. Multiple territories are involved

Sites of Origin for Artery-to-Artery Emboli*Overview of Site of Origin for Artery-to-Artery Emboli*

1. Artery-to-artery embolism:
 - a. Carotid System:
 - i. Bifurcation of common and external carotid arteries
 - ii. T-portion (ACA and MCA) at the siphon
 - iii. From giant distal aneurysms (carotid; MCA)
 - iv. Embryologic connections from the basilar artery to the carotid (rare cause of a posterior circulation embolus to reach the anterior circulation) that include persistent:
 1. Trigeminal
 2. Otic
 3. Hypoglossal
 4. Proatlantal
 - b. Intimal tears from dissection of the carotid are a source of emboli
 - i. Repair of carotid ulcers or stenosis (that cause flap intimal defects or dissection)
2. Vertebrobasilar system sources:
 - a. Arch of the aorta (mobile plaques); rarely descending aorta plaques
 - b. Vertebral artery
 - c. Basilar artery
 - d. Dolichoectatic vertebral basilar arteries
 - e. Giant aneurysms (particularly at the top of the basilar)
3. Predilection for specific sites of embolic termination:
 - a. Arterial bifurcations
 - b. Pial superficial MCA branches
 - c. Upper and lower trunks of the MCA
 - d. Distal basilar artery (top of the basilar)
 - e. Posterior cerebral arteries
 - f. Areas of greatest cerebral blood flow (CBF):
 - i. 40% of the anterior circulation emboli go to the MCA territory

- ii. Tendency to affect same location within an arterial territory due to laminar flow
- g. Aortic arch is the source of 25% of posterior circulation emboli
- h. 25% of emboli go to VB system (less than 20% of blood flow goes to this circulation)

Differential Diagnosis of Artery-to-Artery Embolism

1. Proximal extracranial and intracranial arteries
 - a. Ulcerated and stenotic lesions
2. Dissection of arteries
 - a. Thrombus at the site of the intimal tear
3. Post-surgical sites (flaps, sutures)
4. Inflammatory arterial disease:
 - a. Giant cell arteritis
 - b. Takayasu's disease
 - c. Infectious arteritis
 - d. Autoimmune arteritis
5. Thrombi within aneurysms:
 - a. Dolichoectatic arteries
 - b. Saccular (giant aneurysms)
 - c. Fusiform aneurysms
6. Fibromuscular dysplasia
7. Cancer:
 - a. Direct invasion of arteries
 - b. Promotion of clots within arteries encased by tumor
8. Hypercoagulable states
9. Aortic arch atherosclerosis with embolus:
 - a. Infarcts MCA territory and brachial plexus
 - b. Supraclavicular portions of the brachial plexus are supplied by ascending deep and transverse arteries
 - c. Infraclavicular portions of the plexus are supplied by 3–4 branches of the axillary arteries
10. Multiple brain gas embolisms:
 - a. Ingestion of hydrogen peroxide:
 - i. O₂ embolism
 - ii. Predominantly to gray matter
 - b. Air embolism
 - i. Vascular surgical procedures:
 1. Open heart surgery
 2. Head and neck surgery in the sitting position. Air enters the jugular vein
 - c. Pelvic vein insufflation (air) during pregnancy
11. Spectacular shrinking deficit (MRI evaluation):
 - a. Profound hemispheric ischemia
 - b. Resolves over hours to days
 - c. Minimal residual deficits
 - d. Rapid embolic lysis and fragmentation
 - e. 90% of emboli migrate or are recanalized within 2–3 weeks
12. Fat embolism:
 - a. Broken long bones in young patients
 - b. Hip replacement surgery (even in elderly patients)
 - c. Acute syndrome:
 - i. Interstitial lung involvement with low pO₂
 - ii. Petechiae across the anterior chest wall

- iii. Site predilection for emboli:
 1. Retina (fat globules visible)
 2. Corpus callosum
 3. Centrum semiovale
 4. Superficial pial vessels
- iv. Fat globules noted in the urine
- v. Mechanism
 1. Emboli pass through the lungs into the arterial circulation
 2. Precipitation of fat from chylomicra
- d. Late syndrome:
 - i. 4–7 days following the event
 - ii. Acute confusion
 - a. Decreased pliability
 - b. Irregular surfaces
 - c. Turbulent blood flow
- 3. Platelets are activated by turbulence
- 4. Thrombus formation is related to valve device turbulence
- 5. Abnormalities of blood flow distal to stenotic or incompetent valves cause:
 - a. Prolonged contact of blood and platelets
 - b. Formation of platelet and red cell fibrin thrombi
- 6. Atrial and ventricular enlargement from stenotic or incompetent valves:
 - a. Enlarged left atria (mitral stenosis or incompetence)
 - b. Prolonged contact of blood and platelets with cardiac and valve surfaces induces thrombus formation
- 7. Lambl's excrescences on valve cusps

Cardiogenic Sites of Origin for Cerebral Emboli

General Characteristics of Cardiogenic Origin Sites for Cerebral Emboli

1. Ejection fraction less than 30%:
 - a. Contact factors of clotting mechanisms are activated (slow blood flow)
 - b. Large atria
 - c. Areas of muscle hypokinesia in the ventricles
2. Valve leaflets:
 - a. Activation of platelets by shear forces
 - b. Consequent dilatation of left atrium with arrhythmia
 - c. Nidus for infection
 - d. Platelet fibrin deposition from prothrombotic conditions
 - i. Non-bacterial thrombotic emboli (DIC; cancer)
 - e. Myxomatous valve and chordae tendineae degeneration
 - f. Calcific aortic valve degeneration
3. Patent foramen ovale (PFO)
4. Atrial septal aneurysm (ASA)
5. Combination of PFO + ASA
6. Cardiac tumors:
 - a. Primary
 - b. Metastatic
7. Less common types and sources of emboli:
 - a. Lodge in the carotid artery (Calcium; cartilage)
 - b. Vertebrobasilar arteries at sites of narrowing
 - c. Esophageal cardiac fistula ("MAC attack"); swallowed food particles can embolize

Valvular Heart Disease as a Source of Emboli

General Characteristics of Valvular Heart Disease as a Source of Emboli

1. Approximately 10–20% of patients with valvular heart disease embolize

Neuropathology of Valvular Heart Disease as a Source of Emboli

1. Valvular outlet obstruction is caused by:
 - a. Commissural adhesions
 - b. Leaflet dystrophic calcification
2. Functional properties of stenotic valves:

Structural Causes of Valvular Heart Disease Associated with Emboli

Neuropathology of Structural Causes of Valvular Heart Disease Associated with Emboli

1. Rheumatic mitral and aortic valve stenosis and incompetence
2. Bicuspid aortic valve (congenital)
3. Mitral annulus calcification
4. Calcific aortic stenosis
5. Mitral valve prolapse
6. Bacterial endocarditis
7. Non-bacterial thrombotic endocarditis
8. Prosthetic heart valves
9. Left ventricular assist devices (LVAD)
10. Antiphospholipid syndrome
11. Fibrin valvular Lambl's excrescences

Aortic Valve Disease as a Structural Cause of Valvular Heart Disease Associated with Emboli

General Characteristics of Aortic Valve Disease Associated with Emboli

1. Embolization occurs more commonly after cardiac catheterization than spontaneously
 - a. Emboli possibly as high as 33% for patients with calcific stenosis
 - b. The mitral valve embolizes more frequently than the aortic valve

Clinical Manifestations of Aortic Valve Disease Associated with Emboli

1. Topographical strokes in large vessels
2. Associated emboli to:
 - a. Retina (white and irregular, calcium deposits)
 - b. Coronary arteries
 - c. Renal arteries

Neuropathology of Aortic Valve Disease Associated with Emboli

1. Calcific aorta valve disease (CAVD) is the most common cause of acquired valve disease
2. Initial phase is the cause of thickening of the cusps

3. Advanced stages are associated with biomineralization and reduction of the aortic valve area. The former (early phase) is aortic valve sclerosis (AVS)
4. Patients with AVS and AS have higher osteopontin levels than controls
5. Lipoprotein-associated phospholipase A2 (encoded by the PLA2G7 gene) may play a pivotal role:
 - a. Valve tissue is infiltrated by lipids and inflammation may play a role in the destructive process by mineralization of valve interstitial cells
6. Microthrombi are found in up to 53% of aortic stenotic valves at necropsy

Neuroimaging of Aortic Valve Disease Associated with Emboli

1. Post transcatheter aortic valve implantation (TAVI)
 - a. Stroke of major arteries approximately 3%
 - b. Silent cerebral embolic lesions
 - i. Higher rates after TAVI compared with standard aortic valve repair

CT of Aortic Valve Disease Associated with Emboli

1. Rarely demonstrates calcific material in large arteries

Mitral Valve Disease as a Structural Cause of Valvular Heart Disease Associated with Emboli

General Characteristics of Mitral Valve Disease Associated with Emboli

1. This valve most often involved in rheumatic fever
2. There is often concomitant aortic valve disease

Clinical Manifestations of Mitral Valve Disease Associated with Emboli

1. Embolism in mitral stenosis:
 - a. Occurs in 10–20% of patient's
 - i. Approximately 50–75% of these are to the brain
 - b. Atrial fibrillation greatly increases the risk of embolism
 - c. Incidence of embolization possibly 1.5% per year
 - d. Mitral insufficiency is a rare cause of cerebral embolism

Neuropathology of Mitral Valve Disease Associated with Emboli

1. Percutaneous trans-septal mitral commissurotomy (PTMC) has replaced surgical commissurotomy in selected patients with rheumatic mitral stenosis
 - a. Systemic embolism occurs in .5 to 5% of procedures with 1% going to the brain
 - b. Periprocedural embolism during PTMC is caused by a pre-existing thrombus in the left atrial appendage
 - c. Papillary fibroelastoma occurs on leaflets

Neuroimaging of Mitral Valve Disease Associated with Emboli Transesophageal Echocardiographic (TEE) of Mitral Valve Disease

1. TEE to evaluate the valve along with cardiac catheterization:

- a. Thrombus in the left atrial appendage is a contraindication to PTMC

MRI of Mitral Valve Disease

1. Topographical stroke in usual embolic sites
2. Increased incidence of silent brain infarction; increased if AF present

Mitral Annulus Calcification (MAC) as a Structural Cause of Valvular Heart Disease Associated with Emboli

General Characteristics of Mitral Annulus Calcification

1. Degeneration of the fibrous support of the valve
2. Common in the elderly
3. Associated with chronic kidney disease
4. More common in women than men
5. Caseous calcification of the mitral annulus (CCMA) is a rare variant:
 - a. Liquifactive necrosis within a spheroid zone of mitral annular calcification

Clinical Manifestations of Mitral Annulus Calcification

1. Increased risk of stroke:
 - a. Each millimeter of thickening as documented by echocardiogram increases the relative risk of stroke (RR) by 1.24X
2. MAC is accompanied by myocardial infarction and AF
3. May develop superimposed SBE
4. Concomitant atrial and ventricular enlargement
5. AF conduction defect

Neuropathology of Mitral Annulus Calcification

1. Calcification occurs:
 - a. Posterior portion of the mitral annulus ring
 - b. May project into the cavity of the left ventricle

Neuroimaging of Mitral Annulus Calcification

1. Topographic patterns of embolic stroke

CT/MRI of Mitral Annulus Calcification

1. ECHO CT and MRI used to evaluate the valve lesion and to differentiate MAC from other cardiac lesions

Mitral Valve Prolapse as a Structural Cause of Valvular Heart Disease Associated with Emboli

General Characteristics of Mitral Valve Prolapse

1. Mid systolic murmur:
 - a. Failure of mitral valve leaflets to coapt
 - b. Some patients have abnormal left ventricular contractions
2. Most commonly diagnosed cardiac valve lesion:
 - a. Prevalence of 5–20% in the general population
 - b. More common in women than men

Clinical Manifestations of Mitral Valve Prolapse

1. Clinical symptomatology:
 - a. Small percentage of patients develop severe mitral insufficiency with congestive heart failure (CHF)

- b. Atrial fibrillation may develop in elderly patients with myocardial infarction (MI) and enlarged left atria
- c. Associated with Marfan's syndrome, osteogenesis imperfecta and Ehlers–Danlos syndrome
- d. Rare endocarditis on myxomatous valves
- e. Low rate of cerebral embolization

Neurologic Features of Mitral Valve Prolapse

1. Emboli occur in young patients often without other associated risk factors
2. Strokes and transient ischemic attack (TIA) occur
3. Approximately 10% of patients have atrial fibrillation concomitantly with the stroke
4. Platelet dysfunction is reported in some patients with mitral valve prolapse:
 - a. Shortened survival time
 - b. Increased levels of beta-thromboglobulin and platelet factor IV
5. Recurrent embolic stroke is rare

Neuropathology of Mitral Valve Prolapse

1. Disruption of valve collagen by infiltration of myxomatous material
2. Thickened and elongated chordae tendineae
3. Infiltration of the mitral valve annulus
4. Fibrosis and thickening of the endocardial surface of the valve leaflets
5. Transferring growth factor β family cytokines may be pivotal

Neuroimaging of Mitral Valve Prolapse

Echocardiography of Mitral Valve Prolapse

1. Echocardiographic evaluation:
 - a. 2 mm or greater movement of the coapted anterior or posterior valve leaflets
 - b. Valve leaflets are displaced into the left atrium during systole
 - c. Mitral valve thickening or redundancy
 - d. Regurgitation
 - e. Commissural prolapse of the mitral valve identified on 3 dimensional Transesophageal echocardiography (TEE)
 - f. Topographic stroke from embolization

Prosthetic Heart Valves as a Structural Cause of Valvular Heart Disease Associated with Emboli

General Characteristics of Prosthetic Heart Valves

1. Mechanical valves are:
 - a. Metal and carbon alloys
 - b. Bioprosthetic valves:
 - i. Heterography from pig and cow pericardium or valves
2. Non-tissue valves:
 - a. Thrombus forms at the component tissue interface or in areas of stenosis

3. Incidence of embolization is related to the degree of thrombogenicity:
 - a. Non cloth covered prosthetic valves > cloth covered prosthetic valves > tissue valves

Clinical Manifestations of Prosthetic Heart Valves

1. Increased risk for embolization:
 - a. Caged ball valve prosthesis
 - b. Mitral valve (associated with atrial fibrillation)
 - c. Multiple prosthetic valves
 - d. Age > 70 years
 - e. Atrial fibrillation
 - f. Decreased left ventricular ejection fraction
 - g. Subacute bacterial endocarditis (SBE)
 - h. Pregnancy and the puerperium
2. Mitral valve embolize > aortic valves
3. Risk of bioprosthetic valve embolization equals that of mechanical valves that are adequately anti-coagulated
4. Size of the cerebral infarction is due to:
 - a. Size of the embolus
 - b. Stability of the embolus
 - c. Adequacy of the collateral circulation

Neuropathology of Prosthetic Heart Valves

1. Dacron rings are a nidus for platelet activation and adhesion
2. Prosthetic material activates intrinsic clotting cascade; erythrocyte-fibrin thrombi form
3. Degeneration of bioprosthetic valves:
 - a. Deposition of white platelet fibrin thrombi
 - b. Cusp sinuses of bioprosthetic mitral valves:
 - i. Undergo fibrosis and calcification
 - ii. Nidus for thrombi

Neuroimaging of Prosthetic Heart Valves

MRI of Prosthetic Heart Valves

1. Topographical large vessel stroke

Transesophageal Echocardiography (TEE) of Prosthetic Heart Valves

1. TEE to evaluate the valves

Endocarditis on Prosthetic Valves as a Structural Cause of Valvular Heart Disease Associated with Emboli

General Characteristics of Endocarditis on Prosthetic Valves

1. Occurs in 3–6% of patients:
 - a. Early endocarditis <60 days; from perioperative bacteremia: skin, wound or contaminated valves; organisms: staph epidermidis or aureus; gram-negative bacteria; diphtheroids; fungi; mycobacteria; and legionella
 - b. Late prosthetic valve endocarditis >60 days post-operatively; streptococci, staph epidermidis
 - c. The risk of endocarditis is similar for mechanical and bioprosthetic valves
 - d. Most common symptoms and signs; fever, new or changing murmur, systemic embolization or congestive heart failure

- e. Early endocarditis: rapid hemodynamic deterioration, conduction defects, poor peripheral perfusion
- f. Mortality for prosthetic valve endocarditis is 30–80% for the early form and 20–40% for the late form
- g. Infection with organisms other than streptococcus usually results in valve replacement

Neuroimaging of Endocarditis on Prosthetic Valves

1. In patients with left-sided infective valve endocarditis (study of 139 patients):
 - a. Acute ischemic lesions (55%)
 - i. Small lesions of less than 10 mm (60%)
 - ii. Multiple lesions (77%)
 - iii. Lesions were noted in multiple vascular territories (64%)
- b. Silent brain infarcts (>50%)
 - i. Peripheral intracranial aneurysm
 - ii. Peripheral hemorrhages from mycotic aneurysms
 - iii. Rare SAH

Laboratory Evaluation of Endocarditis on Prosthetic Valves

CSF Evaluation of Endocarditis on Prosthetic Valves

1. Pleocytosis < 300 cells/mm³
2. Neutrophilic early and lymphocytic late
3. Slight increase of protein
4. Sugar if affected (30 to 40 mg/dl)
5. May have normal CSF

Subacute Bacterial Endocarditis (SBE) as a Structural Cause of Valvular Heart Disease Associated with Emboli

General Characteristics of Subacute Bacterial Endocarditis

1. Natural valves: staph epidermidis, staph aureus and group D streptococcus are the most common organisms
2. Prosthetic valves: aspergillus most common for early emboli; strep viridans for late emboli
3. New epidemiology:
 - a. Older patients
 - b. Intravenous drug abuse patients
 - c. Tricuspid valve is more frequently involved
4. 20% of patients with endocarditis suffer cerebral emboli:
 - a. Small cortical or subcortical bland infarcts
 - b. Large infarcts are secondary often to staph aureus
5. 50% of infected prosthetic valves cause cerebral emboli
6. Neurologic complications are similar for native and prosthetic valves

Neuropathology of Subacute Bacterial Endocarditis

1. Valve pathology:
 - a. Calcified valves
 - b. Prosthetic valves
 - c. Rheumatoid valves
 - d. Mitral valve prolapse
 - e. Myxomatous mitral valves
2. 30–40% of emboli may occur from normal valves
 - a. Aortic > mitral
3. Sterile vegetations may embolize

Clinical Manifestations of Subacute Bacterial Endocarditis

Systemic Symptoms of Subacute Bacterial Endocarditis

1. Intermittent fever and fatigue
2. Backache is common, early
3. Embolization to other organs; large artery occlusion suggests fungus
4. Loss of weight and appetite
5. Multiple immune abnormalities

Neurologic Signs and Symptoms of Subacute Bacterial Endocarditis

1. Cerebral and retinal transient ischemic attack (TIA)
 - a. Most common early in the course of the infection
2. Brain ischemia
 - a. 15–19% of patients
3. Ischemic stroke may occur after treatment has started
4. Intracranial hemorrhage:
 - a. 2.8–7% of patients
 - b. Hemorrhagic transformation of bland infarcts
 - c. Large hemorrhages occur:
 - i. Concomitant use of anticoagulants
 - d. Rupture of mycotic aneurysms
 - i. Occur in peripheral subpial vessels
 - e. Intracranial hemorrhage occurs at or near time of presentation
 - i. May have had a preceding transient ischemic attack
 - f. Mycotic aneurysms may rupture after bacterial treatment
 - g. Hemorrhagic transformation may occur with tissue plasminogen activator (tPA) therapy

Encephalopathy as a Structural Cause of Valvular Heart Disease Associated with Emboli

General Characteristics of Encephalopathy Associated with Emboli

1. Most common with staph aureus:
 - a. Toxic metabolic factors
 - b. Secretion of interleukins (IL-6) with subsequent cerebral edema
 - c. Associated brain infarcts and micro-abscesses

Meningitis as a Structural Cause of Valvular Heart Disease Associated with Emboli

General Characteristics of Meningitis Associated with Emboli

1. Embolization of bacteria to meningeal arteries:
 - a. Presentation with neck and back pain prior to neurologic symptoms
 - b. 1.1–6.4% of patients with endocarditis have meningitis

Vegetations as a Structural Cause of Valvular Heart Disease Associated with Emboli

General Characteristics of Vegetations Associated with Emboli

1. Millimeters to centimeters in size

- a. Fungi are the largest
2. Potential for embolization is related to:
 - a. Size
 - b. Friability
3. Valve most likely to embolize
 - a. Mitral > aortic > tricuspid
4. May be culture negative
5. May occlude peripheral arteries (usually fungus)

Non-Infective Endocardial Lesions as a Structural Cause of Valvular Heart Disease Associated with Emboli

General Characteristics of Non-Infective Endocardial Lesions Associated with Emboli

1. Occurs primarily in systemic lupus erythematosus (SLE), the antiphospholipid antibody syndrome (APLS) and non-bacterial thrombotic endocarditis (NBTE) from cancer
2. Probable similar pathogenesis
3. All three entities are associated with:
 - a. Hypercoagulability
 - b. Thrombocytopenia
 - c. Embolic stroke
 - d. Platelet thrombi on valve and endocardial tissues
 - e. Emboli to the spleen, kidney and rarely, to the heart
4. Non-infective valve lesions are associated with:
 - a. Ergotamine
 - b. Methysergide
 - c. Dexfenfluramine
 - d. Phentermine
 - e. Carcinoid (high serotonin levels)
 - f. Leukemia
 - g. Elevated proinflammatory cytokines
 - h. Increased VIII, vWF and fibrinogen
5. Strands
 - a. May be demonstrated by transesophageal echocardiography:
 - i. Strands of mobile tissue attached to valve and endocardial surfaces

Clinical Manifestations of Non-Infective Endocardial Lesions Associated with Emboli

1. Association of stroke and strands:
 - a. Young patients
 - b. Mitral and aortic strands
 - c. Low recurrent stroke risk
 - d. Occurs in patients with SLE, APLAS and NBTE

Neuropathology of Non-Infective Endocardial Lesions Associated with Emboli

1. Filamentous strands are known as Lambl excrescences:
 - a. Located on the atrial surfaces of mitral valves or the ventricular surfaces of aortic valves
 - b. Strands are composed of:
 - i. Cellular connective tissue core covered by epithelium
 - ii. 1–10 mm in length

- iii. May be related to fibrinous deposits on valve surfaces
- iv. May spread to the endocardium and papillary muscles
- c. Prevalence by TEE (transesophageal echocardiography)
 - i. Approximately 4% on mitral valves
 - ii. 1.7% on aortic valves
 - iii. Incidence possibly 10% in patients who have suffered embolization

Antiphospholipid Antibody Syndrome as a Structural Cause of Valvular Heart Disease Associated with Emboli

General Characteristics of Antiphospholipid Antibody Syndrome Associated with Emboli

1. Antiphospholipid antibodies are a heterogeneous family
2. In general the venous system is more involved than the arterial
3. The antiphospholipid antibody is classified as primary or secondary:
 - a. Secondary forms can occur with systemic lupus erythematosus or other collagen vascular diseases
 - b. Primary and secondary forms are clinically indistinguishable

Clinical Manifestations of Antiphospholipid Antibody Syndrome Associated with Emboli

1. Some patients may have antibodies and are asymptomatic
2. If the antibodies are associated with infection or medications:
 - a. They are often transient
 - b. Have a restricted range of immunoreactivity
 - c. Are not associated with clinical symptomatology
3. Ischemia can occur in any vascular territory
4. Embolic mechanism from predominantly mitral valve lesions (demonstrated by 2-dimensional transthoracic echocardiography)
5. Women may be at higher risk
6. Recurrent transient ischemic attack (TIA) and stroke with presence of anticardiolipin antibodies and lupus anticoagulant

Neuropathology of Antiphospholipid Antibody Syndrome Associated with Emboli

1. Vegetations are prominent along valve closure lines and leaflets
2. They may spread to papillary muscle and endocardium
3. Same pathology is noted with lupus verrucous endocarditis (Libman-Sacks)
4. Thickened valves

Neuroimaging of Antiphospholipid Antibody Syndrome Associated with Emboli

Trans Doppler Echocardiography of Antiphospholipid Antibody Syndrome

1. Cerebral microemboli may be detected
2. Abnormal in 1/3 of patients

MRI of Antiphospholipid Antibody Syndrome

1. Small foci of high signal intensity in T2-weighted sequences throughout the brain
2. Demonstrated in one study:
 - a. Number and size of white matter lesions with clinical symptoms (>8 mm size)
 - b. Verebral atrophy

Laboratory Evaluation of Antiphospholipid Antibody Syndrome Associated with Emboli

1. Patients demonstrate lupus anticoagulant
2. Anticardiolipin antibody (IgG or IgM)
3. Patients with clinical features of antiphospholipid antibody syndrome may have embolic stroke and a negative screen for antibodies

Non-Bacterial Thrombotic Endocarditis as a Structural Cause of Valvular Heart Disease Associated with Emboli**General Characteristics of Non-Bacterial Thrombotic Endocarditis Associated with Emboli**

1. Associated most often with cancer (particularly mucinous adenocarcinoma, prostate, lung, or melanoma)
2. Other Associations:
 - a. SLE
 - b. APLAS
 - c. Pneumonia
 - d. Perforated ulcer
 - e. Wasted immunosuppressed patients
 - f. Severe gram negative infection
 - g. Pheochromocytoma
 - h. Compensated disseminated intravascular coagulation (DIC)

Clinical Manifestations of Non-Bacterial Thrombotic Endocarditis Associated with Emboli

1. Both small and large vessel occlusions occur in the cerebral or systemic circulation
 - a. Cerebral emboli with stroke occur in 50% of patients with valve lesions
2. Often associated with DIC but also occur concomitantly with SAH, ICH and thrombotic stroke
 - a. Elevated D-dimer seen in this context

Neuropathology of Non-Bacterial Thrombotic Endocarditis Associated with Emboli

1. Order of valve involvement:
 - a. Mitral > aortic > tricuspid > pulmonary
 - b. Deposits are along lines of valve coaptation and consist of degenerating platelets, fibrin and leukocytes
 - c. Bivalvular lesions occur
 - d. Vegetations are bland and less than 5 mm in size

Lupus Verrucous Endocarditis as a Structural Cause of Valvular Heart Disease Associated with Emboli

1. Fibrous thickening of valves
2. Vegetations prominent along valvular closure lines and leaflets

3. Spread to the papillary muscles and endocardium
4. Associated with cerebral embolism
5. Aortic and mitral valves are primarily affected

Cardiomyopathy as a Structural Cause of Heart Disease Associated with Emboli**Overview of Cardiomyopathy Associated with Emboli**

1. Embolism is most common in dilated cardiomyopathies with an ejection fraction less than 30%
2. Loss of normal subendocardial trabeculations
3. Stasis of blood; prolonged contact of platelets and contact factor XIII
4. Mural thrombi form within the trabeculae of the cardiac apex
5. Embolism is less frequent in hypertrophic cardiomyopathy unless there is concomitant atrial fibrillation
6. Associated with the stasis of blood with congestive heart failure (CHF)
7. The cardiomyopathies associated with emboli:
 - a. Idiopathic
 - b. Post-partum
 - c. Viral
 - d. Myocarditis (idiopathic)
 - e. Ischemic cardiomyopathy
 - f. Sarcoidosis
 - g. Amyloidosis
 - h. Endocardial fibroelastosis
 - i. Mitochondrial myopathies
 - j. Dystrophinopathy (Duchenne muscular dystrophy; Becker's muscular dystrophy)
 - k. Inflammatory muscle disease (Inclusion body myositis; dermatomyositis; polymyositis)
 - l. Nemaline myopathy
 - m. Glycogen storage disease (glycogen debrancher deficiency)
 - n. Scapuloperoneal dystrophy with mental retardation
 - o. Desmin myopathy
 - p. Myofibrillar lysis myopathy
 - q. Fabry's disease
 - r. Cocaine abuse
 - s. Endocrinopathies (acromegaly, hypothyroidism, adrenal insufficiency)
 - t. Congenital myopathies
 - u. Barth syndrome
 - v. Senger's syndrome
 - w. McCloud syndrome
 - x. Emery-Dreifuss muscular dystrophy

Hypertrophic Cardiomyopathy as a Structural Cause of Heart Disease Associated with Emboli**General Characteristics of Hypertrophic Cardiomyopathy Associated with Emboli**

1. Hypertrophic Cardiomyopathy (HCM) is the most common genetic disease of the heart
2. Greater than 1000 mutations have been identified primarily in genes that encode sarcomeric proteins

3. Prevalence of 1:500 in the general population
4. The most common cause of sudden death in young patients and athletes
5. Predominantly autosomal dominant
 - a. Autosomal recessive, X-linked and mitochondrial patterns of inheritance have been reported
6. Asymmetric hypertrophy of the left ventricular septum that causes:
 - a. Variable obstruction of left ventricular outflow from systolic anterior displacement of the mitral valve
 - b. Concomitant structural abnormality of the mitral valve
7. The penetrance of left ventricular hypertrophy (LVH) is age-dependent and incomplete
8. Annual mortality rate of HCM is <1% in the general community

Clinical Manifestations of Hypertrophic Cardiomyopathy Associated with Emboli

1. Asymmetric hypertrophy of the left ventricular septum that causes:
 - a. Variable obstruction of the left ventricular outflow from systolic anterior displacement of the mitral valve
 - b. Concomitant structural abnormality of the mitral valve
2. Syncope with prolonged exercise
3. Atrial fibrillation associated with left atrial enlargement occurs late in the course of the disease with a low rate of cerebral embolization
4. Rare concomitant subacute bacterial endocarditis (SBE) of mitral valve or of the annulus calcification or may be causative
5. Sudden death

Neuropathology of Hypertrophic Cardiomyopathy Associated with Emboli

1. Increased left ventricular mass and thickened wall
2. Increased interventricular septum
3. Fibrosis at the junction of the septum to the anterior and posterior walls of the left ventricular
 - a. The thickened septum may bulge into the left ventricular that diminishes the end diastolic lumen space which may block ventricular outflow
 - b. Valve leaflets and chordae tendineae become thickened by fibrosis
 - c. Histological findings
 - i. Myocyte and myofibrillar disarray; "herringbone" or "pin wheel" configurations occur

Neuroimaging of Hypertrophic Cardiomyopathy Associated with Emboli

MRI of Hypertrophic Cardiomyopathy

1. Cardiac-MR methods assess diastolic dysfunction

Trans Doppler Echocardiography of Hypertrophic Cardiomyopathy

1. TDE evaluation of decreased myocardial relaxation velocities

Hereditary Cardiomyopathies as a Structural Cause of Heart Disease Associated with Emboli

General Characteristics of Hereditary Cardiomyopathies Associated with Emboli

1. Categories of familial dilated cardiomyopathies (FDCM):
 - a. Mutations in contractile protein genes
 - b. Dystrophinopathies:
 - i. Affected boys and men
 - ii. Women carriers of Becker or Duchenne mutations
 - iii. Mitochondrial disorders
 - iv. Sarcoglycanopathies
 - v. Limb girdle myopathies
 - vi. Rare disorders
2. Genetics of FDCM
 - a. Allelic and locus heterogeneity

Clinical Manifestations of Hereditary Cardiomyopathies Associated with Emboli

1. Syncope
2. Palpitations
3. Dyspnea
4. Heart failure
5. Exertion induced sudden death
6. Angina
7. Anesthetic complications (malignant hyperthermia)

Neurologic Features of Hereditary Cardiomyopathies Associated with Emboli

1. Cerebral emboli occur in patients with:
 - a. Ejection fractions of <30%
 - b. Trans echo cardiogram that demonstrate:
 - i. "Smoke" (echoic signals that signal altered intracardiac blood flow)

Familial Hypertrophic Cardiomyopathy (FHCM) as a Structural Cause of Heart Disease Associated with Emboli

General Characteristics of Familial Hypertrophic Cardiomyopathy Associated with Emboli

1. Clinical onset from fetal life to adulthood
2. Mutations in genes that encode cardiac contractile proteins:
 - a. Most frequent mutations:
 - i. B-myosin heavy chain
 - ii. High penetrance
 - iii. High incidence of sudden death
 - b. Less common mutations in genes for:
 - i. Essential light chain proteins
 - ii. Regulatory light chain proteins
 - iii. Myosin-binding proteins

Clinical Manifestations of Familial Hypertrophic Cardiomyopathy Associated with Emboli

1. Clinical syndromes of familial hypertrophic cardiomyopathy

- a. Autosomal dominant in some families
- b. Penetrance is age dependent
- c. Clinical heterogeneity within families

Neuropathology of Familial Hypertrophic Cardiomyopathy Associated with Emboli

1. Penetrance:
 - a. B-myosin high penetrance
 - i. High incidence of sudden death
 - b. B-myosin low penetrance
 - i. Benign course
2. Mutation specific causes of sudden death:
 - a. Myocardial ischemia that induces:
 - i. Syncope
 - ii. Presyncope
 - iii. Sudden death
 - b. Heart block
 - c. Pre-excitation syndrome
3. Mutations causing functional deficits:
 - a. B-myosin heavy chain
 - i. Affects head-rod junction
 - b. Expression of mutations in skeletal muscle that cause:
 - i. Decreased isometric force
4. Mutations expressed in skeletal muscle:
 - a. Heart and skeletal muscle affected concomitantly
 - b. B-myosin heavy chain; myosin light chains, and tropomyosin are affected
5. Variance in degree of heart muscle pathology
 - a. Focal heart muscle pathology vs generalized heart muscle involvement

Dystrophinopathy as a Structural Cause of Heart Disease Associated with Emboli

General Characteristics of Dystrophinopathy Associated with Emboli

1. The more limited the patients' exercise tolerance is proportional to lesser symptomatic cardiomyopathy
2. EKG abnormalities in Becker and Duchenne muscular dystrophy increase dramatically with age
3. Duchenne muscular dystrophy carrier women
 - a. 38% abnormal cardiograms
4. Becker muscular dystrophy carrier women
 - a. 34% abnormal cardiograms
5. 8% of Duchenne muscular dystrophy carriers suffer dilated cardiomyopathy
6. X-linked cardiomyopathy:
 - a. Similar dystrophin gene type mutation in some; others are new mutations:
 - i. High CPK
 - ii. Dystrophic myopathy by skeletal muscle biopsy
7. Sarcoglycanopathy:
 - a. Patients with dilated cardiomyopathy:
 - i. Point mutation in gene for alpha sarcoglycan

Mitochondrial Cardiomyopathy as a Structural Cause of Heart Disease Associated with Emboli

General Characteristics of Mitochondrial Cardiomyopathy Associated with Emboli

1. Dilated cardiomyopathy:
 - a. More common in patients with maternally inherited point mutations
 - b. Mutations most common in:
 - i. Mitochondrial DNA-encoded t RNA's
2. MELAS-3243 mutation
 - a. Dilated cardiomyopathy
3. Progressive external ophthalmoplegia (PEO):
 - a. Dilated cardiomyopathy
 - b. Multiple mitochondrial DNA deletions
 - c. Eastern Arabian Peninsula (most common)
4. Kearns-Sayre syndrome:
 - a. Dilated cardiomyopathy
 - b. Adolescents with stroke
 - c. Predominant cardiac feature is heart-block
5. Patients with dilated cardiomyopathy identified with:
 - a. Complex I, III, and IV mitochondrial complex deficits

Rare Myopathies with Emboligenic Cardiomyopathy

1. Myofibrillar lysis myopathy
2. Scapuloperoneal dystrophy with mental retardation
3. Glycogen debrancher deficiency
4. Nemaline myopathy
5. Desmin myopathy
6. Left ventricular non-compaction syndrome
7. Centronuclear myopathy

Hereditary Dysrhythmias Associated with Embolic Stroke – Prolonged QT Syndromes

General Characteristics of Prolonged QT Syndromes Associated with Embolic Stroke

1. Prolongation of the QT interval
 - a. Corrected for heart rate
2. T-wave abnormalities
3. Bradycardia
4. Ventricular tachyarrhythmias
5. Polymorphic ventricular tachycardias
6. Torsades de pointes (Ventricular fibrillation)
7. Defects of cardiac repolarization

Clinical Manifestations of Prolonged QT Syndromes Associated with Embolic Stroke

1. Syncope
2. Seizure
3. Sudden death
4. Triggers:
 - a. Exercise
 - b. Emotion
 - c. Noise

- d. Lack of sleep
- 5. Romano-Ward syndrome
 - a. Autosomal dominant
 - b. Most common form
 - c. No hearing loss
- 6. Jervell
 - a. Rare
 - b. Autosomal recessive; gene is HERG (or KCNH2 in new nomenclature)
 - c. Sensorineural deafness
- 7. Lang Nielson
 - a. Cardiac defect is autosomal dominant
 - b. Deafness is recessive

Neuropathology of Prolonged QT Syndromes Associated with Embolic Stroke

- 1. Heterogeneous genetic defects:
 - a. Mutation in the cardiac potassium channel HERG (KCNH2)
 - b. Reduces the delayed rectifier KCN currents
 - c. A trafficking defect that cause failure of delivery of the mutant protein to the plasma membrane

Cardiac Tumors That Embolize – Atrial Myxoma

General Characteristics of Atrial Myxoma Associated with Emboli

- 1. Cardiac myxoma is the most common benign cardiac tumor
- 2. 75 to 80% are situated in the left atrium
- 3. Occurrence is 2:1 female preponderance
- 4. Age of onset between 30 and 60 years of age
- 5. Familial form – Carney complex

Clinical Manifestations of Atrial Myxoma Associated with Emboli

- 1. Congestive heart failure
- 2. Constitutional symptoms occur in up to 90% of patients and include:
 - a. Muscle weakness
 - b. Arthralgia
 - c. Fever
 - d. Weight loss
 - e. Fatigue
- 3. Cardiac symptoms:
 - a. Syncope (change of cardiac output)
 - b. Tripopnea:
 - i. Right atrial myxoma
 - ii. Shortness of breath with position change (blockage of right ventricle outflow)
 - c. Heart murmur usually MI > MS (with mitral valve disease)
 - d. Occasionally a cardiac “plop” can be auscultated. Tumor falls into the valve and obstructs it
 - e. Rare bilateral myxomas
 - i. Project from right atrium to left and through a patent foramen ovale
 - f. Less than 10% are in the ventricles

Neurological Signs and Symptoms of Atrial Myxoma Associated with Emboli

- 1. Superficial pial MCA territory most commonly affected (by emboli)
- 2. Peripheral aneurysm of superficial blood vessels:
 - a. Some aneurysms are proximal
 - b. Small proportion are located in the posterior circulation
- 3. Rupture of the aneurysms with SAH or hemorrhagic infarctions
- 4. Delayed progressive neurologic signs may be rarely seen
- 5. 30–50% of cardiac myxomas embolize (common presentation)
- 6. Rare embolization to the spinal cord
- 7. Sudden death (possible coronary artery embolus)
- 8. Intraparenchymal metastasis

Neuropathology of Atrial Myxoma Associated with Emboli

- 1. Atrial myxoma:
 - a. Arise from either side of the atrial septum in the region of the fossa ovalis
 - b. Left atrium > left ventricle:
 - i. May have simultaneous origin from both atria
 - c. Attached to the atrial wall or are pedunculated and cause valve obstruction
 - d. Gelatinous round, polypoid masses covered with platelet fibrin clots
- 2. Myxomatous aneurysm:
 - a. Fusiform in shape
 - b. Multiple
 - c. Located distally on the arterial tree
 - d. Putative mechanism of aneurysm formation:
 - i. Viable tumor emboli penetrate the endothelium
 - ii. Grow subintimally
 - iii. Destroy the arterial wall
 - iv. Accompanied by displacement of smooth muscle, connective tissue proliferation and a mild inflammatory response

Neuroimaging of Atrial Myxoma Associated with Emboli

- 1. Ischemic stroke in embolic territorial distributions
- 2. Multiple distal fusiform aneurysms primarily in the anterior circulation
- 3. Intraparenchymal microhemorrhages

Cardiac Tumors That Embolize – Papillary Fibroelastoma

General Characteristics of Papillary Fibroelastoma Associated with Emboli

- 1. A rare benign cardiac tumor that is approximately 10% of all primary cardiac tumors
- 2. Approximately 90% of these tumors occur in cardiac valves

Clinical Manifestations of Papillary Fibroelastoma Associated with Emboli

- 1. Most tumors are asymptomatic

2. Myocardial infarction
3. Rare manifestations:
 - a. Pulmonary embolism
 - b. Congestive heart failure
 - c. Syncope
 - d. Ventricular fibrillation
 - e. Sudden death
4. Neurologic complications
 - a. Embolic stroke

Neuropathology of Papillary Fibroelastoma Associated with Emboli

1. Tumors most commonly involve the aortic valve followed by the mitral valve
2. Rare sites of origin:
 - a. Mitral chordae tendineae
 - b. Right atrial endocardium
 - c. Endocardial surface of both ventricles
 - d. Papillary muscles and the interventricular septum
3. Gelatinous masses with a characteristic “sea anemone” appearance due to multiple delicate papillary fronds
 - a. Tumors are usually less than 15 mm in diameter
 - b. Attached to the endocardium by a short thin stalk
 - c. Histologic evaluation:
 - i. Myxoid connective tissue containing a mucopolysaccharide matrix and elastic fibers covered by endothelial cells

Neuroimaging of Papillary Fibroelastoma Associated with Emboli

MRI of Papillary Fibroelastoma

1. Topographic MRI embolic stroke

Echocardiography of Papillary Fibroelastoma

1. Small mobile homogeneous valvular or endocardial masses that are attached to the valves or endocardium by short pedicle
2. Speckled appearance near its edges that correlates with the papillary projection on the tumor surface

Cardiac Tumors That Embolize – Rhabdomyoma

General Characteristics of Rhabdomyoma Associated with Emboli

1. Benign cardiac tumors that are often associated with tuberous sclerosis and less frequently neurofibromatosis, type 1 (NF1)
2. Almost any organ of the body may be affected
3. The tumors may spontaneously regress

Clinical Manifestations of Rhabdomyoma Associated with Emboli

1. Cardiac:
 - a. Heart failure
 - b. Arrhythmias
 - c. Obstruction
 - d. Wolff-Parkinson-White syndrome (WPW)
2. Emboli to the cerebral circulation of tumor fragments

Neuropathology of Rhabdomyoma Associated with Emboli

1. Sites of origin:
 - a. Right ventricle (35%)
 - b. Interventricular septum (33%)
 - c. Left ventricle (22%)
2. Approximately 50% show partial regression
3. In approximately 60% of patients the tumor is associated with tuberous sclerosis
 - a. Some of the cells in the cardiac rhabdomyomas are identical to cardiac Purkinje cells
4. Tumors may be located deep in the myocardium

Neuroimaging of Rhabdomyoma Associated with Emboli

MRI of Rhabdomyoma

1. Topographic embolic stroke

Transthoracic Echocardiography of Rhabdomyoma

1. Used to monitor the tumor

Differential Diagnosis of Cardiac Tumors Associated with Emboli

1. Rhabdomyoma
2. Atrial and ventricular myxomas
3. Fibroelastoma
4. Histiocytoma
5. Hemangioma
6. Hamartoma
7. Undifferentiated
8. Fibroma
9. Metastatic tumors
10. Leiomyosarcoma
11. Angiosarcoma

Differential Diagnosis of Intracardiac Lesions Associated with Emboli

1. Cardiac tumors
2. Metastatic tumors to the heart
 - a. Hypernephroma (through the inferior vena cava)
 - b. Squamous cell lung carcinoma (through the pericardium)
 - c. Malignant melanoma (able to attach to the endocardium)
3. Ball valve thrombus
4. Mural thrombus:
 - a. Following myocardial ischemia
 - b. Within ventricular aneurysm
5. Thrombi within septal aneurysms

Paradoxical Emboli

General Characteristics of Paradoxical Emboli

1. Primarily a venous origin clot that accesses an intracardiac shunt to cause a stroke
2. Four criteria for diagnosis:

- a. A venous thrombus in the peripheral venous system or rare causes (fat, air, fibrocartilage, amniotic fluid)
- b. A right to left cardiac shunt is present
- c. An increased right to left pressure gradient exists:
 - i. Occurs transiently during the cardiac cycle but can be exacerbated by Valsalva maneuvers
- d. A thrombus is identified in the arterial circulation
3. A probable major cause of cryptogenic stroke (a pathophysiological mechanism is not determined)
 - a. Possibly 30%–40% of all strokes
 - b. Increased in younger stroke patients
6. Atrial septal aneurysm associated with focal thrombosis (at the septal bulge)
7. Thromboses have been imaged as they transverse a patent foramen ovale and have been identified in a patent foramen ovale at autopsy
8. Higher incidence of deep venous thrombosis in cryptogenic stroke
9. Isolated calf and pelvic vein thrombosis may be associated with cryptogenic stroke; May-Thurner syndrome has an increased incidence of cryptogenic stroke
10. There is a possible relationship between patent foramen ovale, pulmonary embolus and stroke
11. Air embolism:
 - a. Central vein catheter insertion and removal
 - b. Disconnection of a central catheter
 - c. Thoracic or cardiac surgery
 - d. Pulmonary barotrauma
 - e. Cardiac ablation procedures
12. Risk of air emboli from central catheter is 1–2%; increased by:
 - a. Sitting position
 - b. Deep inspiration (during insertion or removal)
 - c. Hypovolemia
 - d. Injection sclerotherapy for varicose veins

Clinical Manifestations of Paradoxical Emboli

1. Pulmonary hypertension is a setting that favors a paradoxical embolus
 - a. May be induced by prior pulmonary emboli
2. Most common setting is an abnormal connection between the right and left sides of the heart
3. Possibly associated with valsalva maneuvers, coughing, defecation and urination

Criteria for Paradoxical Embolism

1. A venous thrombus as a source
2. An anatomical connection from the venous to the arterial circulation
3. A pressure gradient that promotes venous to the arterial circulation
4. A thrombus in the arterial circulation

Neuropathology of Paradoxical Emboli and a Patent Foramen Ovale (PFO)

1. Autopsy material demonstrates that approximately 25–30% of subjects have a patent foramen ovale whose mean diameter is 5 mm; younger patients have slightly larger patent foramen ovals
2. Echo studies demonstrate patent foramen ovale at 10–22% of normal people
3. Possibly a patent foramen ovale is associated with a large percentage of cryptogenic stroke
4. Agitated saline injected into a femoral vein is more sensitive than echo alone in demonstrating a patent foramen ovale:
 - a. Right atrial blood more easily detected toward the interatrial septum if it originate from the inferior rather than the superior vena cava

Associated Features of Patent Foramen Ovale That Favor a Clinical Paradoxical Embolism

1. Atrial septal aneurysm (ASA)
 - a. Also associated with recurrence
2. Motion of the atrial septal aneurysm that directs flow from the inferior vena cava to the interatrial septum
3. Size of the patent foramen ovale
4. Prominent eustachian valve
5. Right atrial filamentous strands

Neuroimaging of Paradoxical Emboli

1. Higher probability of pelvic deep vein thrombosis
 - a. External iliac vein the most commonly involved
 - b. Secundum atrial septal defects
 - i. Flat elliptical shape
 - c. Patent foramen ovale that are large and associated with an atrial septal aneurysm
 - d. Impending paradoxical emboli
 - i. Entrapped in a patent foramen ovale

May-Thurner Disease

Overview of May-Thurner Disease

May-Thurner syndrome comprises left lower extremity swelling secondary to left iliac vein compression. This anatomic abnormality can predispose patients to increased risk of paradoxical embolism and stroke.

General Characteristics of May-Thurner Disease

1. The left iliac vein compresses the right iliac artery at the level of the fifth lumbar vertebrae
2. Left lower extremity edema pain, varicosities and deep venous thrombosis
3. Source of paradoxical emboli is from right to left cardiac shunt
4. Typically presents in the second to fourth decades of life; more common in women than men (3:1)

Clinical Manifestations of May-Thurner Disease

1. Possible paradoxical embolism to the basilar apex
2. Possible increased risk of paradoxical emboli
3. Deep vein thrombosis

Neuropathology of May-Thurner Disease

1. Compression of the left common iliac vein
 - a. Risk factor for lower-extremity deep vein thrombosis

Neuroimaging of May-Thurner Disease

1. Stenosis of the left common iliac vein
2. Normal Left Common Iliac Vein diameter is 6.5 mm
3. Patients with deep vein thrombosis have a left common iliac vein diameter of 4 mm
4. The odds of deep vein thrombosis increased by a factor of 1.68 for each millimeter decrease in left common iliac vein

Differential Diagnosis of Cardiac Sources of Emboli*Ischemic Heart Disease as a Cardiac Source of Emboli*

1. Mural thrombus
2. Congestive heart failure
3. Ejection fraction of less than 30%
4. Ventricular aneurysm
5. Akinetic or hypokinetic segments

Cardiac Arrhythmia as a Cardiac Source of Emboli

1. Chronic or paroxysmal atrial fibrillation
2. Sick sinus syndrome
3. Brady-tachyarrhythmia
4. Long QT interval syndrome
5. Romano-Ward syndrome (AD)
6. Jervell syndrome (AD)
7. Lang-Nielsen syndrome (AR)

Valvular Heart Disease as a Cardiac Source of Emboli

1. Rheumatic mitral stenosis
2. Rheumatic mitral insufficiency (rare)
3. Rheumatic aortic stenosis
4. Bicuspid aortic valve (congenital)
5. Calcific aortic stenosis
6. Mitral annulus calcification
7. Bacterial endocarditis
8. NBTE (marantic endocarditis)
9. SLE (verrucous endocarditis)
10. Antiphospholipid syndrome (APLS)
11. Left ventricular assist devices
12. Prosthetic heart valves
13. Fibrous and fibrinous endocardial lesions

Cardiomyopathy as a Cardiac Source of Emboli

1. All dilated cardiomyopathies
2. Idiopathic
3. Post-partum
4. Viral
5. Ischemic cardiomyopathy
6. Sarcoidosis
7. Amyloidosis
8. Endocardial fibroelastosis

9. Multiple mitochondrial myopathies
10. Duchenne muscular dystrophy
11. Becker's muscular dystrophy
12. Idiopathic dilated cardiomyopathy
13. Variants of dystrophinopathy
14. Inclusion body myositis
15. Dermatomyositis/polymyositis complex
16. Nemaline myopathy
17. Debrancher glycogen storage disease
18. Scapuloperoneal dystrophy with mental retardation
19. Desmin myopathy
20. Myofibrillar lysis

Intracardiac Lesions as a Cardiac Source of Emboli

1. Cardiac tumors (primary):
 - a. Myxoma
 - b. Fibroma
 - c. Fibroelastoma
 - d. Hamartoma
 - e. Hemangioma
 - f. Histiocytoma
 - g. Rhabdomyoma (sarcoma)
 - h. Undifferentiated
 - i. Leiomyosarcoma
 - j. Angiosarcoma
2. Metastatic tumors:
 - a. Hypernephroma
 - b. Melanoma
 - c. Squamous cell carcinoma of the lung
 - d. Colon
 - e. Hepatocellular
 - f. Lymphoma
3. Ball valve thrombus
4. Mural thrombus
5. Ventricular aneurysm with thrombus
6. Septal aneurysm with thrombus

Intracardiac Defects with Paradoxical Embolus

1. Atrial septal defects
2. Ventricular septal defects
3. Patent foramen ovale (PFO)
4. Atrial septal aneurysms
5. PFO plus atrial septal aneurysm

The Aorta as a Source of Emboli*General Characteristics of the Aorta as a Source of Emboli*

1. Large plaques of greater than 4 mm are involved in first-ever cerebral infarction and stroke recurrence

*Clinical Manifestations of the Aorta as a Source of Emboli***Neurologic Signs and Symptoms of the Aorta as a Source of Emboli**

1. Protruding atheroma:
 - a. Related to emboli

2. Ulcerated plaque in the aortic arch may not correlate with atheromatous carotid disease
3. Ascending aorta and arch junction
 - a. Important site for plaques that embolize as is the origin of the innominate artery
4. Frequency of brain infarction correlated with thickness of the aortic wall
5. Complex, thick or mobile plaques > 5 mm have 3 times greater incidence of stroke than patients with plaques <5 mm
6. MCA distribution of emboli
7. Rare brachial plexus arterial supply

Neuropathology of the Aorta as a Source of Emboli

1. Average diameter of an aortic plaque is 19 mm
2. Plaques are frequently on the anterior or posterior right side of the ascending aorta
3. The upper and lower half of the ascending aorta are equally involved
4. Aortic arch plaques
 - a. At the orifice of the innominate artery
5. Complex thick or mobile plaques are most likely to embolize
6. Plaques have disappeared after anticoagulant therapy
7. Anticoagulants theoretically could potentiate cholesterol emboli by:
 - a. Blocking protective clot thrombi that cover plaque ulceration
8. Retrograde flow in aorta causes emboli to both the anterior or posterior circulation
9. Emboli during catheterization

Neuroimaging of the Aorta as a Source of Emboli

Transesophageal Echocardiography (TEE) of the Aorta as a Source of Emboli

1. Plaque grading system:
 - a. 0 mm – 0
 - b. 1 mm – grade 1
 - c. 2 mm – grade 2
 - d. 3 mm – grade 3
 - e. 4 mm – grade 4
 - f. 5 mm – grade 5; mobile complex

Unusual Sources of Emboli – Air Embolism

General Characteristics of Air Embolism

1. Specific settings:
 - a. Extracorporeal membrane oxygenation (ECMO)
 - b. Vascular surgical procedures
 - c. Open heart surgery
 - d. Head and neck surgery in the sitting position (air enters the jugular vein)
 - e. Pelvic vein insufflation (air) during pregnancy
 - f. Complication of gastrointestinal endoscopy
 - g. Ingestion of hydrogen peroxide
 - h. Insertion or removal of a central venous catheter
 - i. Frequency of air embolism in this setting is .1 to 2%
 - ii. Increased risk occurs

Clinical Manifestations of Air Embolism

1. Systemic air embolism
 - a. Arrhythmia
 - b. Hypotension
 - c. Myocardial ischemia
 - d. Right heart failure
 - e. Cardiovascular collapse
 - f. Cardiac arrest
2. Hypoxia cyanosis, respiratory failure
3. Focal neurologic signs
 - a. Eye deviation and hemiparesis
 - b. Failure to regain consciousness after anesthesia
 - c. Cerebral hypoperfusion
 - d. Cerebral edema and coma
4. In the case of ERCP initiated air embolism
 - a. Exacerbated signs when repositioned from a prone to supine position

Neuropathology of Air Embolism

1. High flow ECMO
 - a. Venous gas embolism occurs because of the extracorporeal perfusion system is not efficient enough to remove air microbubbles:
 - i. Any factor that reduces central venous pressure that include:
 1. Deep inspiration during insertion or removal
 2. Hypovolemia
 3. Upright position
 - b. Arterial air embolism occurs:
 - i. Entry of gas into the pulmonary vein
 - ii. Directly into the arteries of the systemic circulation
 - c. Arterial spasm
 - d. Widespread hemispheric distribution
 - e. Air bubbles in subarachnoid vessels

Neuroimaging of Air Embolism

MRI of Air Embolism

1. Diffusion-weighted sequences demonstrate diffuse hyperintensity
2. Air bubbles in cerebral arteries

CT of Air Embolism

1. Low attenuation lesions in the right atrium

Transthoracic Echocardiography of Air Embolism

1. Demonstrates air bubbles in the aorta and ventricular outflow tract

Trans Doppler Echocardiography of Air Embolism

1. Demonstrates microemboli during procedures

Unusual Sources of Emboli – Fat Emboli

General Characteristics of Fat Emboli

1. Fat embolism syndrome (FES):
 - a. Multi-organ disorder
 - b. Long bone fractures; particularly of the femur
 - c. Incidence of .5 to 11% of long bone fractures

Clinical Manifestations of Fat Emboli

1. Systemic complications:
 - a. Hypoxia
 - b. Pulmonary dysfunction
 - c. Petechiae (often over the chest wall)
 - d. Fever
 - e. Tachycardia
 - f. Thrombocytopenia
2. Setting:
 - a. Broken long bones in young patients
 - b. Hip replacement surgery (even in elderly patients)
3. Late syndrome:
 - a. 4–7 days following the event
 - b. Acute confusion
4. Altered mental status
5. Focal neurologic signs
6. Generalized seizures
7. Occurs most frequently in the second to third decade most often 12 to 72 hours after traumatic bone fracture

Neuropathology of Fat Emboli

1. Less common non-traumatic causes of fat embolus syndrome include:
 - a. Soft tissue injury liposuction
 - b. Hepatic failure
 - c. Propofol infusion
 - d. Burns
 - e. Acute sickle cell crisis
 - f. Acute pancreatitis
 - g. Altitude sickness

Pathogenesis of Fat Emboli (2 Theories)

1. Theory 1: release of fat droplets into the circulation from the site of trauma
 - a. Emboli pass through the lungs into the arterial circulation
2. Theory 2: fat droplets reach the capillary bed of the lung from the right heart which causes a ventilation-perfusion mismatch and the acute respiratory distress syndrome:
 - a. The intramedullary pressure in long bones may be the most significant factor in producing fat embolism syndrome
 - b. Multi-trauma patients demonstrate lung intravascular fat is similar to bone marrow fat
3. Experimental studies demonstrate:
 - a. Nitrous oxide mediated disruption of the blood-brain barrier by arterial fat globules cause:
 - i. Transient cerebral edema
 - ii. Neutrophil infiltration
 - iii. Activation of metalloproteinases

Neuroimaging of Fat Emboli

1. Site predilection for emboli:
 - a. Retina (fat globules visible)

- b. Corpus callosum
- c. Centrum semiovale
- d. Superficial pial vessels

CT of Fat Emboli

1. Hypointense areas at the gray-white matter junction consistent with fat globules

MRI of Fat Emboli

1. Brain images at 3 days
 - a. T2-weighted hyperintense areas with restricted diffusion in involved territories

Unusual Sources of Emboli – Decompression Sickness (DCS)*General Characteristics of Decompression Sickness*

1. Type 1 Decompression Sickness – Symptoms of musculoskeletal pain
2. Type 2 Decompression Sickness – Primarily related to the central nervous system
3. Spinal evidence that right to left heart shunts are relevant to decompression sickness
4. Arterial bubbles are more often associated with more serious cases of decompression sickness injury
5. Multiple cerebral infarction in the terminal and watershed areas of pial arteries
6. Subclinical forms of decompression illness exist

Neuropathology of Decompression Sickness

1. Venous gas emboli effects in the endothelium may be the central mechanism in decompression sickness
2. Stationary bubbles are formed in the tissue and produce local damage and intravascular arteriole blockage
3. Nitrogen bubbles are filtered out in the lungs
4. Arterial bubbles block and damage blood vessels in the brain and heart
5. Venous gas emboli cause changes in vessel permeability and disrupt endothelial function
 - a. Pivotal may be the generation of reactive oxygen species

*Neuroimaging of Decompression Sickness**MRI of Decompression Sickness*

1. Terminal and border zone ischemic lesions
2. Cerebral arterial gas embolism (CAGE)
 - a. Multiple lesions
 - b. Large size of the lesions
 - c. Frontal and parietal lobes are primarily affected
 - d. Involvement of cortical gray matter and subcortical white matter
 - e. Cerebellum may be involved

Differential Diagnosis of Unusual Sources of Emboli

1. Air (cardiac and neck surgery, diving accidents)

2. Fat emboli (diabetic ketoacidosis, trauma, pancreatitis)
 3. Nitrogen bubbles from diving (bends), pressure from underwater construction (Caisson's disease)
 4. Calcium (calcific aortic valves, calcified mitral valve annulus)
 5. Fungus balls (subacute bacterial endocarditis; Aspergillus endocarditis)
 6. Bullets (shot gun pellets; rare bullet fragments)
 7. Ectatic arteries (source of emboli)
 8. Aneurysms (giant > 1 cm; tip of the basilar, carotid, middle cerebral artery)
 9. Tumor material
 10. Thrombolytic therapy (lysis of clots that then expose underlying collagen which then forms new less adherent clots)
 11. Iatrogenic occlusive therapy (embolization of AVM's; Gelfoam)
 12. Catheters
 13. Defoaming agents
 14. MAC attack (esophageal fistula to veins)
 15. Talc (IV drug addicts; increased right heart pressure from pulmonary fibrosis; paradoxical embolus)
 16. Fibrocartilage (following orthopedic procedures)
- b. A state of internally oriented cognitive content:
 - i. Self-referential
 - ii. Social cognition
 - iii. Mind wandering
 - iv. Autobiographical memory recall
 - c. Areas that demonstrate fMRI activity of the default mode network (DMN) are:
 - i. Medial prefrontal cortex
 - ii. Anterior cingulate gyrus
 - iii. Precuneus
 - iv. Bilateral temporoparietal junction
 - d. Patients in coma demonstrate no fMRI DMN connectivity
 - i. If some activity is demonstrated the patient may regain consciousness
 - e. DMN/EEG synchrony:
 - i. Absent in VS/UWS; intermediate in MCS and highest in healthy controls
 - f. Brain metabolism in these midline structures:
 - i. Disrupted in VS/UWS and MCS compared to those who have emerged from MCS or are in a locked in state
 - ii. Deactivation of the medial DMN is absent in VS/UWS and decreased in MCS
 - iii. Changes in DMN functional connectivity relate to self-related conscious mentation
 - iv. Normal wakefulness has resting state activity in:
 1. Posterior cingulate
 2. Frontal areas
 3. Areas important for self-referential thought
 - v. The "intrinsic" network
 1. Coincides with the default mode network (DMN)
 - vi. The "extrinsic network"
 1. The lateral frontoparietal areas
 2. Activated during goal-directed behavior
 3. Linked to cognitive processes of external sensory input (somatosensory, visual, auditory stimuli)
 - vii. Metabolic activity in the vegetative state/unresponsive wakefulness syndrome (VS/UWS)
 1. Decreased activity in a widespread fronto-temporo-parietal associative cortical network associated with decreased levels of consciousness
 - viii. PET data:
 1. Recovery of MCS
 - a. Right lateralized recovery of the external awareness network
 2. Ability to follow commands:
 - a. Recovery of dominant left lateralized language network
 3. Similar findings occur in transient dissociative states of unresponsive wakefulness:
 - a. Absence seizures

Ischemic Encephalopathy

Consciousness

Overview

1. Consciousness is a combination of both the waking states and experience
 - a. A linear relationship exists between wakefulness and awareness of the surroundings and ourselves
2. Vegetative state/unresponsive wakefulness syndrome (VS/UWS)
 - a. Maintain awake periods evidenced by eye opening
 - b. Never respond to visual, somatosensory or auditory stimuli
 - c. Sleep-wake cycle is entrained
3. Minimal conscious state (MCS)
 - a. Fluctuating signs of awareness
 - b. Demonstrates non-reflexive behaviors
 - i. Visual pursuit
 - ii. Follow some commands
4. Self-consciousness
 - d. Response to stimuli that modify behavior which implies awareness of patient's surroundings and an action
 - e. Response to self-referential stimuli – patients own name or face (self-detection)

Neuroanatomical Correlate of Consciousness

Overview

1. During the resting state determined by fMRI: the default mode network (DMN)
 - a. Subjects are not performing a task

- b. Complex partial seizures
- c. Sleep walking
- d. Automatic reflex motor behavior in absence of response to commands
- e. Transient decreased activity in fronto-temporo-parietal associative areas
- ix. Functional separation of the dorsal and ventral posterior cingulate cortex (PCC):
 1. Ventral PCC is integrated within the DMN:
 - a. Involved with memory retrieval and planning (internally directed cognition)
 - b. Dorsal PCC:
 - i. Connectivity to the frontal lobes
 - c. Differential regional activity of the PCC dependent upon:
 - i. Arousal state
 - ii. Internal vs external attention
 - iii. Breadth of attention (narrow vs broad)
 - d. Dorsal PCC involved with the control of attentional focus (interactive with PFC)
- 2. An Operational Definition of Unconsciousness:
 - a. A within-network loss of connectivity of a widespread fronto-parietal network
 - b. A between-network hyper connectivity of the medial 'intrinsic' network
- 3. Post-anoxic/ischemic levels of consciousness:
 - a. Minimally conscious state:
 1. Intrinsic network/thalamic connectivity involved
 2. Altered internal self-awareness
 - b. Vegetative state/unresponsive wakefulness (VS/UWS):
 1. Dysfunction of the extrinsic/intrinsic networks and thalamus
 - c. Emergence from the minimally conscious state:
 1. Involvement of the posterior cingulate and retrosplenial cortices
 - d. Locked-in syndrome
 1. Involvement of infratentorial nuclei

Arousal Component of Consciousness

1. Arousal pathways originate in the brainstem
 - a. Activate awareness networks in the cerebral cortex:
 - i. From synapses in the thalamus and basal forebrain
 - ii. Direct cortical innervation

The Anatomy of the Ascending Reticular Activating System

Overview

1. Neurotransmitter specific pathways from the brainstem nuclei to:
 - a. Cortex via thalamic and extrathalamic pathways
 - i. Serotonergic pathways from the raphe subnuclei of the rostral pons and midbrain
 - ii. Noradrenergic projections from the locus coeruleus of the rostral pons

- iii. Dopaminergic projections from the ventral tegmental area to the caudal midbrain
 - iv. Cholinergic projections from the pedunculopontine nucleus and laterodorsal tegmental nuclei of the caudal midbrain and rostral pons
 - v. Glutamatergic fibers from the parabrachial nuclear complex of the rostral pons
2. Further networks associated with arousal through connectivity with the ascending reticular activating system (ARAS):
 - a. Hypothalamus
 - i. Regulation of autonomic function
 - ii. Circadian sleep – wake cycles
 - b. Basal forebrain
 - i. Cortical activation
 - ii. ANS integration

The Anatomical Components of the ARAS

Overview

1. The reticular core:
 - a. Mesencephalic and pontine reticular formation
 - b. Bilateral fiber bundle that connects the cuneiform/subcuneiform nuclei in the rostral midbrain to the thalamus, hypothalamus and basal forebrain (demonstrated by Moruzzi and Magoun)
 - i. Includes projections from the pontis oralis nuclei of the rostral pons
 - c. In the rostral midbrain
 1. Bilateral fiber bundle from the mesencephalic/pontine reticular formation bifurcates into a ventral tegmental tract and dorsal tegmental tract
 - a. Ventral tegmental tract (VTT) projects to the hypothalamus
 - b. Dorsal tegmental tract (DTT) projects to the thalamic reticular nuclei
2. Transmitter specific nuclei of the brainstem
3. Projections to the hypothalamus, thalamus, basal forebrain and cortex
4. The thalamus integrates and modulates the brainstem arousal networks. The involved nuclei are:
 - a. The reticular nucleus
 - b. Central lateral nuclei (component of the intralaminar complex)
 - c. Centromedian-parafascicular nuclear complex

New Methodologies

1. Advanced imaging techniques of high angular resolution diffusion imaging (HARDI)
 - a. Elucidate the structural connectivity of the ARAS that is being applied to pathological states of arousal and consciousness

Hypoxic-Ischemic Encephalopathy

General Characteristics

1. Decreased brain perfusion, oxygenation or both

2. Decreased perfusion
 - a. Cardiac arrhythmia or arrest
 - b. Pump failure

The brain is differentially susceptible to hypoxia, hypoglycemia and hypoperfusion. In general, areas most susceptible to hypoxia have the greatest metabolic rate for glucose utilization and ATP requirement. In the case of cardiac arrest, pump failure, and ventilatory failure they suffer first and most severely.

In general, respiratory arrest without circulatory compromise carries a better prognosis. Complete circulatory arrest induces rheological changes that include endothelial cell swelling and viscosity changes that preclude reperfusion of cortical, basal ganglia and thalamic capillary networks. This constitutes the no-reflow phenomena. Hyperglycemia and acidosis at the time of an arrest increase neuronal death. Pre arrest vascular compromise leads to distal field ischemia and stroke primarily in the anterior circulation in those under 40 and in the vertebral basilar system in elderly patients. Prolonged hypoperfusion and anoxia lead to border zone infarction (posterior zone between MCA/PCA territory > anterior zone (MCA/ACA territory). Specific toxins or circumstances involve specific brain areas. Carbon monoxide preferentially affects the medial globus pallidus, cortex and cerebellum. Isolation of speech areas, from perisylvian involvement has also been described. Strangulation or hanging preferentially involves the medial globus pallidus. A single hypoxic event may cause a delayed but progressive leukoencephalopathy that begins 4–10 days following the insult. Cognitive dysfunction, irritability and apathy are prominent as is rigidity of the limbs and ataxia of gait. Some patients with delayed hypoxic leukoencephalopathy have reduced aryl sulfatase A activity. Therapeutic hypothermia has effects on neurologic recovery.

Post-Cardiac Arrest Syndrome

General Characteristics

1. Differential neuronal susceptibility
2. Myocardial dysfunction
3. Systemic ischemia/reperfusion (I/R) response
4. Persistent precipitating pathology

Systemic I/R Response Causes

1. Production of reactive oxygen species (ROS) occurs during arrest
2. Oxidative stress:
 - a. Is a major factor responsible for secondary damage and inflammation in brain ischemia and traumatic injury

Therapeutic Hypothermia

1. Usually applied at 33–34°C for 12–24 hours (increases lactate clearance)
 - a. Associated drugs utilized during treatment:
 - i. Midazolam (GABA agonist)

- ii. Sufentanil (opioid)
 - iii. Cisatracurium (neuromuscular blockade)
- b. Intravascular methods:
 - i. Reach target temperature faster
 - ii. More stable hypothermia
 - iii. Better control of rewarming

2. Benefit of therapeutic hypothermia:
 - a. Control of oxidative stress in I/R induced injury (ischemia/reperfusion)

Side Effects of Therapeutic Hypothermia

1. Immunosuppression
2. Increased infection risk
3. Cold diuresis and hypovolemia
4. Electrolyte disorder
5. Insulin resistance
6. Impaired drug clearance
7. Mild coagulopathy
 - a. Rewarming phase:
 1. Elevation of intracranial pressure
 2. Increased neuroinflammation

Clinical and Pathological Aspects of Post-Cardiac Arrest Hypoxic Encephalopathy

1. Appearance of new ischemic foci
2. Neurologic degeneration associated with accumulation of amyloid protein (AB)
3. Injury of vascular epithelium
 - a. Platelet activation
 - b. Thrombosis of the microvasculature is due to the inflammatory response from leukocyte, T-cell, and macrophage recruitment to ischemic areas:
 - i. Release of proinflammatory chemokines, interleukins and cytokines
 - ii. Disruption of the blood-brain barrier

Differential Susceptibility of Neurons to Hypoxia

1. Hippocampus:
 - a. Sumner's section V, and the amygdaloid complex
 - b. Pyramidal neurons
 - c. CA1 zone
2. Medial laminae of the cerebral cortex
 - a. Layer III–V
 - b. Thalamic projecting neurons to the cortex
3. Globus pallidus/caudate/putamen
 - a. Internal segment of GPi
4. Thalamus:
 - a. Anteroventral nuclei
 - b. Dorsomedial nuclei
 - c. Pulvinar
5. Cerebellum
 - a. Purkinje cells
6. Brainstem tegmental nuclei:
 - a. V, IX, Xth nerves
 - b. Inferior colliculus

- c. Superior olive
- d. Vestibular nuclei
- 7. Spinal cord
 - a. Renshaw cells
 - b. Anterior 2/3 of the cord
 - c. Distribution of the artery of Adamkiewicz (T₁₀–L₁–L₂)

Border Zone Infarction

1. Anterior; ACA/MCA
2. Posterior; MCA/PCA
3. Vascular stripe (between descending pial blood vessels and ascending lenticulo striate arteries)
 - a. 1 cm from the lateral ventricle on MRI
4. Border zone of the cerebellum (level of the dentate nucleus)
5. Subinsular cortical areas
6. Cerebellar cortical artery border zones:
 - a. SCA/PICA
 - b. SCA/AICA

Clinical Patterns of Circulatory Arrest

Brain-Stem Coma

Overview

1. Prolonged hypoperfusion-anoxia
 - a. Dilated pupils
 - b. Absent corneal reflexes
 - c. No doll's eye response (absent vestibular ocular response)
 - d. No response to ice-water caloric (absent VOR)
 - e. Frequent loss of spontaneous respiration
 - f. No spontaneous movement
 - i. Decorticate or decerebrate posture may be seen
2. Selective necrosis of brainstem nuclei
 - a. Affects children and infants most frequently; (Vth nerve involvement) occasionally seen in adults
 - b. No oculoccephalic eye movements (VOR)
 - c. Loss of branchial muscle functioning including the gag reflex
 - d. Stiff extremities; no spontaneous movement
 - e. Automatic movements with stimuli
 - f. Autonomic disinhibition
 - i. Fluctuating blood pressure and cardiac rate
 - g. Loss of spontaneous respiration
3. Brainstem coma secondary to bi-hemispherical coma
 - a. Patients regain brainstem reflexes
 - b. Spontaneous respiration occurs

Cortical Coma (Bilateral Cortical Lesions)

Overview

1. Unresponsive to noise, bright light or voice
2. Respond to painful stimuli
3. Spontaneous movements of the extremities
4. Pupils are normal or small; react to light
5. Eye movements:

- a. Roving from side to side
- b. Midline
- c. Deviated upward
- d. Hyperactive doll's eyes maneuver
 - i. Loss of ocular fixation reflexes that inhibit the vestibular ocular reflex (VOR)
 - ii. Vertical eye movements are present to vestibular ocular reflex (VOR) maneuvers:
 - iii. May be difficult to deviate downward if patient has fixed upward deviation
- 6. Gag reflex intact
- 7. Branchial innervated movements are intact
 - a. Spontaneous blink and swallow reflexes

Corticospinal Tract Dysfunction

Overview

1. Patients may have preserved:
 - a. Adduction/flexion of the shoulder, arms and wrists
2. Noxious stimulation of extensor or flexor upper extremity surface:
 - a. Elicits flexion/adduction of the arms and shoulder
3. Noxious stimulation of lower extremities elicits:
 - a. Extension/adduction of the lower limbs
4. External rotation of the foot; cortical thumb

Intact Corticospinal Tract Signs

Overview

1. Noxious stimuli elicits movements away from afferent input
2. Movement of individual fingers
3. Spontaneous or reactive extension of the upper extremity
4. Abducting movements of the arm or forearm
5. Lower limb noxious stimuli elicits
 - a. Flexion/adduction
6. Supination of the arm at rest and normal position of the foot (extension)
7. Thumb abducted

Progression from Bi-Hemispherical Coma

Overview

Specific features of selective vulnerability of the anoxic-ischemic episode may become prominent. Many patients demonstrate agitation, restlessness, confusion and delirium as they regain consciousness. If the insult has been primarily hypotensive with less generalized anoxia, border zone infarction may be prominent.

Posterior Border Zone Infarction

General Characteristics

1. Bilateral infarction of the MCA/PCA overlap territory
 - a. Parieto-occipital junction
2. Complete or partial Bálint's syndrome
 - a. Simultagnosia:
 - i. Inability to see all objects in the visual field
 - ii. Inability to see all components of one object

- iii. Inability to merge components of an object into a whole
- iv. Optic ataxia:
 - 1. Damage to parietal area 5 and 7. Patients under reach for objects. They have poor eye/hand coordination
- v. Apraxia of gaze:
 - 1. Poor initial scanning of a visual field
 - 2. Inability to look at a specific object on command
 - 3. Inability to break a fixed gaze
- 3. Clumsiness and dysarthria
- 4. Ideomotor, limb kinetic, ideational apraxias
 - a. Laminar necrosis of area 6, 8 (ideomotor; callosal apraxia); posterior parietal areas (ideational apraxia)
- 5. Cortical blindness:
 - a. Laminar necrosis of the occipital cortex
 - b. Anton's syndrome
- 6. Seizures:
 - a. Most often generalized
 - b. Difficult to treat
- 7. Myoclonus:
 - a. Multifocal
 - b. Generalized
 - c. Exaggerated by stimuli or movement
 - d. Repetitive and generalized > 30 minutes is a bad prognostic sign following cardiac arrest
- 8. Persistent Vegetative state/unresponsive wakefulness syndrome (VS/UWS):
 - a. Severe laminar necrosis:
 - i. Appear awake and have brain stem function
 - ii. No response to stimuli:
 - 1. Eyes may track a moving object
 - iii. Retain sleep-wake cycle
 - iv. Eyes intermittently open
- 9. Cerebellar dysfunction
 - a. Metronomic eye movements; eyes rhythmically oscillate side to side
 - b. Generalized ataxia
 - c. Lance-Adams syndrome:
 - i. Spontaneous, arrhythmic fine and course movements
 - ii. Exaggerated by voluntary movement
 - iii. Action myoclonus
 - iv. Associated with gait ataxia
 - v. Damage to dorsal raphe serotonergic neurons in addition to Purkinje cells and cerebellar pathways
 - vi. Probable associated border zone cerebellar infarcts of the PICA/SCA and AICA
 - vii. May progress after the initial insult

Anterior Border Zone Infarction

General Characteristics

- 1. Bilateral infarction of the anterior and middle cerebral artery border zone territories
- 2. "Man in the Barrel" syndrome:
 - a. Shoulder and arm are primarily affected; hand stronger than shoulder; legs spared
 - b. Frontal eye fields involved (area 8, 10):
 - i. Roving cortical eye movements (disinhibited from gaze centers)
 - ii. Too easily obtained doll's eye maneuvers (uninhibited VOR)
- 3. Asymmetries have been described:
 - a. Unilateral arm paralysis
 - b. Head and eye deviation to the more affected side
- 4. Stupor from extensive bilateral lesions

Memory Loss Following Cardiac Arrest

General Characteristics

- 1. Severe damage to the pyramidal cells of the hippocampus
 - a. CA I; Sumner's section V
 - b. Amygdaloid complex
 - c. Medial temporal lobes
- 2. Clinical sequelae
 - a. Severe short term memory loss. Poor encoding of new memories over 3 minutes. Registration is intact (object recall less than 15 seconds). Long term memory and retrieval are relatively spared

Laminar Necrosis

General Characteristics

- 1. Layers III–V of the cortex are damaged throughout. Speech, motor, and visual areas affected clinically more prominently than the parietal lobe
- 2. Isolation of the speech areas:
 - a. Combination of laminar necrosis and anterior and posterior border zone infarction
 - b. Transcortical motor and sensory aphasia
 - c. Complete perisylvian involvement
 - i. Patient can only repeat; cannot initiate or perceive speech
 - d. Severe dysarthria
 - i. Damage to corticobulbar fibers for speech emanating from the frontal operculum

Basal Ganglia and Thalamus Dysfunction After Cardiac Arrest

General Characteristics

- 1. Prolonged partial ischemia:
 - a. Hypoxia precedes circulatory insult
 - b. Damage most severe in the globus pallidus interna, caudate, putamen, AV, DM and pulvinar nuclei of the thalamus
 - c. Hanging, strangulation, carbon monoxide poisoning produce a similar dissociation between blood flow and oxygenation
 - d. Clinical sequelae:
 - i. Eyes open and fixed
 - ii. Abnormal twitches and movements (choreoathetosis)

- iii. Rigidity of extensor and flexor muscles
- iv. Decorticate posturing
- v. Mute and unresponsive

Delayed Leukoencephalopathy

General Characteristics

1. Generally young patients who have suffered strangulation, drowning, inhalation of noxious gases or carbon monoxide poisoning

Neuropathology

1. Diffuse demyelination that may progress to hemorrhagic white matter necrosis
2. Basal ganglia involvement (GP)
3. Possible relationship to decreased Arylsulfatase A in some patients

Clinical Manifestations

1. Initial coma associated with:
 - a. Quadriplegia
 - b. Atonia
 - c. Involuntary limb movements
2. Progression to:
 - a. Dystonic rigid state
 - i. Relative preservation of the cortex
 - ii. Severe damage to basal ganglia
 - iii. Generalized demyelination
3. Delayed deterioration starts between 4–40 days in some patients; activity may worsen the process
4. Parkinsonism
5. Psychosis
6. Cognitive decline

Neuroimaging

MRI

1. Diffuse hyperintensity of cerebral white matter on FLAIR sequences

Hypoxic-Ischemic Spinal Cord Damage

General Characteristics

1. Selective vulnerability of the spinal cord:
 - a. Upper and lower thoracic cord is most often involved
 - b. Territory of the great radicular artery of Adamkiewicz
 - i. Origin T10–T12 to L-2; supplies the lumbar cord and the conus medullaris
 - c. Upper and lower thoracic regions border zones of the anterior feeding vessels (those that comprise the unpaired anterior spinal artery) ASA
 - d. Sulcal arteries from the anterior spinal arteries supply the ventral horns; circumferential arteries from the posterior paired spinal arteries and the circumferential branches of the ASA supply the lateral components of the cord. The internal spinal cord watershed is the corticospinal tracts, the border zone between the sulcal and circumferential arteries. Paired dorsal spinal arteries supply the posterior columns

Clinical Manifestations

1. Spinal cord hypotensive damage is unusual as the cord is perfused at a much lower pressure than the cerebral circulation (approximately 60 mm Hg)
2. Ischemic injury involves the anterior 2/3 of the cord
3. Flaccid paralysis of the lower extremities is noted early; spasticity supervenes:
 - a. Loss of bowel and bladder continence
 - b. Sensory level to temperature and pin prick at lower thoracic levels
 - c. Atrophy and fasciculation of the legs/supervenes
4. Rare acute rigidity

Neuropathology

1. Renshaw cell involvement
2. Loss of glycine and spinal cord inhibition

Prognostic Indicators in Patients That Have Suffered Ischemic-Hypoxic Injury

Early (Minutes to 6 Hours)

Vital Signs

1. Blood pressure
 - a. Severe hypertension
 - i. Increased ICP
 - ii. Normal cardiac function
 - b. Profound hypotension
 - i. Severe cardiac damage
 - ii. Vasomotor center damage (brainstem)
 - c. Fluctuating blood pressure
 - i. Vasomotor center or connections are damaged (dorsolateral medulla and pons)
 - ii. Autonomic disruption (posterior hypothalamus afferents to intermediolateral column of the spinal cord)
 - d. Herniation
 - i. Hypertension to sudden hypotension
 1. Disruption of the vasomotor centers and connections in the dorsolateral medulla and pons
2. Pulse
 - a. Regular full slow pulse (50–60/min)
 - i. Kocher–Cushing reflex from ICP
 - b. Thready rapid pulse (120 minute)
 - i. Cerebral herniation
 - ii. Cardiac failure
 - iii. Disruption of vasomotor centers and their connections at a brainstem level
3. Respiratory pattern by CNS Level
 - a. Cheyne’s–Stoke (basal ganglia/thalamic)
 - b. Periodic breathing (basal ganglia/thalamic)
 - c. Central neurogenic-hyperventilation (midbrain)
 - i. Need to Rule out:
 1. Acidosis
 2. Low pO₂
 3. Uninhibited breathing Kölliker–Fuchs nucleus
 - a. Pneumotatic center

4. Apnea (Pons)
5. Cluster (medullary)
6. Ataxic (medullary)
7. Biot's (medullary couplet breathing)
4. Temperature
 - a. General rule is that temperatures above 105 degree F° are central rather than from sepsis

Hyperthermia

General Characteristics

1. Anterior hypothalamic damage
2. Drugs: dopamine receptor D₂ agonists or their sudden withdrawal, INH (isoniazid), cocaine, amphetamine, phenothiazine (rare)
3. Blood in the 3rd ventricle

Hypothermia

General Characteristics

1. 92–93 degree F° (posterior hypothalamic damage)
 - a. Hypothyroidism; pan-hypopituitarism
 - b. Drugs (phenothiazine based)
2. 97–98 degrees Fahrenheit
 - a. Endocrine failure (thyroid; pan-hypopituitarism)
 - b. Hypoglycemia
 - c. Liver and renal failure (usually 1 degree Fahrenheit decrease)
 - d. Phenobarbital

Level of Consciousness

Overview

Profound coma implies damage to the lateral medullary reticular formation, the dorsal pontine tegmentum periaqueductal gray of the midbrain, intralaminar nuclei of the thalamus or bilateral cerebral cortex. The brainstem is much less vulnerable to hypoperfusion and anoxia than the cortex and therefore severe brainstem dysfunction implies hemispheric damage with a poor prognosis for a good functional recovery. A patient who is fully alert and awake 6 hours after a cardiac arrest or hypoxic-ischemic event improves rapidly over twelve hours and has a good prognosis. Twenty four hours to alertness may be a very important prognostic assessment time.

Acute Levels to Be Assessed Are:

1. Fully Alert
2. Lethargic
3. Obtunded
4. Stuporous
5. Comatose

Chronic Levels of Consciousness

1. Vegetative state/unresponsive wakefulness syndrome (VS/UWS)
2. Recovery from Minimal conscious state (MCS)
3. Locked-In syndrome (fully awake; can respond to commands with vertical eye movements)

Brainstem Reflex Assessment at 6 Hours

General Characteristics

1. Gag reflex – IX, X (medulla)
2. Corneal – V – pons
3. Vestibular ocular reflexes (VOR)
 - a. VIIIth cranial nerve (vestibular nuclear afferents)
 - b. Medial longitudinal fasciculus (innervation of EOM)
 - c. VIth and IIIrd cranial nerve
4. Pupils
 - a. Dilated to 4–5 mm after 3–4 minutes of cardio-pulmonary arrest
 - i. Rule out atropine or sympathomimetic drug administered during resuscitation procedures
 - b. Cortical or pretectal level
 - i. Non-reactive to light
 - c. Dilated to 3 mm and non-reactive to light or noxious stimuli
 - i. Midbrain level
 - ii. Cadaveric
 - d. Dilated to 2–3 mm
 - i. Reactive to light
 - ii. Thalamic/basal ganglia level
 - e. 0.5 mm pupil
 - i. Pontine level
 - ii. Reactive to light
 - f. 1 mm pupil
 - i. Medullary level
 - ii. Sympathetically denervated (unopposed parasympathetic input)
 - iii. Rule out narcotics
 1. Demerol may not affect pupils; 1/3 of the time it does
 - iv. Rule out drugs with parasympathomimetic action (antidepressants)
5. Persistent pupillary dilatation poor prognostic indicator
6. Return of brainstem reflexes early is a good prognostic sign

Evoked and Spontaneous Limb Movements

General Characteristics

1. Spontaneous limb movement – good prognostic sign
2. Evoked decerebration and decortication – poor prognostic indicator
3. Myoclonus:
 - a. Persistent and stimulus sensitive – poor prognostic sign
 - i. Loss of cortical inhibition
 - ii. Damage to the nucleus gigantocellularis of the brainstem
4. Seizure
 - a. First 24 hours not prognostic
 - b. Status epilepticus – poor prognostic sign at any time after an ictus

Clinical Manifestations

Late Prognostic Signs (More than 24 Hours)

Good

1. Awake and alert

2. Return of brainstem reflexes
3. Eye opening with ocular fixation reflexes
4. Noxious stimuli evoke withdrawal reflexes

Bad

1. Persistent depressed level of consciousness
2. Absent brainstem reflexes
3. Noxious stimulation evoke decortication or decerebration
4. Eyes open with:
 - a. Roving eye movements
 - b. Uninhibited doll's eye maneuver
 - c. Persistent vertical ocular deviation
5. Spontaneous and evoked myoclonus
6. Status epilepticus
7. Persistently dilated pupils

Neuroimaging

MRI

1. Watershed infarcts of cortical and deep territories
2. Cortical infarcts
3. Blurring of the gray white junction
4. Obliteration of the perimesencephalic cisterns with mid-brain compression
5. T₂ weighted signal abnormalities of laminar necrosis (areas III and V of the cerebral cortex)

EEG

1. Diffuse slowing in the delta and theta range
 - a. All survivors at some point
2. Periodic lateralizing epileptiform discharge
 - a. Isolated areas of cortex
3. Epileptiform activity
4. Alpha coma (bad prognostic sign)
 - a. 9–12 cycles/second
 - b. Transitory
 - c. Frontal central parietal rather than occipital distribution
 - d. Does not vary with external stimuli

Angiography, Doppler or SPECT

1. Brain Death: absence of intracranial circulation

fMRI

1. Brain Death: no activity of either the intrinsic or extrinsic network

Sepsis Following Successful Cardiopulmonary Resuscitation

General Characteristics

1. Early development of a systemic inflammatory response syndrome that includes increased levels of:
 - a. C-reactive protein (CRP)
 - b. Tumor necrosis factor alpha
 - c. Interleukin 6
 - d. Procalcitonin (PCT)

2. PCT (Procalcitonin):
 - a. Marker of bacterial infection
 - b. Predictor of sepsis (associated mortality)
 - c. May be the result of post-resuscitation disease
 - d. Levels may be modulated by hypothermia
 - e. 1 mg/ml threshold for bad outcome
3. Ischemia (reperfusion injury)
 - a. Occurs with the return of spontaneous circulation

Dilatative Arteriopathy

General Characteristics

1. Enlarged tortuous dilated arteries
2. Primary involvement of the intracranial vertebral and basilar arteries
 - a. Carotid and intracranial anterior circulation less frequently involved
3. Diminished blood flow of the penetrating branches of large arteries
 - a. Branch territory pontine infarcts
4. Transcranial Doppler studies:
 - a. Reduced mean blood flow velocity
 - b. Normal peak flow velocity
5. Reduced antegrade flow within the ectatic artery
6. Thrombus formation may occur in dilated arteries with obstruction of perforators and distal embolization

Clinical Features

1. Causes compression parenchyma: particularly of the medulla and pons as well as cranial nerves. The latter is associated with:
 - a. Tic douloureux (V)
 - b. Vertigo/tinnitus (VIII)
 - c. Torticollis (XI)
 - d. Hemifacial spasm (VII)
 - e. Facial palsy (VII)
 - f. Lower cranial neuropathies (dysarthria)
 - i. Less frequently compressed
2. Hydrocephalus:
 - a. Compression of the IIIrd ventricle
3. Ataxia and motor weakness:
 - a. Compression of the brainstem; middle cerebellar peduncle and pontine and pyramidal tract
4. Compression of medulla and pons
 - a. Severe hypertension from irritation of the vasomotor centers
 - b. Spastic gait and dysarthria
 - c. Vestibular deficits
 - d. Cerebellar ataxia

Associated Specific Diseases

1. Marfan's syndrome
2. Ehlers-Danlos syndrome

3. Children with AIDS
4. Fabry's disease
5. Children and adults with sickle cell disease

Associated General Risk factors

1. Older age
2. Male sex
3. Hypertension
 - a. Left ventricle hypertrophy
 - b. Dilated and pulsatile brachial arteries with prominent aortic notch pulsations
4. History of myocardial infarction
5. Increased diameter of the thoracic aorta

Mechanisms of Cerebrovascular Disease

1. Distortion of the orifices of arterial branches
2. Decreased blood flow of penetrating branches
 - a. Decreased blood flow velocities
 - b. Reduced antegrade flow
 - c. Increased contact factor-endothelial contact time including thrombus formation and emboli
3. Fusiform aneurysms

Pathology

1. May occur in children and adolescents (some evidence of familial tendency)
2. Deficiencies of the muscularis and internal elastic lamina
3. Irregular thickness of the media
4. Thickening of the media
 - a. Increased fibrinoid material and lipids
5. Gaps in the internal elastic lamina
6. Intimal thickening
7. Increase in the vaso vasorum
8. Fusiform aneurysms

Molecular Mechanisms Underlying Dilatative Arteriopathy

1. Penetrating arterial diseases and dilatative arteriopathy are:
 - a. Arterial wall rather than the intima and endothelium
2. Arterial media disease may be associated with up regulation of metalloproteinases
 - a. Increased metalloproteinases may increase the permeability of the BBB
 - b. Permeability of the BBB is a factor in leukoaraiosis

Small Vessel Disease Features of Dolichoectasia

1. Lacunar infarction
2. Leukoaraiosis
3. "État criblé"
 - a. Dilated Virchow-Robin spaces around penetrating arterioles

Intracranial Arterial Dolichoectasia

General Characteristics

1. Neurovascular compression syndromes

2. Triventricular hydrocephalus
3. Isolated IIIrd, Vth, and VIIIth, XIIth nerve palsy by compression from basilar of vertebral arteries
4. IIth nerve compression from dolichoectatic supraclinoid carotid arteries
5. Putative mechanism:
 - a. Deposition of glycosphingolipids in the lysosomes of the smooth muscle of arterial walls
 - b. Possible cause of ICH (loss of structural integrity of vessel walls)
 - i. Hypertension from concurrent vessel disease
 - ii. Both hemi and heterozygotes

Fibromuscular Dysplasia

General Characteristics

1. Probably multietiological; HLA association
2. May affect any cerebral somatic artery
3. Primarily affects medium-sized muscular arteries at specific sites:
 - a. Distal 2/3 of renal arteries
 - b. Distal extracranial vertebral artery (adjacent to C2 vertebrae)
 - c. Distal carotid with rare involvement of:
 - i. Cavernous carotid
 - ii. Arteries of Circle of Willis

Clinical Features

1. Most commonly affects Caucasian women in the 4th to 6th decades
2. Occurs in infants and children with involvement of:
 - a. Renal, severe hypertension
 - b. Splanchnic
 - c. Cervical-cranial vessels
3. Incidence of less than 1% of routine cerebral arteriograms
4. Associated with intracranial aneurysms and dissections
5. ICH from associated HCVD due to renal artery involvement (including dissection)
6. Spontaneous cervical and intracranial artery dissection
7. Male presentation described:
 - a. Abdominal pain
 - b. Systemic signs
 - c. Hypertension
8. Associated dissection of the coronary arteries occur
9. Subarachnoid hemorrhage presentation
10. Arterial dissection with appropriate territorial infarction
11. A relatively benign condition
 - a. Few recurrent cerebrovascular episodes

Neuropathology

1. Fragmentation of the arterial media with rings of fibrous and muscular hyperplasia cause:
 - a. Saccular dilatations of the artery
 - b. Arterial wall involvement:
 - i. Adventitial form:

1. Narrowing of the vascular lumen by fibrous tissue hypertrophy that surrounds the artery
- ii. Intimal form:
 1. An increase of the fibrous components of the intima
 - a. Concentric narrowing of the lumen
 - b. About 5% of patients
 - c. Children and adolescents
- iii. Medial form:
 1. Most common
 2. Constricting bands of fibrous dysplastic tissue and proliferating muscle cells in the media
 3. Alternating with areas of medial thinning (disruption of the elastic membrane)
 - a. Leads to luminal dilatation
 - b. "String of beads" arteriographic pattern
2. Aging
 - a. Parallel aortic elastic fibers fragment
 - b. Decrease of smooth muscle cells
3. Pregnancy
 - a. Elastic fiber fragmentation
 - b. Hypertrophy/hyperplasia of smooth muscle cells
4. Chromosome abnormalities
 - a. Marfan's syndrome
 - i. Defect of fibrillin-1; increased elastin
5. Gene abnormality
 - a. Fibrillin-1 defect (15q 21.1)
 - b. Deletion of TGF-B receptor
 - c. ALK 5 (activin receptor-like kinase 5)
6. Medial smooth muscle cell apoptosis
7. Metalloproteinase and elastin
8. Hemodynamic abnormality (increased aortic flow)
9. Intrinsic abnormalities of the aortic wall in congenital heart diseases

Neuroimaging

1. Bilateral ICA involvement is frequent
 - a. Pharyngeal component of the artery
 - i. Level of C2 and spares the bifurcation and intracranial carotid artery
 - ii. 20% of patients have concomitant involvement of the vertebral arteries
 - b. Rare: intracranial FMD
 - c. "String of beads" arterial lesions may be concurrent with tertiary constrictions and aneurysmal dilatation
 - d. Shelf-like segmental stenosis from fibrous septa and webs
 - e. Enlarged carotid bulbs

Aortic Medial Abnormalities [Gsell-Erdheim]

General Characteristics

1. Ascending aorta may dilate in congenital heart disease
2. Aortic dilatation is well recognized in:
 - a. Marfan syndrome
 - b. Turner syndrome
 - c. Bicuspid aortic valve
 - d. Coarctation of the aorta
3. Congenital heart disease and aortic medial abnormalities occur with:
 - a. Single ventricle
 - b. Persistent truncus arteriosus
 - c. Transposition of the great arteries
 - d. Hypoplastic left heart syndrome
 - e. Tetralogy of Fallot
4. The CHDs with aortic dilatation are associated with:
 - a. Decreased elasticity and stiffness of the aorta and cause
 - i. Increased afterload and ventricular hypertrophy

Mechanisms of Structure Alteration of the Ascending Aorta Media

1. Systemic hypertension
 - a. Abnormalities of medial elastin and collagen

Pathology

1. Cystic medial necrosis
2. Elastin fragmentation
3. Fibrosis
4. Media necrosis

Clinical Features

1. Aortic dissection
2. Coronary artery dissection
3. Carotid artery aneurysm
4. Giant aneurysm of the ascending aorta

Radiation Induced Arterial Disease

General Characteristics

1. Delayed radiation-related strokes most often reported following X-RT for:
 - a. Leukemia
 - b. Hodgkin's disease
 - c. Brain tremors
2. Risk of stroke
 - a. Leukemia survivors: about 6%
 - b. Brain tumor: 29%
 - c. Hodgkin's disease: 83/100,000 patients
 - d. Increased in a dose-dependent manner
3. Major pathology in vascular injury; dependent upon:
 - a. Dose of irradiation
 - b. Location of irradiated nervous tissue – those areas with more surrounding tissue receive less dose
 - c. Order of vessel vulnerability:
 - i. Capillaries and sinusoids (most sensitive)
 - ii. Arterioles and small vessels
 - iii. Medium-sized vessels
 - iv. Large arteries (least sensitive)
 - d. Typical lesions are not in the usual areas for atherosclerosis

- i. Often not a bifurcation
 - ii. Long arterial segments are involved
- 4. Cellular pathology
 - a. Denudation of the endothelial layer
 - b. Infiltration of foam cells and histiocytes and fibroblasts
 - c. Collagen formation in the subendothelium and intima
 - d. Myointimal proliferation and fibrosis
 - e. Calcification; adventitial fibrosis
 - f. Fragmentation of the internal and external elastic membranes; inflammatory changes
 - g. A proliferative small vessel proliferative endocarditis

Clinical Features

1. Acute radionecrosis presenting as a mass (MR spectroscopy demonstrates no lactic acid peak which distinguishes it from recurrent glioma)
2. Chronic dementing illness
 - a. All systems may be involved (Parkinsonism, ataxia, corticospinal deficits, subcortical apraxia and cognitive slowing)
3. Moyamoya disease of basal arteries
 - a. Children and young adults
 - b. Prevalent with NF1 and higher doses of X-RT
4. Focal brain infarcts and strokes
5. Spinal cord
 - a. Sulcal artery infarction with Brown-Sequel syndrome
 - b. Upper extremity parenthesis (C5–C6)
 - c. Spastic paraparesis
6. Long segment stenosis of extracranial arteries
 - a. Transient ischemia
 - b. Stroke
 - c. Intracranial vascular occlusive disease
7. Delayed symptoms
 - a. Months to years after X-RT
 - b. Mass lesions in the brain or spinal cord
 - c. Fibrinoid degeneration of blood vessels, coagulative necrosis and gliosis
8. Delayed dementia with focal signs
 - a. Brain atrophy and leukoencephalopathy
 - b. Diffuse loss of white matter
 - i. Some patients demonstrate enhancement of focal lesion

Stroke and Substance Abuse

Opiates

General Features

1. Heroin most widely abused opiate
 - a. Administration:
 - i. I.V. or subcutaneously
 - ii. Smoked or sniffed

Cerebrovascular Complications

1. Decreased perfusion of the medial prefrontal cortex; anterior cingulate cortex and precuneus

2. Increased arterial stiffness and contributes to vascular aging
3. I.V. use:
 - a. Septic embolization with *Staphylococcus Aureus* and candida that cause:
 - i. Mycotic aneurism (may have premonitory symptoms)
 - ii. Infectious vasculitis
 - b. Septic aneurysms are peripheral and may rupture with or without treatment
4. Hemorrhagic stroke:
 - a. Consequence of hepatitis (decreased clotting factors)
 - b. Heroin nephropathy (hypertension and uremia)
 - c. Meningitis
 - d. HIV/AIDS

Angiography

1. Some patients demonstrate large or small vessel arteritis
 - a. Possible autoimmune etiology (eosinophilia, hypergammaglobulinemia)
2. Stroke mechanisms in heroin abuse:
 - a. Vascular aging
 - b. Hypotension and hypoventilation (acute)
 - i. Bilateral GP infarction
 - c. Infective endocarditis with mycotic aneurysm
 - d. Embolization of adulterants:
 - i. Pentazocine and tripeleminamine
 - ii. Parenteral paregoric, meperidine and hydromorphone
 - e. Heroin myelopathy:
 - i. Some patients with ischemia of the anterior spinal arteries

Amphetamines

General Features

1. These agents include:
 - a. Dextroamphetamine
 - b. Methamphetamine
 - c. Methylphenidate
 - d. Ephedrine
 - e. Pseudoephedrine
 - f. Phenylpropanolamine (PPA)
2. Cause increased dopamine and serotonin nerve neurotransmission
3. Damage dopamine and serotonin nerve terminals; methamphetamine causes cardiomyopathy
4. Administration is oral, sniffed or smoked in a crystalline form (“ice”, crystal meth”)
5. Necrotizing periarteritis; spontaneous ICH (often in hypertensive areas; microinfarcts in small vessels and atherosclerosis is accelerated)
6. Autopsy of overdose patients reveal:
 - a. Petechial hemorrhage and cerebral edema
 - b. Dextroamphetamine predominated
 - c. Severe headache concomitant with drug use

- d. CT: SAH or ICH
- e. Some patients demonstrated bleeding/vasculitis
- 7. I.V. methamphetamine:
 - a. Necrotizing arteritis
 - b. Infarction or hemorrhage in the hemisphere, the cerebellum and brainstem
 - c. Involved vessels are smaller than those affected by PAN
- 8. PPA cerebrovascular involvement
 - a. Hemorrhagic stroke

MDMA

(N-methyl-1-(3,4-methylenedioxyphenyl)propan-2-amine or methylenedioxymethamphetamine: "Ecstasy")

- 1. Causes both ischemic and hemorrhagic stroke
- 2. I.V. use of crushed methylphenidate tablets: microembolization of talc
- 3. Increases the release and inhibits uptake of NE, serotonin, DA
- 4. Mechanisms of stroke similar to those of cocaine and amphetamine
- 5. Cardiac arrhythmias and embolism may be important

General Characteristics of Both Salts

- 1. Alternatives to cocaine and methylenedioxymethamphetamine
- 2. 3,4 methylenedioxymethcathinone (methylone)
- 3. 3,4-methylenedioxypyrovalerone (MDPV)
- 4. Synthetic cathinones
 - a. Target plasma membrane transporters for DA, NE and serotonin
 - i. Mephedrone and methylone act as non-selective transporter substrates
 - b. Stimulates non-exocytotic release of DA, DA and serotonin. Effects are analogous to amphetamines
 - c. MDPV only blocks dopamine and norepinephrine

Clinical Features

- 1. Neurological complications
 - a. Hallucinations
 - b. Delirium
 - c. Euphoria
 - d. Tachycardia
 - e. Hyperthermia
 - f. Delayed responses
 - g. Agitation/psychosis
 - h. Cardiomyopathy
 - i. Myoclonus/seizures
- 2. Cerebrovascular effects
 - a. Non-specifically reported
 - b. Cardiac dysfunction and hypertension are prominent

Cocaine

General Features

- 1. Blocks reuptake of monoamine neurotransmitters at synaptic nerve endings (binds to transporter proteins)

- 2. Intranasal preparation
 - a. Cocaine hydrochloride
 - b. Ischemic stroke; intracranial hemorrhage
- 3. Smoke-able form:
 - a. Alkaloid form "crack"
 - b. Can be utilized in large doses over a long duration (hours to days)
 - c. Ischemic and hemorrhagic stroke

Clinical Features

- 1. Cerebrovascular complications
 - a. TIA
 - b. Infarctions of cortical/subcortical territories that include the hemispheres; thalamus, brainstem, spinal cord and retina
 - c. Strokes in pregnant women and neonates
 - i. Vasospasm
 - ii. Premature separation of the placenta (cocaine taken prior to delivery)
 - d. Rare vasculitis
 - e. Delayed vasospastic ischemic infarction is common (hours to days)
 - f. Hemorrhagic stroke
 - i. Intracerebral and subarachnoid hemorrhage
 - ii. 20% of hemorrhages have underlying
 - 1. Vascular malformation
 - 2. Saccular aneurysm
 - a. Increase vasospasm after aneurysmal rupture
 - 3. Bleeding into embolic infarction or glioma
 - 4. Post-partum patients and their neonate
 - iii. Other cocaine induced stroke mechanisms:
 - 1. Myocardial infarction and cardiomyopathy with embolus
 - g. Multiple infarcts occur:
 - i. High incidence of hemorrhagic transformation
 - h. Aggregation and de-aggregation of platelets; effects on antithrombin III, protein C, NF- κ B (nuclear factor kappa-light-chain-enhancer of activated B-cells), activator protein-1
 - i. Platelet rich arterial thrombi
 - j. Activates the endothelium that promotes platelet vWF interaction
 - i. vWF-platelet strings
 - k. Vasoconstrictive metabolite can last for days to weeks

Phencyclidine

General Features

- 1. Phencyclidine (PCP: a dissociative anesthetics similar to ketamine
- 2. Effects NMDA (antagonist), nACh (antagonist) and dopamine (agonist) receptors
- 3. Possible PCP receptors on cerebral vessels
- 4. Stored in fat and therefore re-mobilization can occur with recurrent symptoms for days or months

Clinical Features

1. Cerebrovascular disease and PCP
 - a. Hypertension occurs following use or can be delayed
 - b. Hypertensive encephalopathy
 - c. Trans-monocular blindness
 - d. PCP related SAH
 - e. Hemorrhagic stroke

Lysergic Acid Diethylamide (LSD)*General Features*

1. LSD is an ergot that, in high doses, causes hypertension
2. Patent hallucinogen

Clinical Features

1. LSD and cerebrovascular disease
 - a. Ischemic vascular disease (patients less than 25 years of age); 2 patients with large artery involvement; delayed stroke occurs
 - b. Mechanism:
 - i. May effect serotonin receptors with consequent vasospasm
 - c. Angiography
 - i. Progressive narrowing and occlusion of ICA
 - ii. Generalized arterial bleeding

Marijuana*General Features*

1. Most widespread recreational drug in the USA
2. Cannabinoids have physiological role in:
 - a. Cerebral autoregulation
 - b. Vascular tone
 - c. Cardiac physiology

Clinical Features

1. Associations with stroke, myocardial infarction and lower limb arteritis
 - a. Myocardial infarction may occur with concomitant use
 - b. Extremity arterial disease occurred in younger male patients primarily in one extremity
2. Cerebral vascular disease
 - a. Ischemic stroke
 - b. Reversible vasoconstriction syndrome (described in 2 patients)
 - c. Stroke associated with anabolic steroid use

Ethanol*General Features*

1. Ethanol consumption and coronary artery disease fits a "J-shaped" curve (a small amount is protective and larger amounts are detrimental)
 - a. Cardioembolic risk often MI in heavy drinkers (>300 grams/week)
 - b. Thromboembolism in alcoholic cardiomyopathy

2. A J-shaped curve exists for ischemic stroke and ethanol consumption
 - a. Linear correlation of ICH
 - b. >60 grams/day increased stroke risk for ischemic and hemorrhagic stroke
3. Heavy ethanol consumption:
 - a. Increases carotid artery atherosclerosis
4. Putative mechanisms
 - a. Ethanol acutely and chronically increases blood pressure
 - b. Lowers LDL and increases HDL
 - c. Lowers fibrinogen activity
 - d. Increases factor VIII levels
 - e. Increases platelet reactivity to adenosine diphosphate
 - f. Decreases plasma fibrinogen levels
 - g. Increases prostacyclin
 - h. Stimulates endothelial release of endothelin
5. Alcohol withdrawal
 - a. Causes Hemoconcentration
 - b. Rebound platelet hyperaggregability

Tobacco*General Features*

1. Increases the risk for both ischemic and hemorrhagic stroke
2. Smokeless tobacco:
 - a. Increases ischemic stroke risk and acute coronary dysfunction
 - b. Accelerates atherothrombosis
 - c. Increases HCVD and metabolic syndrome
3. Mechanisms for smoking and cerebrovascular disease
 - a. Ischemic and hemorrhagic stroke is increased with concomitant oral contraceptive use
 - b. Increases atherosclerosis
 - c. Decreases blood oxygen carrying capacity (carbon monoxide from smoke has a higher affinity for hemoglobin than does oxygen)
 - d. Nicotine damages the vascular endothelium
 - e. Increased platelet reactivity
 - f. Decrease prostacyclin
 - g. Increases blood fibrinogen levels
 - h. Induced polycythemia increases blood viscosity
 - i. Paradoxical benefit effect on in-hospital mortality
 - j. May have benefit in blood pressure and flow in MCA
 - i. Changes in baroreflex sensitivity (lowers)

Hemorrhagic Vascular Disease**Epidemiology of Hemorrhagic Vascular Disease***Overview*

Hypertension is the major cause of intracranial hemorrhage. The age of the patient and underlying medical condition point to specific other etiologies of hemorrhagic vascular disease.

Spontaneous intracranial and subarachnoid hemorrhage cause approximately 10 to 15% of strokes. In patients less than 40 years of age, vascular malformations, aneurysms, cavernous angioma, illicit drugs and head trauma are the usual causes. In elderly patients, congophilic angiopathy accounts for approximately 10% of intracranial hemorrhages. Approximately 10% of patients treated with fibrinolytic agents after myocardial infarction bleed. Approximately 5 to 10% of patients on warfarin or heparin bleed at some point during their therapy. The rate of ICH on anticoagulation is approximately 0.3% per year. Evidence of prior vascular disease is common as patients with ICH have T₂ weighted hyperintensities in cerebral white matter, lacunes and old infarction 68% of the time. There is a correlation of spontaneous ICH with small chronic microhemorrhages, hemorrhages, and ischemic lesions in elderly patients. Hemorrhagic transformation occurs after tPa in approximately 6% of patients.

Hypertensive Hemorrhagic

General Characteristics

1. The most common cause of ICH
2. Blood pressure is generally 220–240 mm of Hg systolic and 110–120 mm of Hg diastolic
 - a. In several studies the peak systolic pressure is 160–190 mm Hg
 - b. The pressure may be confounded by the Kocher-Cushing reflex
 - i. Secondary hypertension due to pressure on the vasomotor neurons of the dorsolateral medulla and dorsal tegmental pons
3. Many patients present without a known prior history of hypertension
 - a. Examination often reveals
 - i. An enlarged aortic knob (uncoiled)
 - ii. Thickened and tortuous peripheral blood vessels (radial and brachial arteries)
 - iii. Hypertensive changes in the retinal arteries
 - iv. Loud A2 and a prominent S4 gallop
 - v. Sustained cardiac impulse

Risk Factors

1. Exposure to cold weather
 - a. Stimulation of the sympathetic vasoconstrictor response
2. Dental procedures
 - a. Irritation of the trigeminal nerve
3. Increased cerebral blood flow
 - a. Carotid endarterectomy (hyperperfusion syndrome)
 - b. Following surgical repair of congenital heart defects
 - c. Cardiac transplantation
 - d. Post-migraine

Differential Diagnosis of Hemorrhagic Vascular Disease

The major categories of hemorrhagic vascular disease are:

1. Hypertension

2. Aneurysm, arteriovenous malformation, venous malformation, cavernous hemangioma
3. Medical causes of platelet or clotting factor dysfunction
4. Hemorrhagic transformation of ischemic stroke
5. Anticoagulation
6. Drug abuse (methamphetamine, cocaine, PPA)
7. Thrombolytic agents
8. Congophilic angiopathy (CCA)
9. Cold exposure
10. Post-carotid endarterectomy syndrome
11. Severe migraine
12. Tumor
13. Surgery
14. Moyamoya disease
15. Trauma
16. Alcohol
17. Hemorrhagic transformation of ischemic stroke
18. Hemorrhagic transformation following tPa
19. Ischemia/reperfusion syndrome

Hypertensive Hemorrhage

Hypertensive hemorrhage occurs in very specific places the most common of which are:

1. Basal ganglia – 60% (caudate 10%; putamen 50%; GP1 40%)
2. Thalamus – 20%
3. Cerebellum – 15%
4. Pons – 5%
5. Lobar – 10%
6. Pontine – 5%
7. Medulla – rare <1%
8. Midbrain – rare <1%

If hemorrhages are not found in these locations, they are most likely caused by systemic illness, congenital vascular anomalies, anticoagulation or drugs.

Clinical Manifestations

Clinical Manifestations of Intraparenchymal Hemorrhage

The onset of hypertensive intraparenchymal hemorrhage is most often during wakefulness as a patient pursues the usual activities of daily living. Maneuvers that cause a sudden rise in blood pressure such as heavy lifting, coitus, prolonged vomiting, coughing or straining at stool have been noted to cause hemorrhage with increased frequency. Unusual causes of hemorrhage are related to specific circumstances. Approximately 30% of ICH are due to aneurysm, AVM, and cavernous angioma occur during sleep.

Most patients when first examined are alert (50%) with the remaining being lethargic (25%), stuporous or comatose (25%). The onset may be acute or is gradual over minutes to hours with the neurologic deficit steadily progressive. CT and MRI serial evaluations have demonstrated that expansion occurs in the first 6 hours in approximately 20% of patients while 15% expand during the next 6–12 hours and 6% between 6–24 hours. Expansion may be dramatic. In patients

who suffer hemorrhage from a bleeding diathesis expansion may occur insidiously over days.

Focal deficits and consciousness are preserved at the ictus. Headache and vomiting may be absent. In subarachnoid hemorrhage, headache is severe, reaches maximum intensity almost instantly and focal neurologic signs are minimal. Loss of consciousness in SAH is much more frequent at the ictus than that which occurs with intraparenchymal hemorrhage. Embolism produces the greatest neurologic deficit at onset, is accompanied by a higher percentage of seizures than ICH and a lesser degree of headache. Patients who suffer emboli, particularly to the stem of the left MCA appear stunned. Ischemic vascular disease is more frequent during sleep or the early morning and is accompanied frequently with deficits of a cortical nature such as aphasia or denial of contralateral space. Headache is common in ischemic disease with posterior circulation ischemia causing it more frequently than that from the anterior circulation. Rarely is it a predominant feature.

Headache from intraparenchymal lesions occurs frequently as the hematoma develops and stretches the overlying dura, displaces the venous sinuses and major blood vessels at the base of the brain or spills into the subarachnoid space. Early in the course of the hemorrhage, the stretched dura may project pain to the overlying skull and scalp but most often the headache is projected frontally. The anterior and middle fossa dura and the forehead are innervated by V1 (somatic visceral convergence) and thus lesions in these fossae project to somatic representations of V1. Displacement of the posterior 1/3 of the sagittal sinus may also cause frontal headache. The dura of the posterior fossa is innervated by the posterior roots of C1–C2 and cranial nerves IX and X. Hematomas in the posterior fossa usually project pain to the basiocciput, posterior cervical areas or the trapezius ridge. They may project to the brow, the somatic representation of C2. Displacement of the tentorium and irritation of its under surface (innervated by C1–C2, IX and X) may cause pain in the inner ear. The upper leaflet of the tentorium is innervated by V1. Many patients who have suffered an intraparenchymal bleed are too lethargic to describe their headache accurately. Headache is most common with lobar and cerebellar hematomas due to their close approximation to the dura and may be accompanied by signs of meningeal irritation. Headache increases with hematoma enlargement and is associated with vomiting and deterioration of the level of consciousness. Head tilt to the side of the hematoma, unilateral forced eye closure (ipsilateral to the side of the hematoma) and C2 headache are most suggestive of a cerebellar hemorrhage.

Severe neck stiffness, photophobia, sore eyes, Brudzinski and Kerning's signs suggest caudate hemorrhage with direct rupture into the ventricular system. Hyperthermia, rarely greater than 103° may be present. Thalamic and cerebellar hemorrhage may also be associated with early ventricular extension. Larger putaminal hemorrhages rarely rupture into the ventricular system at onset.

The focal deficits and topography of each type of hemorrhage will be described in detail. Specific neurological deficits suggest a characteristic hemorrhage:

1. A deeply comatose patient with head and eyes deviated to the side of the lesion, a flaccid hemiparesis and hemisensory defect with periodic breathing is characteristic of a deep pallidal hemorrhage
2. Inability to walk, dysarthria, nystagmus with quadriplegia suggests a cerebellar hemorrhage
3. A patient whose eyes are down and in with a greater sensory than motor deficit is sentinel for a thalamic bleed
4. An elderly patient with arm, face weakness who has suffered a seizure suggests a lobar congophilic hemorrhage

Vomiting and nausea may occur at the ictus of an intraparenchymal hemorrhage due to the sudden increase of ICP that is transmitted to the mechanosensitive emetic center of the floor of the IVth ventricle or distortion of the IVth ventricle itself. Vomiting stops as pressure is relieved by displacement of CSF into the spinal subarachnoid space, overbreathing that effects a decrease of pCO₂ and consequent reduction of cerebral blood flow as well as intracranial shifts of brain parenchyma. As the hematoma expands further, vomiting and nausea return due to exhaustion of compensatory mechanisms.

Persistent vomiting out of proportion to dizziness is suggestive of an ischemic lesion of the brainstem. Vomiting with change of head position is characteristic of a mass in the IVth ventricle. Inability to vomit in the face of a strong urge to do so is characteristic of an intrinsic medullary lesion. A smooth gradual deterioration of neurological function over minutes to hours with concomitant headache and vomiting is most consistent with supratentorial intraparenchymal hemorrhage. Headaches are most often seen with larger hemorrhages whereas deep parenchymal lesions may be asymptomatic. Approximately 30% of patients suffer headaches at the ictus, another 20% develop it during evolution of their neurologic deficits and up to 40% may have no headache. Many of the latter patients are lethargic or obtunded at the time of evaluation. Lobar and cerebellar hemorrhages have the highest incidence of headaches due to their proximity to the meninges. Patients with cerebellar hemorrhage vomit shortly after the ictus. Approximately 50% of patients with posterior circulation headaches vomit. Ischemia in this distribution causes vomiting in 1/3 of patients which tends to be more persistent and is not associated with obtundation and stupor. Patients with migraine have severe persistent vomiting accompanied by dizziness and vertigo but minimal focal deficits and no depression of consciousness. Bickerstaff's migraine (vasospasm of the vertebrobasilar arteries) may be associated with transient loss of consciousness and there have been reports of migraine patients who become comatose.

Seizures occur in approximately 15% of patients who suffer an intraparenchymal bleed. They are most common in

lobar hemorrhages which occur at the gray-white junction and excite the overlying cerebral cortex. Seizures are rare in putaminal hemorrhages. They suggest an underlying cavernous angioma, arteriovenous malformation or transformed embolic stroke. A 10 ml hemorrhage is minimal, 45 ml is severe and greater than 100 ml is usually fatal.

Topographical Syndromes

Caudate Hemorrhage

General Characteristics

1. Approximately 7% of ICH
2. Medial hemorrhages:
 - a. Blood dissects into the ipsilateral frontal horn
 - b. Dense hemorrhage is noted at the caudate head
 - c. Ventricular dilatation occurs ipsilaterally > contralaterally

Clinical Manifestations

1. Small hemorrhage: no prominent motor, sensory or visual loss
2. Symptoms: mimic intraventricular bleed or SAH: neck stiffness, severe headache, nausea and vomiting, decreased level of consciousness

Lateral Caudate Hemorrhage

General Characteristics

1. Larger than medial hemorrhage
2. Spreads laterally or posterolaterally into the putamen or anterior or posterior limb of the internal capsule

Clinical Manifestations

1. Headache, vomiting, decreased level of consciousness
2. Hemiparesis, hemisensory loss, ipsilateral conjugate deviation of the eyes with inability to look to the contralateral side (may be dolled across the midline in 12 to 24 hours); in general, minimal sensory loss
3. Less severe and transient signs if the hemorrhage is limited to the internal capsule
4. If blood spreads inferiorly; Horner's syndrome
 - a. Horner's syndrome (ipsilaterally)
5. Right caudate hemorrhage: neglect or mania
6. Left caudate hemorrhage: aphasia, confusional state, disorientation
7. Memory loss (if hemorrhage involves internal capsule and AV nucleus of the thalamus)

Differential Diagnosis

1. HCVD
2. Infarct with hemorrhagic transformation (lenticulostriate, recurrent artery of Heubner)
3. Arteriovenous malformation
4. Carotid aneurysm rupture
5. Moyamoya disease (with hemorrhage)
6. Ependymal vascular malformation

Striatocapsular Hemorrhage

Clinical Manifestations

1. Mild dysarthria and dysphagia
2. Contralateral hemiparesis
3. Contralateral hemisensory deficit
4. Lacunar type syndrome

Anterior Type

General Characteristics

1. 11%; Heubner's artery territory
2. Small caudate hematoma
3. Ruptures into lateral ventricle

Clinical Manifestations

1. Severe headache (similar to subarachnoid hemorrhage)
2. Contralateral hemiparesis – less than 50%
3. Acute confusion; abulia; (lasts approximately one week)
4. Dominant hemisphere: transcortical motor aphasia (transient)

Middle Type

General Characteristics

1. Medial lenticulostriate artery territory
2. <10%; moderate in size (<30 cc; spreads anterolaterally)
3. Primary involvement globus pallidus and medial putamen

Clinical Manifestations

1. Conjugate deviation of the eyes to the side of the lesion
2. Contralateral hemiparesis (mild to moderate)
3. Anomia; global aphasia (transient)

Posteromedial Type

General Characteristics

1. Anterior choroidal artery territory
2. 4% of striatocapsular hemorrhages
3. Small hematoma in posterior limb of internal capsule

Clinical Manifestations

1. Spreads rostrally; pressure on medial putamen or lateral thalamus

Posterolateral Type

General Characteristics

1. Posterior medial branches of the lateral lenticulostriate arteries territory
2. Approximately 33% of striatocapsular hemorrhage
3. Areas affected:
 - a. Posterior 50% of the putamen; moderate in size (35 cc); extend often to the anterior putamen
 - b. Posterior limb of the internal capsule (retrolenticular portion); rupture into anterior horn of the lateral ventricle

Clinical Manifestations

1. Impaired consciousness

2. Cheyne–Stokes or periorotic respiration
3. 2–3 mm reactive pupils
4. Severe flaccid contralateral hemiparesis
 - a. Arm, leg, face, equally involved
5. Dominant hemisphere
 - a. Anterior > posterior aphasia
6. Non-dominant hemisphere
 - a. Severe visuospatial neglect
7. Pure Sensory loss if the thalamus is involved

Lateral Type

General Characteristics

1. Lateral branches of the lateral lenticulostriate arteries
2. Approximately 20% of striatocapsular hemorrhage
3. Areas involved:
 - a. Elliptical hematoma between the putamen and insular cortex
 - b. Often ruptures into the lateral ventricle

Clinical Manifestations

1. Contralateral hemiparesis
2. Neglect for contralateral space (NDH)
3. Language dysfunction (DH)

Massive Hemorrhage

General Characteristics

1. Approximately 25% of lenticulo striato hemorrhage
2. Entire striatocapsular territory involved

Clinical Manifestations

1. Severe flaccid contralateral hemiparesis
 - a. Arm, face, leg equally involved
2. Lethargy to coma
3. Ipsilateral conjugate eye deviation
 - a. Wrong way eyes observed in a percentage of patients
4. Poor prognosis

Putaminal Hemorrhage

General Characteristics

1. Most common location for basal ganglia hemorrhage in hypertensive patients (40%)
2. Largest hemorrhages involve:
 - a. Medial and most anterior portion of the posterior putamen
 - b. Anterior 2/3 of the posterior limb of the internal capsule
 - c. Putative mechanism: rupture of Charcot–Bouchard aneurysms of the large lateral lenticulostriate arteries
 - d. Symptoms depend on the amount of blood extravastion

Clinical Manifestations

1. Abrupt onset of neurologic deficit while awake
2. Approximately 30% have headache at onset and 20% more develop it as the process evolves
3. Vital signs:

- a. Level of consciousness:
 - i. 50% alert at presentation; others obtunded to comatose
 - ii. Blood pressure elevated: 220–240 to 110–140 mmHg
 - iii. Pulse rate tends to be slow and full at 60–70/minute, a rapid thready pulse appears with herniation

4. Respiratory pattern

- a. Most often periodic respiration, inspiratory and expiratory build up and decline with irregular apneic periods. The longer the apneic periods the graver the prognosis
 - i. Rarely Cheyne–Stokes pattern

5. Pupils:

- a. At presentation are usually diencephalic at 2–3 mm and reactive to light, change with evolution of the hematoma and consequent herniation

6. Posture:

- a. Early at presentation:
 - i. Pronated arm with early cortical thumb (adducted) contralateral to the lesion; externally rotated leg contralaterally
 - ii. Right-sided lesion
 1. Patient angled in bed neglecting contralateral space (non-dominant hemisphere)

7. Mental status:

- a. Left-sided lesion (dominant hemisphere)
 - i. Fluent aphasia with intact repetition unless the arcuate fasciculus is disrupted by the lesion
- b. Non-dominant hemisphere
 - i. Visual neglect for left hemispheric space
 - ii. Motor impersistence
 - iii. Constructional dyspraxia

8. Cranial nerve examination:

- a. Contralateral VII paralysis
- b. Head deviated to the side of the lesion
- c. Eyes slightly below the midline if the midbrain oculomotor center for upgaze (riMLF) is compressed
 - i. Conjugate deviation of the eyes to the side of the lesion
 - ii. If the patient is alert pupils may be normal; as obtundation supervenes pupils are diencephalic at 2–3 mm

9. Motor examination:

- a. Flaccid contralateral hemiparesis
 - i. Internal capsule involvement with brain shock
 - ii. More anteriorly in the posterior limb faciobrachial paresis; leg less involved (topographically and bilaterally innervated)
 - iii. Rarely patients may have contralateral increased tone if the putamen is primarily involved
 - iv. Rarely; ipsilateral adventitious movement occur (descending pyramidal or extrapyramidal pathways are stimulated)

- v. Motor impersistence with right-sided lesions
- 10. Sensory examination:
 - a. Contralateral hemisensory deficit to all modalities
 - b. Neglect of left-sided space with right-sided lesions
- 11. Reflexes:
 - a. Depressed on the paretic side
 - b. Positive Babinski or intermediate toe on the paretic side; bilateral Babinski signs if there is severe pressure

Transtentorial Herniation (Massive Hemorrhage (100 cm³) of blood)

General Characteristics

1. Anatomy:
 - a. Compression and torque of the midbrain at the level of the tentorium
 - i. Obliterated ambient cisterns
 - ii. Trapped contralateral temporal horn
 - iii. Rupture of midline penetrating arteries of the pons, midbrain and thalamus (Duret's hemorrhage)
 - iv. Compression and infarction of the PCA under the ipsilateral tentorium
 - v. Lateral pineal shift of 10 mm
 - vi. Downward pineal shift of 7 mm
 - vii. Intraventricular extension of blood with herniation

Clinical Manifestations

1. Vital signs:
 - a. Stupor to coma
 - b. Blood pressure of 90–60 mm/Hg as herniation occurs
 - c. Central neurogenic hyperventilation (20–40 breaths/minute)
 - d. Thready pulse at 100–120 beats/minute
 - e. Temperature 103–105° Fahrenheit dependent on presence of intraventricular blood or posterior hypothalamic damage
2. Cranial nerve impairment:
 - a. Paralyzed horizontal gaze; eyes below the midline (5–10°)
 - b. Ipsilateral pupil smaller then dilates; may become oval ("tad pole") as IIIrd nerve is compressed under P-COM artery
3. Posture and reflexes:
 - a. Bilateral decerebrate posture
 - b. Bilateral Babinski response

Anterior Putaminal Hemorrhage

General Characteristics

Anatomy

1. Anterior putamen
2. Anterior limb of internal capsule

Clinical Manifestations

1. Mild hemiparesis
2. No sensory loss
3. Broca's aphasia; anterior extension

Posterior Putaminal Hemorrhage

General Characteristics

1. Anatomy
 - a. Involves posterior 1/3 of the internal capsule
 - b. Extreme posterior extension of the putamen

Clinical Manifestations

1. Hemisensory loss greater than hemiparesis
2. Inferior quadrantanopia or hemianopia with left dominant posterior putaminal hemorrhage
3. Wernicke's type aphasia:
 - a. If the hemorrhage extends into the isthmus of the temporal lobe
 - b. Undercuts or involves posterior speech areas. Inferior temporal gyrus thought to be involved in semantic aphasia. Dissection of blood into periventricular white matter
4. Non-dominant hemisphere demonstrates neglect, spatial and apractic deficits

Rare Presentations of Putaminal Hemorrhage

1. Pure motor hemiplegia
2. Hemichorea
3. Clumsy hand syndrome
4. Hemiballism
5. Sensorimotor stroke
6. Ataxic hemiparesis
7. Trauma

Asymptomatic Putaminal Hemorrhage

General Characteristics

1. 1.5% of stroke patients (hemorrhagic transformation)
2. 9.5% of putaminal hemorrhage
3. Minor hemorrhage (less than 20 ml)

Hemorrhagic Disease

Neuroimaging

1. Spot sign:
 - a. A bright spot on computed tomography and angiography source images
 - b. Predictive of hematoma growth
 - c. 50% of putaminal hemorrhages have a spot and tail sign (a linear density extending from the MCA toward the spot sign)
 - d. Hematoma volume, spot signs, and intra-hematoma striatic arteries predict acute deterioration

Globus Pallidus Hemorrhage

General Characteristics

1. Often spared from ischemic injury
2. Hemorrhagic and necrotic lesions occur:
 - a. Carbon monoxide
 - b. 3,4-methylene dioxymethamphetamine

- c. Cocaine
 - d. Opiates (5–10% of addicts)
 - e. Cyanide poisoning
 - 3. Medial lenticulostriate artery territory
 - 4. Hypertensive patient with Cushing reflex
 - 5. BP 220/120 – 240/120–130 mmHg
 - 6. Approximately 50% obtunded within minutes to hours after ictus. Progressive deterioration of level of consciousness
 - 7. Periodic or Cheyne's-Stokes respiration
 - 8. Pupils 2–3 mm poorly reactive to light
 - 9. Pulse rate of 50–60 beats/minute full at onset
 - 10. Eyes conjugately deviated below the horizontal 5–10°
 - 11. Head and eyes deviated to the side of the lesions
 - 12. Dense contralateral hemiparesis: arm, face, and leg relatively equally involved; flaccid tone (destruction of medial components of posterior limb of the internal capsule)
 - 13. Dense hemisensory deficit to all modalities (disruption of medial portion of the posterior limb of the internal capsule); thalamic projections
 - 14. Depressed reflexes contralaterally; may be increased ipsilaterally
 - 15. Contra or bilateral Babinski's signs
 - 16. Progression to decerebrate rigidity and central herniation
- 3. Vertical skew deviation:
 - a. Eyes are down on the side of the lesion
 - b. Abnormal displacement is constant in all fields of gaze
 - 4. Disconjugate gaze:
 - a. Limited abduction (pseudo VI nerve palsy)
 - b. Visual fixation from the adducted eye
 - c. Increased convergence vectors neutralize abduction (visual fibers descend into the anterior medial thalamus) and cause eyes to look down and in
 - 5. Pupils:
 - a. 2–3 mm poorly responsive to light
 - b. Afferent arc disrupted
 - 6. Hemorrhage may extend into:
 - a. Diencephalic mesencephalic junction
 - b. Quadrigeminal plate
 - 7. Wrong way eyes

Thalamic Sensory Loss

- 1. All primary modalities affected including vibration:
 - a. Rarely also occurs with a lesion of the dorsal column nuclei
 - b. May split the frontal bone of the forehead
- 2. Patient aware of a line that bisects the body:
 - a. Bilateral sensory loss around the umbilicus
 - b. 20% of patients describe the quality as numb or heavy; 80% describe active paresthesias, formication or burning (VPL)
 - c. May have bilateral intraoral numbness or sensory loss (VPM)
 - d. Tips of all fingers may be numb (VPI as fibers destined for VPL are separated here)
 - e. After 6 weeks to 3 months Déjérine-Roussy syndrome may appear:
 - i. Decreased primary modality sensation in the involved area
 - ii. Static and dynamic mechano-allodynia of the involved area
 - iii. Thermal hyperalgesia particularly to cold in some component of the area of sensory loss
 - iv. Hyperpathia in some component of the area of sensory loss:
 - 1. Pain threshold increased
 - 2. Once threshold is exceeded pain reaches maximum intensity too rapidly
 - 3. Pain is overwhelmingly severe
 - 4. Poorly localized with a deep visceral quality
 - 5. Not stimulus bound (continues after the stimulus is withdrawn)
 - 6. Occurs spontaneously

Territorial Thalamic Hemorrhage

General Characteristics

- 1. 4 major categories dependent on involved vascular territories
 - a. Thalamogeniculate artery (P1) territory
 - b. Thalamoperforate or thalamic subthalamic perforate artery (P1) territory
 - c. Tuberothalamic (polar arteries)
 - i. Originate from the P-COM
 - d. Lateral posterior choroidal artery (P3)
- 2. Most hemorrhages are posterior to descending pyramidal tracts
 - a. Sensory loss greater than motor

Clinical Manifestations

- 1. Ocular manifestations
- 2. Thalamic sensory loss
- 3. Thalamic aphasia
- 4. Behavioral or cognitive deficits
- 5. Thalamic motor abnormalities

Ocular Clinical Manifestations

- 1. Paralysis of upgaze pressure at the level of the superior colliculus, oculomotor center for upgaze the riMLF (rostral interstitial nucleus of the medial longitudinal fasciculus)
- 2. Eyes “down” and “in” in primary gaze (as if looking at the tip of the nose)

Thalamic Aphasia

- 1. Nuclear involvement
 - a. Anterior ventral nucleus
 - b. Pulvinar nucleus
 - c. Dorsomedial nucleus

Clinical Characteristics

1. Normal conversation early
2. Fluent aphasia
3. Jargon intrusions
4. Relatively good comprehension
5. Repeat or duplicate words or syllables at the ends of words in spoken and written language
6. Paraphasic errors
7. Anomia
8. Perseveration

Behavioral and Cognitive Dysfunction

1. Anterior ventral nuclear lesion
 - a. Abulia
 - b. Waxing and waning levels of consciousness throughout the day
2. Dorsomedial nuclear lesion
 - a. Amnesic syndrome
 - b. Anosognosia
 - c. Visual spatial dysfunction

Thalamic Motor Dysfunction

1. Thalamic drift: prominent metacarpal pharyngeal flexion with the thumb adducted into the palm; downward
2. Ataxia of stance (area X involved)
3. Mild limb ataxia (disruption of frontal cortical – thalamic distributed network); Bruns' ataxia variant
4. Contralateral choreatic or dystonic movements
5. Contralateral severely abnormal posture (patient lying on an arm behind his back)

*Topographic Hemorrhages of the Thalamus**Posterolateral (Thalamogeniculate Artery Territory)**Clinical Manifestations*

1. Largest and most common thalamic hemorrhage
2. Thalamic sensory and motor involvement
3. Internal capsule may be compressed with consequent sensorimotor deficits
4. Leg sensation and eye movements transiently and minimally involved

*Anterior or Anterior Lateral Hemorrhage**Clinical Manifestations*

1. Tuberothalamic (polar artery) territory
2. Apathy
3. Abulia
4. Hypersomnolence
5. Waxing and waning level of consciousness
6. Thalamic aphasia

*Posteromedial (Thalamoperforate or Thalamic Subthalamic-Thalamoperforate Arteries)**Clinical Manifestations*

1. Thalamic eye signs:

- a. Pupillary involvement
 - b. Vertical gaze dysfunction
2. Impaired consciousness
 3. Ruptures into the IIIrd ventricle
 4. Compresses the diencephalic mesencephalic junction
 5. Early hydrocephalus

*Posterior Dorsal Lesions**Clinical Manifestations*

1. Posterior choroidal artery territory
2. Pulvinar involved
3. Aphasia
4. Minimal transient sensorimotor involvement (overlapping blood supply to posterior limb of the internal capsule)
5. Rare: neglect, apraxia, amnesia

Sub-Cortical Lobar Hemorrhage*General Characteristics*

1. 10% of ICH; higher frequency in patients <45 years
2. Develop beneath the gray white junction
3. After absorption of blood products there is a "slit like scar"
4. Expand linearly along white matter pathways
5. Undercuts the overlying cerebral cortex
 - a. Epileptogenic
 - b. 15–30% seizures occur at onset
6. Parietal and occipital lobes more frequently affected than frontal lobes

Clinical Manifestations

1. Sudden onset during activity
2. Headache
3. Vomiting in 30–40% during the first hour
4. Seizures 15–30% at onset, focal and status epilepticus (frontal lobe most common)
5. 5–20% present in coma

Differential Diagnosis of Lobar Hemorrhage

1. HCVD (patients <45 years)
2. Cerebral amyloid angiopathy (>65 years)
3. Arteriovenous malformation (<30 years)
4. Cavernous angioma
5. Coagulopathy
6. Illicit drug use
7. Trauma
8. Aneurysm

Frontal Hematoma*Clinical Manifestations*

1. Headache – 80%
2. Vomiting – 80%
3. Seizure – 25–30%
4. Impaired consciousness (lethargy to obtundation) – 50%
5. Gaze preference 30–40%

*Topographic Diagnosis of Frontal Hematoma***Dorsal Anterior***Clinical Manifestations*

1. Cognitive behavioral features:
 - a. Abulia
 - b. Initiate nothing
 - c. If stimulated:
 - i. Short terse answers
 - ii. Slow processing of information
2. Frontal eye field involvement (area 8, 10)
 - a. Eyes conjugately deviated to the side of the lesion; may be dolled across the midline after 12–24 hours from the ictus
3. Dorsolateral prefrontal cortex involvement (DLPC)
 - a. Left-sided executive frontal lobe dysfunction
 - i. Poor memory retrieval
 - b. Right side (non-dominant)
 - i. Disinhibition
 - ii. Poor judgment
 - iii. Witzelsucht (inappropriate jocularity)
 - iv. Bilateral lesions, bowel and bladder incontinence (second frontal gyrus)
4. Area 4 involvement
 - a. Brachiocephalic hemiparesis
 - b. Head and eye deviation to the side of the lesion (if extends to area 8 and 10)
 - c. Lesions above the frontal horn of the lateral ventricle
 - i. Frontal headache
 - ii. Contralateral predominant leg weakness

Inferior Frontal Hematoma*Clinical Manifestations*

1. Below frontal horns of lateral ventricle
2. Impaired consciousness
3. Contralateral brachiocephalic hemiparesis and hemisensory loss
4. Rare presentation:
 - a. No motor or sensory loss
 - b. Abulia

Orbital Frontal Hematoma*Clinical Manifestations*

1. Impaired consciousness
2. Agitated delirium
3. Most often etiology is head trauma:
 - a. Windshield injury in MVA
 - b. Falls (associated basilar skull fracture)
4. Semantic language dysfunction
5. Autonomic dysregulation:
 - a. Cardiac arrhythmia (area 11,12)
 - b. Hypertension

Paracentral Hematoma*Clinical Manifestations*

1. Primary involvement of Brodmann's area 4, 3, 1 and 2

2. Contralateral brachiocephalic motor and sensory deficits
3. Anterior (area 44) aphasia:
 - a. Transcortical motor
 - b. Decreased ability to write out of proportion to weakness (Exner's area 45)
4. Focal and generalized seizures
5. Lesion above the frontal horn:
 - a. Headache (frontal and primarily ipsilateral)
 - b. Contralateral leg weakness

Differential Diagnosis of Frontal Hematoma

1. HCVD – 20%
2. AVM – 25–30%
3. Cavernous angioma – 25–30%
4. Aneurysm – 25–30%
5. Anticoagulation – 10%
6. Congophilic angiopathy – 5–10%
7. Trauma – 10%
8. Illicit drug use – 10%

Parietal Hematoma*General Characteristics*

1. Unilateral headache
 - a. Temporoparietal early; then frontal extension
2. Seizures (20–30% at onset)
3. Contralateral cortical sensory loss
4. Contralateral parietal motor dysfunction (loathness to move extremity)
5. Neglect of the contralateral visual field

*Topographic Parietal Hemorrhage***Anterolateral Parietal Hemorrhage***Clinical Manifestations*

1. Parietal movement disorder
 - a. Updrift of the affected hand with “piano playing” fingers
 - b. Loathness to move
 - c. Sensory ataxia during all components of movement
 - d. Abnormal arm position at rest
 - e. Imprecise fine movement
2. Non-congruent inferior quadrantanopsia in 50% of patients (lesion must extend greater than a depth of 1 cm)
3. Posterior aphasia (dominant hemisphere)
4. Neglect of contralateral space (non-dominant hemisphere)

Anterior Medial Parietal Hemorrhage*Clinical Manifestations*

1. Similar clinical syndrome to lateral hemorrhage
2. Depressed consciousness
3. May extend into the thalamus

Large Posterior Parietal Hematoma*Clinical Manifestations*

1. Seizure at onset

- a. Aura of contralateral spatial tilt
- 2. General deficits:
 - a. Posture copy
 - b. Two point discrimination
 - c. Graphesthesia
 - d. Stereognosis
 - e. Localization of a body part or limb in space
 - f. Extinction of double simultaneous stimulus (contralateral to the lesion)
 - g. Alloesthesia
 - h. Point localization

Non-Dominant Parietal Hemisphere Hematoma

Clinical Manifestations

- 1. Constructional apraxia
- 2. Dressing apraxia
- 3. Posterior type of alien hand (NDH > DH)
- 4. Contralateral spatial neglect
- 5. Anosognosia
- 6. Asomatognosia
- 7. Geographical confusion (NDH > DH)
- 8. Depression of optokinetic nystagmus (eyes deviate to side of the lesion)
- 9. Geometric and colored patterns that moves in contralateral visual field (NDH = DH)

Dominant Left Parietal Lobe Hemorrhage

Clinical Manifestations

- 1. Transcortical sensory aphasia
- 2. von Gerstmann's syndrome components
 - a. Right left confusion
 - b. Finger agnosia
 - c. Acalculia
 - d. Dysgraphia
 - e. Failure to cross the midline
- 3. Dysgraphia and dyslexia (Brodmann's area 37,40,41)
- 4. Alexia without agraphia (Brodmann's area 39,40)
- 5. Bilateral failure to localize body parts
- 6. Poor visual manual dexterity (Brodmann's 5,7 projects to area 4)
- 7. Parietal motor dysfunction
- 8. Bilateral parietal hemorrhage
 - a. Parietal avoidance behavior

Left Inferior Parietal Hematoma

Clinical Manifestations

- 1. Deficits of reading, writing and calculation
- 2. Nominal aphasia (supramarginal gyrus)

Right Inferior Parietal Hematoma

Clinical Manifestations

- 1. Constructional dyspraxia
- 2. Poor visual spatial relationships
- 3. Inability to draw or copy

Temporal Hematoma

Clinical Manifestations

- 1. Agitation and/or delirium (R > L)
- 2. Wernicke's type aphasia (DH)
- 3. Herniation with slight or without hemiparesis
- 4. Insidious decline of consciousness followed by IIIrd nerve paralysis
- 5. Headache:
 - a. Pre-auricular
 - b. Periorbital
- 6. 20% of temporal lobe hematomas have seizures
- 7. Visual field superior quadrantanopsia

Left Temporal Lobe Hematoma

Clinical Manifestations

- 1. Fluent aphasia
- 2. Anomia, paraphasic errors, poor comprehension

Right (Non-Dominant) Temporal Hematoma

Clinical Manifestations

- 1. Confusion without focal signs

Posterior Left Hematoma

Clinical Manifestations

- 1. Wernicke's aphasia
- 2. Right homonymous quadrantanopsia
- 3. Minimal hemiparesis or hemisensory deficit

Inferior Basal Temporal Hematoma

Clinical Manifestations

- 1. Blood in the basal cisterns or cortical sulci suggests AVM or aneurysm

Medial Extension of Temporal Lobe Hematoma

Clinical Manifestations

- 1. Basal ganglia internal capsule compression or destruction
- 2. Contralateral hemiplegia and hemisensory deficit
- 3. Wernicke's or transcortical sensory aphasia
- 4. Horizontal gaze palsy contralaterally
- 5. Right temporal lobe hematoma with extension to the parietal lobe
 - a. Left-sided spatial hemi inattention and neglect
- 6. Partial IIIrd nerve paralysis
 - a. Poor pupillary light response
 - b. Partial IIIrd nerve paralysis (uncal entrapment of the nerve; compression under the posterior communicating artery)

Occipital Lobe Hematoma

Clinical Manifestations

- 1. Headache in or around the ipsilateral eye
- 2. If visual fields' deficit is present:
 - i. Patient is aware of visual loss but may ascribe it only to the contralateral temporal field (may miss ipsilateral nasal cut)

3. Visual neglect of contralateral field if the hematoma extends into the parietal lobe
4. Rare weakness

Medial Occipital Hemorrhage

Clinical Manifestations

1. Headache (C2 distribution or radiates to the ipsilateral eye)
2. Congruent homonymous hemianopia if above and below the calcarine fissure
 - a. Dense quadrantanopia
 - b. Respects the midline
3. Visual field variants depend on topography
 - a. Checkerboard deficit (lesions above and below calcarine sulcus) or opposite sides
 - b. Superior or inferior quadrantanopsia
 - c. Posterior lesions (sparing the temporal crescent)
 - d. Occipital pole lesions (loss of macular vision)
4. No depression of consciousness
5. No memory loss
6. No weakness

Lateral Occipital Hemorrhage

Clinical Manifestations

1. Headache at onset (similar to medial occipital lobe radiation)
2. No visual field deficit
3. No sensorimotor or behavioral deficit
4. If extension is into the parietal lobe or medially:
 - a. Depressed level of consciousness
 - b. Contralateral neglect
 - c. Agitation
 - d. Congruent contralateral homonymous hemianopia

Neuroimaging

1. Susceptibility weighted imaging:
 - a. A 3D gradient echo MRI sequence
 - b. Measures phase and magnetic data for post-processing
 - c. Detects blood, iron, calcium and deoxygenated hemoglobin content in the brain parenchyma
 - d. Scan time is 5–10 minutes, 2 gradient-echo 2 minutes
 - e. Extremely valuable technique for microbleeds in CAA and hypertensive hemorrhages; the former are cortical and the latter are in the basal ganglia
2. Intraoperative computed tomography is now utilized in lobar hemorrhage surgery:
 - a. Able to access real time in 3D information on residual hematoma
 - b. Evaluate unexpected bleeding
3. The sign score correlates with ICH expansion
4. Good functional outcome:
 - a. Hematoma volume of less than 30 ml
 - b. Significant independent neurological predictions in-hospital survival:
 - i. BG/IC bleed
 - ii. Less than 30 ml of blood
 - iii. No midline shift
 - iv. No intraventricular extension

Primary Intraventricular Hemorrhage

Differential Diagnosis

1. Subependymal vascular malformation
2. Cavernous angioma
3. Dissection of caudate hematoma
4. Angioma of the choroid plexus (children)
5. Vertebral artery aneurysm (IVth ventricle)
6. Moyamoya
7. Lenticulostriate aneurysm (blood in IVth ventricle)
8. Cocaine
9. IVth ventricular ependymoma
10. Leukemia/lymphoma
11. Intraventricular cavernoma

Clinical Manifestations

1. Similar to subarachnoid hemorrhage
 - a. Severe headache
 - b. Meningeal signs
 - c. Stiff neck
 - d. Early vomiting
 - e. Lethargy
 - f. Bilateral hyperreflexia
 - g. Positive Babinski sign
 - h. Hyperthermia
 - i. Brainstem compression
 - j. Seizure

Deleterious Effects of Intraventricular Hemorrhage

1. Direct mass effect
2. Impairment of Pacchionian granulations
3. Dysfunction of CSF circulation
4. Acute obstructive hydrocephalus
5. Delayed intraventricular hemorrhage
 - a. Associated with worse outcomes
 - b. Associated with atrial fibrillation
 - c. Higher rate of warfarin use
 - d. More likely to develop hematoma expansion
 - e. Hemorrhage in the lentiform nuclei more likely to evolve into IVH rather than thalamic or caudate lesions
 - f. Usually occur within the first 72 hours in the hospital
6. Site of bleeding:
 - a. Vasculature of subependymal region
 - b. Choroid plexus

Infratentorial Intraparenchymal Hemorrhage

Cerebellar Hemorrhage

General Characteristics

1. 10% of intracranial hemorrhages
2. Anatomy involves:
 - a. The area of the dentate nucleus
 - b. At the level of the anastomosis of distal PICA and SCA
 - c. Long perforating branches of the SCA may be involved
 - d. Rarely:
 - i. Vermis hemorrhage (5%):

1. Medial branches of PICA and the SCA
- ii. Hemorrhage extension
 1. Ipsilateral hemisphere
 2. Opposite hemisphere or vermis
 3. Rarely to the brainstem
 4. Cerebellar peduncles with rupture into IVth ventricle

Clinical Manifestations

Early Signs and Symptoms

1. Inability to walk, rarely to sit or stand (pressure on descending pontine and middle cerebellar peduncle fibers)
2. Falling to the side of the lesion
3. Vomiting
4. Headache (occipital, neck, C2 radiation)
5. Dysarthria
6. Rotary nystagmus (greater to the side of the lesion, occasionally gaze paretic to the opposite side); floccular nodular lobe and PPRF involvement (pressure)
7. Rare loss of consciousness at the ictus

Evolving Neurologic Signs

1. Vth nerve palsy (side of the lesion)
 - a. Ipsilateral forced eye closure (to prevent diplopia)
 - b. Head tilt (C2 root irritation) to the ipsilateral side
2. Smaller ipsilateral pupil
3. Failure to check greater than dysmetria or terminal 1/3 ataxic arm movement
4. Severe gait ataxia
5. Quadripareisis without quadriplegia
6. Increased lower extremity reflexes without Babinski's signs

Large Hemorrhage (Greater than 3 cm)

Clinical Manifestations

Early Brainstem Compression

1. All signs and symptoms noted that are with smaller lesions but telescoped in time
2. Stupor to coma
3. Lateral gaze palsy (eyes deviated to side of the lesion) pressure on the para pontine reticular formation paralyzes contralateral conjugate gaze
4. Quadripareisis (basilar strokes there is severe quadriplegia)
5. Bilateral Babinski's signs
6. Bilateral pontine pupils (<0.5 mm; reactive to light)
7. Central neurogenic hyperventilation (CNH)

Terminal Signs and Symptoms

1. Caudal cerebellum involved
 - a. Medullary cardiovascular and respiratory centers involved
 - i. Respiratory arrest
 - ii. Vasomotor collapse
 - iii. Decerebration
 - iv. Coma

Neuroimaging

MRI

1. Obliteration of the cerebellopontine angle cisterns
2. Displacement of the IVth ventricle
3. Hydrocephalus
4. Rarely upward herniation with vermian compression of the collicular plate
 - a. Gaze palsy > pupillary defects
5. Hydrocephalus of lateral and third ventricles

Small Hemorrhages with Survival

Clinical Manifestations

1. Mild gait ataxia
2. Rotary nystagmus (to the side of the lesions)
3. Signs and symptoms of hydrocephalus
 - a. Dementia
 - b. Abulia
 - c. Gait ignition failure in addition to ataxia (parapontine nucleus compressed)
 - d. Hyperreflexia legs > arms

Lateral Cerebellar Hematoma

Clinical Manifestations

1. Cranial nerve involvement:
 - a. V, VI, VII and VIII
 - b. Concomitant ataxia (ipsilaterally)

Cerebellar Vermian Hemorrhage

Clinical Manifestations

1. Medial PICA and SCA vessels rupture
2. Rare
3. Severe headache
4. Vomiting
5. Quadripareisis
6. Coma

Differential Diagnosis

Differential Diagnosis of Cerebellar Hemorrhage vs Basilar Artery Occlusion

Basilar Artery Occlusion

1. Sudden onset (both)
2. Sentinal hemiparesis
3. Herald hemiplegia
4. Quadriplegia
5. "Ocular bobbing"
6. Horizontal gaze paralysis
7. No cerebellar signs
8. Collapse
9. Central Neurologic Hyperventilation – Early
10. Pupil changes (less than 0.5 mm) – Early
11. Pin-point pupils
12. Vth nerve palsy – Late
13. Coma – Early
14. CNH – Early

Cerebellar Hemorrhage

1. Sudden onset (both)
2. Quadriparesis (Cerebellar)
3. Rotary or horizontal nystagmus (Cerebellar)
4. Conjugate deviation to the ipsilateral side
5. Failure to check (greater than dysmetria) – Early
6. Severe gait ataxia
7. CNH – Late
8. 1 mm pupils ipsilateral greater than contralateral side
9. Coma – Late
10. Forced ipsilateral eye closure
11. VIth nerve palsy – Late

Differential Diagnosis of Cerebellar Hemorrhage

1. HCVD (PICA/SCA vessels; dentate nucleus)
2. AV malformation
3. Hemangioblastoma (lateral lobes)
4. Cavernous angioma (may be multiple)
5. Associated with Von Hippel-Lindau (retinal and spinal angiomas)
6. Metastasis
7. Anticoagulation (INR > 5 on coumadin)
8. Ischemic transformation of infarct (PICA;AICA;SCA)
9. Trauma
10. Venous malformation (usually don't bleed)
11. Coagulopathy
12. Spinal surgery

*Primary Pontine Hemorrhage**General Characteristics*

1. Location:
 - a. Midventral pons (at the level of Vth nerve or junction of basis pontis and tegmentum)
 - b. Oval shape: destroys the center of the ventral tegmentum and basis pontis
 - c. Dissects:
 - i. Rostrally to the midbrain
 - ii. Rarely to the medulla
 - iii. Commonly into the IVth ventricle
 - iv. Rarely ruptures through the pial surface with spread to the clivus
2. Caused by rupture of paramedian basilar penetrating artery

Clinical Manifestations

1. Decreased level of consciousness or coma early in the course
2. Hypertension early evolves to vascular collapse during evolution (pressure on vasomotor center of lateral medulla, lateral pontine and pons)
3. Central neurogenic tegmentum hyperventilation early (20–40 breaths/min to apneustic gasps prior to death)
4. Early hemiparesis
5. Quadriplegia with increased tone of all extremities during evolution

6. Headache (basiocciput) and vomiting (occasional); sudden onset
7. Gradual asymmetric onset (occasional)
8. Asymmetric weakness of face and extremities
9. Abnormal movements:
 - a. Shaking tremors (partial decerebration)
 - b. Shivering and fasciculation (chest wall)
 - c. Dystonic posture versus decerebration
10. Weakness or paralysis of the face, pharynx, palate and tongue
11. Ocular manifestations:
 - a. Pinpoint pupils < 0.5 mm that are reactive to light (destruction of descending sympathetics vs activation of parasympathetics)
 - b. Anisocoria
 - c. Skew deviation (greater part of hemorrhage to the side of down eye)
 - d. Bilateral paralysis of horizontal gaze
 - i. Destruction of the parapontine reticular forma (center for horizontal gaze)
 - e. Ocular bobbing (eyes driven down and float up; vestibular tonic drive of upgaze mechanism)
 - i. May be unilateral
 - f. Up-bobbing (may be unilateral)
 - g. Ocular dipping (rapid down and upward movements), may be unilateral
 - h. 1 and one half syndrome (ipsilateral destruction of the parapontine reticular forma with concomitant destruction of the posterior crossing fibers of the MLF; patient can only abduct the ipsilateral eye)
 - i. Pontine exotropia (lateral and down deviation of the contralateral eye), the only voluntary eye movement is contralateral abduction
 - j. Posterior MLF syndrome (convergence is preserved)
 - k. Paralysis of upgaze if there is midbrain extension and destruction of the riMLF

Rarer Symptoms and Signs

1. Prior to coma:
 - a. Bilateral deafness (trapezoid body)
 - b. Severe dizziness and vertigo
 - c. Gustatory abnormalities (dysgeusia)
 - d. Preservation of reflex horizontal gaze
 - e. Locked in syndrome (destruction of ventral pons)
 - f. Hallucinations (between 3–50 days following the ictus)
 - g. Hyperhidrosis (contralateral)
 - h. Neurogenic bladder (destruction of the pontine micturition center)
 - i. Hypo- or hyperthermia (> 105° Fahrenheit); 104° Fahrenheit often is sepsis

Prognosis

1. Most often death in 24–48 hours, rarely a patient survives 7–10 days

Unilateral Basilar or Tegmental Basilar Hemorrhage*General Characteristics of Paramedian Hemorrhage*

1. Exclusively or predominantly on one side of the pons
2. Basotegmental hemorrhage is usually larger than those confined to one side of the pons

Clinical Manifestations

1. Small lateral basal hematomas
 - a. Present as:
 - i. Pure motor hemiparesis
 - ii. Ataxic hemiparesis
 - iii. Clumsy hand dysarthria syndrome
 - b. Dissection of lateral basal lesions into the tegmentum
 - i. Cranial nerve V, VI, VII deficits
 - ii. Contralateral hemiparesis

Differential Diagnostic Points Separating Hemorrhage Versus Lacunar Strokes

1. Occipital headache (hemorrhage)
2. Nausea or vomiting (hemorrhage)
3. No alteration of consciousness with lacunar stroke

Paramedian Tegmental Hemorrhage

1. Position sense and higher sensory modality loss in the contralateral arm, face and leg
2. Ipsilateral one-and-a-half syndrome ($1\frac{1}{2}$ syndrome)
3. Motor dysfunction of the contralateral extremities:
 - a. Ataxia
 - b. Decerebration
 - c. Dystonia

Lateral Pontine Tegmental Hemorrhage

1. Rupture of small penetrating vessels from long circumferential arteries
2. Pupillary defects:
 - a. Anisocoria (smaller ipsilateral pupil, normal reactivity)
3. Ocular motility defects:
 - a. Paralysis of ipsilateral conjugate gaze
 - b. One-and-a-half syndrome (if posterior MLF affected)
 - c. Intranuclear ophthalmoplegia (posterior type)
 - d. Ipsilateral VIth nerve deficit
 - e. Pontine exotropia
 - f. Ocular bobbing, dipping
4. Cranial nerve deficits:
 - a. V, VI, VII
5. Moderate hemiparesis
 - a. Bilateral weakness may occur at ictus; ipsilateral deficit clears
 - b. Limb and truncal ataxia, ipsilateral > contralateral, may be bilateral

Clinical Differential Points of Lateral vs Paramedian Lesion

1. Quadriparesis or quadriplegia (paramedian)
2. Contralateral hemisensory deficit: (lateral)

- a. Lemniscal modalities and spinothalamic deficits contralaterally
3. Rare findings:
 - a. Decreased hearing (trapezoid body); paramedian lesion
 - b. Dysarthria (posterior 1/3 of ventral tegmentum)
 - c. Dysphagia (corticobulbar fibers X, XII)
 - d. Decreased ipsilateral V (corresponding decrease of corneal reflex)
 - e. Bilateral ptosis (rare)
 - f. Convergent and divergent eye movements associated with:
 - i. Ipsilateral facial numbness
 - ii. Contralateral sensory deficits
 - iii. No motor abnormality

Differential Diagnosis of Primary Pontine Hemorrhage

1. Hypertensive cardiovascular disease
 - a. Middle aged patients
2. Vascular malformations (younger patients)
 - a. Von Hippel-Lindau disease
 - b. Zona-Bannayan syndrome
 - c. Cobb's syndrome
 - d. Cavernous angioma
 - e. Capillary telangiectasia (rarely bleed)
3. Anticoagulation
4. Coagulopathy
5. Trauma (associated with basilar skull fracture)

Midbrain Hemorrhage*General Characteristics*

1. Isolated spontaneous midbrain hemorrhages are rare
2. Location is usually in the tegmentum

*Clinical Manifestations***Neurologic Features**

1. IIIrd, IVth nerve palsies
2. Dorsal midbrain syndrome
3. Convergence, retraction, nystagmus (PAG)
4. Vertical one-and-a-half syndrome
5. Unilateral and bilateral INO (anterior type)
6. Bilateral total ophthalmoplegia
7. Vertical gaze palsies
8. Weber's, Claude's, Nothnagel, Benedict's syndrome

Unusual Signs and Symptoms

1. Pure sensory stroke
2. Unilateral asterixis
3. Upper extremity dystonia
4. Peduncular hallucinosis
5. Retrograde amnesia
6. Spindle coma

Differential Diagnosis

1. Vascular malformations (40%)

2. Bleeding diatheses (5%)
3. Arterial hypertension (25%)
4. Undetermined in 1/3 of patients

Medullary Hemorrhage

General Characteristics

1. Approximately 0.5–1% of ICH
2. Bleeding can occur from:
 - a. Direct penetrating arteries of the distal vertebral artery
 - b. Branch arterial rupture from PICA, AICA or anomalies of the vertebral artery (basilarization of the vertebral artery)
 - i. Hemorrhage may be involved with concomitant cerebellar infarct
 - c. Dorsal branches of PICA:
 - i. Supply the dorsal medulla
 - ii. Concomitant cerebellar infarction if these arteries rupture
 - d. Anticoagulation

Clinical Manifestations

1. Headache is common initially
2. Neurologic deficit correlates with medial or lateral symptoms as seen with infarction
3. Partial or complete lateral medullary syndrome depending on specific arterial rupture
4. Vascular malformations
5. Hypertension

Unusual Neurologic Features

1. Ipsilateral facial pain
 - a. May be “salt and pepper like” particularly around the eye
 - b. Involvement of the trigeminal tract and nucleus
2. Ipsilateral VIIth nerve palsy
 - a. Aberrant cortico-bulbar pathway that traverses the upper medulla
3. Hiccough (singultus)
 - a. N tractus solitarius, nucleus ambiguus
4. Oculomotor disturbances:
 - a. Vertical or oblique diplopia
 - b. Upside down vision
 - c. Ocular tilt reaction
 - d. Involvement of the nucleus prepositus and medial longitudinal fasciculus
 - e. Vestibular nuclei
 - i. Usually at the level of the inferior olive
 - ii. Lateral pulsion to the side of the lesion
5. Opalski syndrome
 - a. Ipsilateral hemiparesis
 - b. The lesion is below C2 (the decussation of the pyramidal tracts)
6. Central respiratory dysfunction
 - a. N. and tractus solitarius

- b. Dorsal and ventral respiratory nuclear groups
7. Central vasomotor interruption
 - a. N. and tractus solitaries (NTS)
 - b. Central sympathetic vasomotor fibers
 - i. Nucleus raphe magnus
 - ii. Nucleus ambiguus
8. Ipsilateral tongue involvement (cranial nerve XII or hypoglossal fascicles)
9. Babinski–Nageotte syndrome
 - a. Wallenberg (no hemiparesis) with contralateral hemiparesis
10. Ceston–Chenais syndrome
 - a. Babinski–Nageotte
 - i. No ipsilateral ataxia (spared ICP)

Secondary Pontine Hemorrhage

General Characteristics

1. Diencephalic herniation:
 - a. Stretch and rupture of paramedian pontine penetrators from the basilar artery (Duret’s hemorrhage)
 - b. Associated midline thalamic and midbrain hemorrhages
2. Blood dyscrasia
3. Coagulopathy
4. Sudden severe increase of intracranial pressure

Prognostic Factors for Intraparenchymal Hemorrhage

1. Size of hematoma and level of consciousness
 - a. $<10 \text{ cm}^3$ – excellent prognosis
 - b. $<45 \text{ cm}^3$ – fair to good prognosis
 - c. $>60 \text{ cm}^3$ – poor prognosis
 - d. $>85 \text{ cm}^3$ – death
2. Other predictors of prognosis
 - a. Intraventricular hemorrhage
 - b. Hydrocephalus
 - c. Edema
3. 30 day mortality – approximately 45%
 - a. 50% of deaths occur in the first 48 hours
4. Pineal displacement laterally $<10 \text{ mm}$
 - a. $<5 \text{ mm}$ ventrally good prognostic sign
5. Lower mortality in lobar ICH than deep hemispheric hemorrhage

Neurologic Deterioration in Non-Comatose Patients with Supratentorial Intraparenchymal Hemorrhage

General Characteristics

1. Occurs in approximately 1/3 of patients
2. Greatest first hospital day
3. Neurologic deterioration:
 - a. $>45 \text{ ml}$ (60%)
 - b. 10 ml (19%)
4. 30 day mortality of patients with neurologic deterioration approximately 50%; 3% in those that are stable

5. Infarct expansion related to large established hemorrhages is the predominant cause of deterioration
6. Prognosis by size of hematoma volume
 - a. 50 ml or > – 78% deteriorated
 - b. 20–50 ml – 33% deteriorated
 - c. <20 ml – 16% deteriorated
7. Hemorrhage growth 0.8–13%
 - a. Progressive deterioration
 - i. Mass effect
 - ii. Cerebral edema

Clinical Manifestations

Major Diagnostic Features of Intraparenchymal Hemorrhage

1. Gradually progressive neurologic deficit
 - a. Minutes to hours
 - b. Headache and vomiting
2. Exceptions: severe early headache
 - a. Caudate hemorrhage with intravascular extension
 - b. Primary intraventricular hemorrhage
 - c. Early severe motor deficits:
 - i. GPe/GP₁ hemorrhage
 - ii. Large putaminal hemorrhage (usually mid portion)
3. Imaging Analysis (CT/MRI)
4. Early < 24 hours
 - a. Regular and smooth hemorrhage
5. First 48 hours
 - a. Blood fluid levels
6. First 72 hours
 - a. Mild edema and mass effect
7. 3–20 days
 - a. Resolution of the mass which starts at the periphery
 - b. Irregular contents that enhance to be differential from metastatic lesion, lymphoma (particularly in an HIV patient), abscess and inflammatory lesion; often hemorrhage is ring enhancing
8. Specific locations:
 - a. Multiple subcortical white matter hemorrhage
 - i. Leukemia
 - ii. Coagulopathy
 - iii. Disseminated intravascular coagulation
 - b. Cerebellum:
 - i. Anticoagulation (Coumadin; INR greater than 5)
 - c. Lobar in the elderly (65–90 years)
 - i. Congophilic angiopathy
9. Nine weeks:
 - a. Enhancement and mass effect have dissipated

Non-Hypertensive Causes of Parenchymal Hemorrhage and Subarachnoid Hemorrhage

Overview

There are multiple causes of parenchymal and subarachnoid hemorrhage that are not caused by idiopathic hypertension. Many are caused by induced hypertension in patients with underlying cystic aneurysms and vascular malformations. They

frequently have very specific clinical profiles that are diagnostic.

Idiopathic perimesencephalic hemorrhage may account for approximately 10% of all SAH. It rarely occurs with congenital aneurysms and seems more likely to be caused by leakage of blood from the prepontine venous plexus. Most patients have no focal neurologic deficits on admission. The headache associated with this bleed reaches maximum intensity within minutes rather than seconds. There is no loss of consciousness with the ictus and no rebleeding or delayed ischemia. There is some evidence for small aneurysmal bleed from the plexus.

Mycotic aneurysms most often occur in the distal branches of the MCA and cause both intraparenchymal and SAH. They may be the initial presentation of SBE.

Drug abuse with sympathomimetic agents and cocaine induce hypertension and cause hemorrhage as well as ischemic stroke. Cocaine in particular is associated with approximately 20% of ICH from an underlying aneurysm or vascular malformation. Drug abuse and SBE are coextensive.

Elderly non-hypertensive patients with superficial lobar hemorrhages should be suspected of having congophilic angiopathy. These hemorrhages are often recurrent which can be demonstrated by gradient Echo MRI (demonstrates hemosiderin from prior bleeds).

Traumatic intracranial hemorrhages frequently are delayed for 4–7 days after ictus. They occur in the originally damaged brain tissue.

Venous thrombosis with hemorrhage should be suspected in pregnant patients and those in a hypercoagulable state. Preceding headache, lethargy and seizures are common.

Vasculopathy or vasculitis may also cause non-hypertensive hemorrhage.

Differential Diagnosis

Differential Diagnosis of Perimesencephalic Hemorrhage

1. Venous or plexus extravasation
2. Caudate hemorrhage that extends into the subarachnoid space
3. Subependymal AVM
4. Trauma
5. Blood dyscrasias
6. Leakage from small nonaneurysmal arteries on the brain surface
7. Ruptured aneurysms; site of rupture is thrombosed and not identified
8. Dural AVM
9. Cocaine
10. Sympathomimetic drugs
11. Pituitary apoplexy
12. Spinal AVM
13. Traumatic LP

Parenchymal Trauma

1. SAH often located in the superficial areas of the cortical sulci

2. Adjacent to a fracture site or area of intracerebral contusion
3. Basal frontal contusion
 - a. Hemorrhage may mimic rupture of an AcoA (anterior communicating) aneurysm
4. Direct neck trauma
 - a. Tear of vertebral arteries or their feeders in the transcranial canals
 - b. Basilar hemorrhage
5. May be delayed
 - a. Occur 4–7 days in the contused area

Mycotic Aneurysm

1. A common cause of nonaneurysmal SAH and intraparenchymal hemorrhage
 - a. Infective endocarditis
 - b. Aspergillosis infection
2. Most common location
 - a. Distal branches of the MCA
 - b. 10% have a proximal location
3. Most patients suffer ICH at the site of rupture; some present with typical SAH
4. May rebleed
5. May be the initial presentation of bacterial endocarditis
6. Mycotic aneurysms secondary to aspergillosis:
 - a. Proximal carotid location
 - b. Proximal vertebrobasilar system
 - c. Rupture is frequently fatal

General Characteristics

Traumatic Intraparenchymal Hemorrhage

1. Associated SAH which is located in the superficial areas of the cortical sulci
 - a. Adjacent to a fracture site or area of intracerebral contusion
2. Mild head injury complicated by ICH:
 - a. Greater than 80% deteriorate within 24 hours
 - b. About 70% – progression of the hemorrhage is the cause of the deterioration
 - c. Approximately 4% have delayed neurologic deterioration
3. Clopidogrel has a higher risk of hemorrhage than warfarin

Traumatic Basal Ganglia Hematoma

1. Motor vehicle accidents and falls are the primary cause
2. Approximately 25% have a skull fracture
3. Location: putamen > thalamus > caudate
4. High frequency of associated intracranial lesions

Posterior Fossa Traumatic Hematomas

1. Four major categories:
 - a. Contusion and associated ICH
 - b. Diffuse axonal injury
 - c. Associated subdural hematoma
 - d. Diffuse brain swelling

Clinical Manifestations

1. Neurologic signs and symptoms dependent on location of the lesion
2. Cranial nerve VI, VII, VIII and I are frequently damaged; rarely CN II
3. Severe headache, nausea and failure of concentration that may last for months
4. Behavioral changes particularly with frontal lobe and temporal parietal junction deficits
5. Executive function deficits with DLPC lesions; general slowness of cognitive processing
6. Chronic dizziness may be prominent for months
 - a. Rarely direct hemorrhage into the labyrinth

Neuropathology

1. Extravasated blood
 - a. Forms a characteristic circle or ovoid mass within the brain parenchyma
 - b. Distortion and compression of adjacent brain substance
 - c. Perihemorrhage edema occurs
2. Evaluation of the clot:
 - a. A clot forms within hours:
 - i. Prior to its formation there is separation of plasma from RBCs that forms a meniscus. This is more prominent in hemorrhages from anticoagulation
3. The hematoma is often surrounded by petechial hemorrhages from burst arterioles and venules
4. Within days hematoxylin and hemosiderin are present. The hemosiderin is contained within histiocytes that have phagocytized RBCs. Phagocytosis begins approximately 24 hours after the hemorrhage
5. The edema may take days or weeks to clear
6. A smooth walled cavity or yellow-brown scar remains

Traumatic Brain Injury Models

1. Utilizing magnetic resonance (MR) spectroscopy
 - a. Evidence for neuronal-glial metabolic uncoupling
 - b. Activated astrocytic glycolysis with production of lactate and failure of neuronal uptake

Neuroimaging

1. The most commonly used method for bedside calculation of hematoma volume is the ABC/2 method
2. Shape classification of hematoma as a predictor of hematoma growth (regular, irregular and separated)
 - a. Irregular may predict growth
3. Oral anticoagulation-related ICH
 - a. ABC/3 may be more accurate measurement for growth of the hemorrhage
4. Associated neuroaxonal injury
5. Associated vertebral artery stroke with brainstem rotational injuries
6. Herniation with deep basal ganglia and hemispheric hematomas
7. SAH into cisterns

8. Secondary bleeding into the ventriculated system
9. SAH often located in the superficial areas of the cortical sulci
10. Basal frontal hematoma or contusion
 - a. Hemorrhage may mimic rupture of an anterior communication artery aneurysm
11. Associated neck trauma:
 - a. Tear of the vertebral arteries of their feeders in the transcervical canals
 - b. Basilar subarachnoid blood

CT

1. CT angiography “spot sign” predicts expansion on acute intracerebral hemorrhage
 - a. “Spot sign” on CTA source images
 - b. Contrast extravasation (CE)
 - i. Pooling of contrast within the hematoma is another marker of hematoma expansion; a better predictor of growth than the spot sign (for spontaneous ICH)

Hemorrhagic Transformation of Stroke (HT)

General Characteristics

1. Fisher and Adams
 - a. Drew attention to hemorrhagic transformation of ischemic stroke following an embolus
 - b. Proposed the concept of “migratory embolism” based on:
 - i. The observation that the hemorrhagic portion of the infarction was proximal to the embolus whereas distal areas were ischemic
 1. The hemorrhage occurred from the proximal to the embolus whereas distal areas were ischemic
2. The current classification of hemorrhagic transformation of ischemic stroke is wide:
 - a. Small areas of petechial hemorrhage
 - b. Space occupying hematoma

Clinical Manifestations

1. May be classified as symptomatic or asymptomatic
2. A large majority have symptoms prior to 12 hours and almost all by 24 hours (derived from NINDS clinical tPA trial)
 - a. Deterioration of level of consciousness
 - b. Increased weakness
 - c. Headache
 - d. Increased blood pressure and pulse rate
3. A significant proportion of patients have asymptomatic hemorrhages between 36 hours and 3 months (tPA evidence)

Neuropathology

1. Patchy petechial bleeding
 - a. Confined within the vascular territory of the infarction
 - i. Diapedesis of RBCs through ischemic capillaries without vessel rupture

2. Parenchymal hematoma
 - a. Rupture of an ischemic vessel that is caused by reperfusion pressure
 - b. Some patients have overlapping characteristics of hemorrhagic infarction and parenchymatous hematoma

Neuroimaging

CT

1. Patchy petechial or more confluent areas of alteration
2. Indistinct margins
3. Gyriiform pattern of cortical involvement
4. Parenchymal hematoma
 - a. Dense homogenous blood (High attenuation) often with mass effect)

MRI

1. Depends on the stage of the hemorrhage
 - a. Development of hemosiderin produces signal loss in T2-weighted sequences
 - b. Methemoglobin increased signal in T1-weighted sequences

New MRI Classification

1. Based on size, shape, distribution and signal intensity of the hemorrhage
2. ECASS CT classification of HT has been successfully modified for MRI
3. Measurement of BBB permeability utilizing MRI may predict HT
4. BBB disruption during the acute and subacute stages following ischemic stroke is pivotal for the development of cerebral edema and hemorrhage:
 - a. MRI can predict HT based on endothelial cell damage and disruption of the BBB that is reflected by the presence of contrast enhancement in structural brain images
5. Hyperdense middle cerebral artery sign is independently predictive of HT
6. Time to peak perfusion (TTP) as assessed by computed tomography perfusion:
 - a. TTP map-defect was correlated with HT
 - b. HT is correlated with delayed recanalization
 - c. TTP may be a method to predict HT
 - d. Cerebral microbleeds as evaluated by gradient-echo T2-weighted MRI is not correlated with HT
 - e. The mean Alberta stroke program early CT-DWI (a measure of the volume of ischemic tissue) is a marker for HT
 - f. Thrombolytic therapy is associated with 1.8 to 8.8% of ICH

Laboratory Evaluation

1. Biomarkers are increased:
 - a. Occludin (BBB protein)
 - b. Claudin-5 (BBB protein)
 - c. Metalloproteinase

- d. Zonula occludins
- e. S100B protein
- f. Lower VEGF growth factor

Perimesencephalic Subarachnoid Hemorrhage

General Characteristics

1. Definition
 - a. Is a benign variant of SAH with a characteristic pattern of extravasated blood on non-contrast CT and negative findings on cerebral angiography
 - b. Low risk of rebleeding
 - c. 20 to 70% of patients with angiographic negative SAH demonstrate perimesencephalic blood
 - d. Good prognosis

Clinical Manifestations

1. Most patients have no clinical deficits on admission
2. The headache associated with this bleed reaches maximum intensity within minutes rather than seconds
3. No loss of consciousness with the ictus
4. Rare rebleeding
5. Small percentage (<10%) develop hydrocephalus and/or delayed vasospasm

Neuropathology

1. Hemorrhages are located anteriorly to the brainstem, in the interpeduncular cistern, with or without extension to the ambient, chiasmatic and horizontal part of the Sylvian cisterns
 - a. Non-perimesencephalic hemorrhage blood is not located primarily in the interpeduncular cisterns but in the Sylvian cistern, interhemispheric cistern or over the convexity

Differential Diagnosis of Perimesencephalic Hemorrhage

1. Venous or plexus extravasation
2. Caudate hemorrhage that extends into the subarachnoid space
3. Subependymal AVM or malformation
4. Trauma
5. Blood dyscrasias
6. Ruptured aneurysms
 - a. The site of rupture is thrombosed and not identified
7. Dural AVM
8. Leakage from small nonaneurysmal arteries on the brain surface
9. Cocaine and sympathomimetic drugs
10. Pituitary apoplexy
11. Spinal AVM
12. Traumatic LP

Mycotic Aneurysm

General Characteristics

1. An infectious process in the wall of a vessel
2. Primarily seen in the setting I.V. drug abuse and SBE
3. Peripheral arteries are involved more than intracranial one

Clinical Manifestations

1. The number of mycotic aneurysms caused by staphylococcal infections and other acute bacterial organisms has increased (I.V. drug use)
2. An ischemic stroke with neutrophils in the CSF
 - a. MCA territory most common
 - b. Peripheral hemorrhage often with severe subarachnoid blood

Neuropathology

1. Wall destroyed by the infective process
2. An embolic occlusion of a small peripheral arterial branch
3. The aneurysm may occur within days of seeding
4. The aneurysm may rebleed
5. Mycotic aneurysms occur in approximately 10% of patients with infective endocarditis
6. Patients with symptomatic peripheral mycotic aneurysms have a higher incidence of the following complications than asymptomatic peripheral aneurysms:
 - a. Intravenous drug use
 - b. Native valve endocarditis
 - c. Intracranial bleeding
 - d. Septic emboli
 - e. Multiple embolism
 - f. Infectious endocarditis diagnostic delay >30 days
7. A small percentage of patients develop symptomatic peripheral aneurysms after complication of antibiotic therapy
8. The microbiologic profile in diverse but organisms with low to medium virulence appear predominant
9. Lemierre's disease with vertebral artery involvement is reported

Neuroimaging

1. The aneurysms are in peripheral branches of conducting pial vessels
2. Approximately 90% present with hemorrhage
3. Mycotic aneurysms secondary to aspergillosis:
 - a. Proximal carotid location
 - b. Proximal vertebrobasilar system
 - c. Rupture is frequently fatal
4. Lemierre's disease
 - a. Primarily an oropharyngeal disease
 - b. Septicemia; thrombophlebitis of the internal jugular vein (IJV)
 - c. Mycotic aneurysms of the extracranial carotid artery and vertebral artery

Hypertensive ICH

Clinical Manifestations

1. Most common cause of ICH
2. Blood pressure is 220–240 mmHg systolic and 110–120 mmHg diastolic (in general)
 - a. In several studies the peak systolic pressure is 160–190 mmHg

3. Pressure may be confounded by the Kocher–Cushing reflex; secondary hypertension due to the effects of pressure on the vasomotor centers
4. Many patients present without a prior history of hypertension
 - a. General examination may reveal:
 - i. Enlarged aortic knob (uncoiled)
 - ii. Thickened and tortuous peripheral blood vessel (radial and axillary arteries)
 - iii. Hypertensive changes in the retinal arteries
 - iv. Loud A2 and S4 gallop
 - v. Sustained cardiac impulse
 - b. Hypertension induced degenerative changes in vessel walls

Neuropathology

1. Fibrinoid degeneration
2. Microhemorrhages:
 - a. Penetrating arterioles to the basal ganglia, pons, thalamus and cerebellum
 - b. Also noted in arterioles that supply the gray-white junction
 - c. Associated concomitantly with lipohyalinosis and fibrinoid degeneration
 - d. Possible relationship exists between iris microaneurysms and those found in cerebral blood vessels

Non-Hypertensive Causes of Intracranial Hemorrhage (ICH)

Clinical Manifestations

1. Acute changes in blood pressure and blood flow:
 - a. Precipitate rupture of penetrating arteries without prior hypertension
 - b. Microaneurysm on penetrating vessels rupture: Predilection for lenticulostriate arteries (Charcot-Bouchard aneurysm)
 - c. Microbleeds:
 - i. May bleed repeatedly (hemosiderin laden macrophages)
 - ii. Located in penetrating vessels of:
 1. Lenticulostriate (MCA)
 2. Pons
 3. Cerebellum
 4. Gray white cortical junction
 - d. Penetrating arteries may rupture:
 - i. Not at the site of microaneurysms
 - ii. Generalized lipohyalinosis of entire artery
2. Exposure to cold weather
 - a. Stimulation of the sympathetic vasoconstrictor response
3. Dental procedures
 - a. Traction on the trigeminal nerve
 - i. Changes in heart rate and blood pressure
4. Increased cerebral blood flow:

- a. Carotid endarterectomy (hyperperfusion syndrome)
- b. Following surgical repair of congenital heart defects
- c. Cardiac transplantation
- d. Post-migraine
5. Older patients:
 - a. ICH at lower pressure than younger patients:
 - i. Possible relationship to amyloid angiopathy
6. Biphasic presentation of ICH
 - a. Onset of new hypertensive state
 - b. Prolonged hypertension

Underlying Medical Conditions That Are Associated with ICH

1. Coagulopathy
2. Vasculitis
3. Subacute bacterial endocarditis
4. Tumor
5. Trauma
6. Thrombolytic treatment
7. Transformed ischemic stroke:
 - a. Frequently multiple
 - b. Not in classic hypertensive ICH locations

Vascular Malformations

Overview

The major vascular malformations that are clinically relevant are:

1. Arteriovenous malformations
2. Dural arteriovenous malformation
3. Cavernous hemangiomas
4. Developmental Venous malformations
5. Capillary telangiectasia
6. Perimesencephalic aneurysm
7. Cobb's syndrome
8. Sturge-Weber syndrome
9. Von Hippel-Lindau disease
10. Wyburn-Mason disease
11. Osler-Weber-Rendu disease

Parenchymal arteriovenous malformations are abnormal connections of arteries and veins with no capillary bed. The arteries themselves have poorly developed internal elastic lamina and often become stenotic and occluded. In a sizable percentage, these vessels harbor aneurysms. The natural history of an AVM is to enlarge, recruit blood vessels from neighboring circulations and to bleed. They most often present with seizures due to the abnormal neurons and glial tissue within the malformation. They may present with seizures, hydrocephalus or chronic migrainous headaches. These headaches are stereotyped and do not switch sides during different attacks. Some patients note fluctuating bruits concomitant with their pulse. Approximately 2% have a progressive neurologic deficit.

Dural arteriovenous malformations are abnormal arteriovenous shunts within leaflets of the dura mater usually within or near walls of the dural venous sinuses. Headache

may be migrainous or localized to the side of the lesion. Patients suffer increased intracranial pressure, hemorrhage, pulsatile, tinnitus and seizures. Headache may be worse in the supine position. They may become symptomatic during pregnancy.

Cavernous angiomas have no entrapped brain tissue, appear anywhere in the brain, but are often periventricular. They are frequently multiple and especially common in Mexican Americans. They usually are not associated with vascular headache. They most often clinically present with recurrent bleeding with focal neurologic deficit (parenchymal type) seizures and subarachnoid hemorrhage. They have a characteristic “popcorn” appearance on MRI from the mixed signal of old and new hemorrhage. They often hemorrhage at night.

Developmental venous anomalies are the most common type of vascular malformation. They are composed of anomalous veins and have no direct arterial input. They most often are linear tubular structures in the cerebellum with connection to the IVth ventricle and may demonstrate a “caput medusa”. They most often are asymptomatic except when occluded during surgical procedures. In these instances, they may cause cortical infarction in the area of their venous drainage.

Telangiectasias are comprised of capillaries separated by normal brain parenchyma. They are most often seen in the cortex and the pons. They are rarely symptomatic.

Perimesencephalic hemorrhage has recently been recognized as a form of hemorrhage that presents frequently as a subarachnoid bleed without focal findings. Blood on CT is most prominent in prepontine and perimesencephalic cisterns. The process only seems to occur once and has an excellent prognosis. It may represent venous hemorrhage, although recently aneurysms of small arterioles have been demonstrated.

Parenchymal Arteriovenous Malformations

General Characteristics

1. No normal brain within AVM
2. No intervening capillary network between arteries and veins
3. Flow related abnormalities:
 - a. Sump-like effect that causes relative ischemia of the surrounding brain
 - b. Venous congestion and ischemia:
 - i. Arterializations of normal venous drainage
4. 10% as common as subarachnoid hemorrhage
5. Peak presentation in 2nd and 3rd decade
6. The prevalence from autopsy studies is .5–.8%
7. Incidental hemorrhage is 1/100,000 persons
8. Natural history:
 - a. Age at presentation is approximately 33 years
 - b. 2% hemorrhage at 1 year, 14% at 5 years, 31% at 10 years
 - c. Result of rebleeding 6–7% during the first 6 months and then to 3–4% per year
9. Occurrence: parieto-occipital lobe > frontal lobe > temporal lobe

Clinical Manifestations

1. Intracerebral hemorrhage:
 - a. Most common presentation; most often intraparenchymal
 - b. Present as ICH in 71–77% of patients
- c. Supratentorial AVM:
 - i. Hemiplegia/hemiparesis
 - ii. Aphasia, visual field or parietal deficits that are location specific
- d. Deep AVM:
 - i. Focal deficits without impaired consciousness (if small)
 - ii. Acute hydrocephalus if there is rupture into the ventricular system
- e. Cerebellar AVM:
 - i. Small and confined to the cerebellum
 1. Focal ataxia
 2. Minimally symptomatic
 - ii. Large hemorrhages:
 1. Depressed consciousness, nystagmus, ataxia
 2. Head tilt to side of the lesion; VIth, VIIth nerve palsy
 3. Central neurogenic hyperventilation
 4. Quadriplegia
 5. Brainstem compression
2. Subarachnoid hemorrhage:
 - a. Most often associated with larger intraparenchymal hemorrhage
 - i. 10–20% association with aneurysms in afferent arteries that may rupture with typical SAH presentation
 - ii. Rare vasospasm from AVM bleeds as opposed to that from an aneurysm
3. Seizures:
 - a. Second most frequent presentation (18–33%)
 - b. Younger age; larger AVM increases seizure risk
 - c. Symptoms and signs are location dependent
4. Ischemia in association with AVM:
 - a. Mechanisms of neurologic progressive deficits:
 - i. Mass effect
 - ii. Recurrent microhemorrhages
 - iii. Ischemia of surrounding parenchyma
 - iv. Steal phenomenon
 - b. Ischemic neurologic deficits develop in a slow progressive manner
 - i. Acute ischemic syndrome can occur with thrombosis of a major feeding vessel or acute thrombosis of entire AVM
 - ii. Acute stroke symptomatology may occur following venous thrombosis
 - i. Usually following AVM resection in the territory of the formerly arterialized venous system
5. Migraine headache:
 - a. Migraines are most often stereotypical
 - b. Occur ipsilateral to the AVM

- c. Most often the AVM is in the occipital lobe
- d. The headache does not switch sides
- 6. Chronic headache:
 - a. May be severe and progressive both in severity and frequency
 - b. In general occurs with large AVMs:
 - i. Cause increased intracranial pressure and high flow
 - 1. Retrograde arterialization of the normal venous drainage system
 - ii. Cognitive dysfunction
- 7. Hydrocephalus caused by:
 - a. Multiple small hemorrhages that occlude the ventricle or subarachnoid space
 - i. Large hemorrhage with acute internal ventricular obstruction
 - ii. Obstruction of CSF pathways by venous variants
 - 1. Deep high flow AVM
- 8. Fluctuating bruit:
 - a. Concomitant with heart beat
 - b. Rarely heard over the malformation
 - c. Jugular venous hum (heard in the neck or over the supraclavicular fossa)
- 9. Hemi-asymmetry:
 - a. Side contralateral to AVM is affected
 - b. Most severe when the parietal lobe is affected

Neuropathology

- 1. Arteries within the arteriovenous malformation are thin walled with poorly developed internal elastic laminae; there is hypertrophy of the media and endothelial thickening of the affected vessels
- 2. Some afferent vessels become stenotic and occluded
- 3. Increased incidence of aneurysms usually occurring on feeding vessels
- 4. Progressive recruitment of vessels from neighboring circulations
- 5. Composition of the AVM:
 - a. Abnormal gliotic parenchyma is intermixed between component blood vessels
 - b. No capillary bed
 - c. Abnormal dystrophic neurons
- 6. Cerebellar, brainstem and basal ganglia/thalamic AVMs have a greater risk of bleeding
- 7. Smaller AVMs have a greater rate of bleeding:
 - a. Increased intra-arterial pressure may be causative
- 8. Venous drainage patterns that are associated with bleeding:
 - a. A single draining vein
 - b. Deep venous drainage
 - c. Stenosis of a draining vein

Neuroimaging

MRI

- 1. Honeycombed areas; may demonstrate prior bleeds with susceptibility weighted or gradient echo sequences

- 2. Evidence of superficial siderosis; linear lesions suggest subarachnoid blood
- 3. Surrounding cerebral atrophy
- 4. Serpiginous flow voids
- 5. Ventricular dilatation (side of the AVM)
- 6. Intralesional calcification

Arteriography

- 1. Enlarged feeding vessels from several circulations
- 2. Tortuous enlarged draining veins
- 3. Central arterial venous complex of vessels
- 4. Rapid arterial to venous shunts
- 5. Percentage of feeding vessels with saccular aneurysms

Negative Arteriogram with AVM Malformations

- 1. Spontaneous thrombosis
- 2. Obliteration with hemorrhage
- 3. Cavernous angioma or dural anterior venous malformation
 - a. No feeding arteries
- 4. Spinal AVM:
 - a. May mimic intracranial signs and symptoms
 - b. Usually at low cervical and high thoracic levels
 - c. Headache and stiff neck

Features Increasing the Risk of Hemorrhage

- 1. Small malformation
- 2. Exclusively deep venous drainage
- 3. High intranidal pressure

AVM of the Lateral Ventricle

Clinical Manifestations

- 1. Less than 40 years of age
- 2. Small
- 3. Interventricular hemorrhage
- 4. Lateral ventricle usually normal sized
- 5. Caudate nucleus and choroid are other sources of ventricular hemorrhage

Dural Arteriovenous Malformation (DAVM)

General Characteristics

- 1. Abnormal arteriovenous shunts within leaflets of the dura mater
 - a. Usually within or near the walls of dural venous sinuses
- 2. Comprise 10–15% of AVM's
- 3. Pattern of drainage:
 - a. Intradural sinuses
 - b. Cortical or deep venous system
- 4. DAVM's with prominent cortical venous systems have a higher incidence of bleeding than those without
- 5. Symptoms of these malformations are primarily those of venous hypertension that is due or related to:
 - a. Increased arterial input and therefore increased flow through the draining veins
 - b. Venous outflow obstruction

6. Congenital DAVM's

- a. Vein of Galen type:
 - i. Due to retention of an embryonic median pre-cephalic vein; if it persists it becomes the sac for the aneurysmally enlarged vein of Galen

Clinical Manifestations

1. Headache (global and frontal); may be migrainous or localized to the side of the lesion
2. Increased intracranial pressure
3. Hydrocephalus
4. Hemorrhage:
 - a. Signs and symptoms depend on the drainage pattern:
 - i. Solely dural
 - ii. Drainage pattern into the cortical or deep venous system
 - b. Intraparenchymal > subdural > subarachnoid in location
 - c. 30% mortality
 - d. Pulsatile tinnitus
 - e. Seizures
 - f. Cerebral edema with venous hypertension and sinus occlusion
 - g. Postural headache (worse in supine position)

Neuropathology

Etiology of Dural Arteriovenous Malformation

1. Trauma; associated with skull fractures
2. Female hormones: influence placental and uterine vascular growth
3. Dural sinus thrombosis; female > males 2:1 with thrombosis of the lateral sinus and increased venous drainage enlarging dural veins
4. May become symptomatic with pregnancy
5. Thrombosis or stenosis within the draining dural sinus:
 - a. Enlarges the DAVM
 - b. Increases venous hypertension

Location of Dural Arteriovenous Malformations

1. Most common are related to the lateral sinus and involve the transverse or sigmoid portions; approximately 60% of DAVM's
 - a. Feeding vessels of lateral sinus fistulae:
 - i. Occipital, middle meningeal, accessory meningeal from the external carotid artery
 - ii. Ascending pharyngeal (arch of the aorta)
 - iii. Meningohypophyseal trunk of the cavernous carotid artery
 - iv. Dural branches of the vertebral arteries

Cavernous Sinus Dural Fistula

General Characteristics

1. Occur in approximately 16% of DAVM; 2% of patients with head trauma

Clinical Manifestations

1. Orbital venous hypertension causes:
 - a. Proptosis
 - b. Scleral arterialized venous blood; the arteries reach the iris whereas in infection they don't
 - c. Chemosis
 - d. Papilledema
 - e. Glaucoma
2. Cavernous sinus drainage into:
 - a. Petrosal veins and sinuses
 - b. Basal vein of Rosenthal
 - c. Results in brainstem venous hypertension
3. Cranial nerve III, IV, VI and first division of V (V1) may be compromised

Neuropathology

1. Abnormal shunting of blood from the internal and external carotid into the cavernous sinus
 - a. Type A:
 - i. Direct carotid cavernous fistula
 - ii. Large shunted blood volume
 - iii. Dramatic symptoms
 - b. Type B:
 - i. Indirect CCF
 1. No direct communication between ICA-cavernous sinuses
 2. Branches of ICA or ECA and the cavernous sinus
 - c. Type C:
 - i. Fed by dural branches of external carotid artery (ECA)
 - d. Type D:
 - i. Fed by branches of ICA/ECA
 - e. Etiology
 - i. Trauma:
 1. MVA with head injury
 2. Gunshot wounds
 - ii. Rupture of ICA infraclinoid aneurysm

Differential Diagnosis

1. Ehlers-Danlos type IV
2. Fibromuscular Dysplasia (FMD)
3. Arteriosclerosis
4. HCVD
5. Indirect Fistulas:
 - a. Post-menopausal
 - b. Spontaneous
6. Direct Fistulas:
 - a. Trauma
7. Tumors
 - a. Pituitary adenoma
 - b. Metastatic
 - c. Craniopharyngioma
 - d. Hemangioma
 - e. Bone Tumor

- f. Mucocoele
- g. Nasopharyngeal cancer
- h. Hyperthyroidism
- i. Retrobulbar masses

Rare Dural Arteriovenous Fistula's

General Characteristics

1. Incisura of the tentorium 8%
2. Cerebral convexity – sagittal sinus
3. Orbital-anterior falx
4. Drainage into the vein of Galen, straight sinus or posterior falx
5. Acquired adult vein of Galen – DAVF
 - a. Related to dural sinus occlusion
 - b. Supplied by middle meningeal and vertebral artery, PCA and meningohypophyseal branches of the ICA
 - c. Shunt is into the wall of the vein of Galen
 - d. Occasional association of a vein of Galen aneurysm with DAVF has been noted

Prognosis and Natural History

1. An aggressive course is correlated with
 - a. Drainage into subarachnoid and parenchymal veins
 - b. Retrograde flow away from the lesion
2. Spontaneous closure may occur
3. Minimal symptoms for prolonged periods
 - a. Headache
 - b. Pulsatile tinnitus

Spinal Arteriovenous Malformation

General Characteristics

1. Present major classification:
 - a. Type I
 - i. Dural arteriovenous fistula (AVF)
 - b. Type II
 - i. Intramedullary glomus AVM
 - c. Type III
 - i. Juvenile or combined AVM
 - d. Type IV
 - i. Intradural perimedullary AVF
2. Spetzler and Kim Classification
 - a. Extradural
 - b. Extra-intradural
 - c. Intradural
 - i. Ventral or dorsal fistulae
 - ii. Intramedullary
 1. Compact
 2. Diffuse
 3. Conus medullaris arteriovenous malformations

Clinical Manifestations

1. Local back pain
2. May present with Brown-Séquard distribution
3. Sudden onset of paralysis with spinal shock at the level of bleed
4. Headache may occur (intracranial meningeal irritation)

Neuropathology

1. Tangled masses of tortuous arteries, veins and abnormal connection channels
2. Lack of development of a capillary bed
3. Veins have thickened collagenous walls; proliferation of fibroblast
4. Reduplicated, interrupted and distorted internal elastic lamina
5. Arterial supply derived from medullary arteries

Dural Arteriovenous Fistulas

General Characteristics

1. Approximately 90% of patients have neurologic deficits
2. Predilection for men

Clinical Manifestations

1. Back pain occurs in approximately 40% of patients
2. Symptoms may worsen after exercise
3. Hemorrhage may be initiated by coagulopathy or anticoagulants
4. Unusual cause of progressive weakness with bladder involvement
5. Compression of the cords and roots (radiculomyelopathy); formerly referred to as Foix-Alajouanine syndrome

Neuropathology

1. The arteriovenous shunt is located within the dural layer of the spinal canal
 - a. Connects branches of a radiculomeningeal artery with the veins of the spinal cord in the intervertebral foramen
 - b. Arterialization of the venous drainage of the spinal cord circulation causes a chronic congestive myelopathy
 - c. Rare

Neuroimaging

1. Associated vascular anomalies occur with intradural AVM not AVF
2. Greater than 90% of patients that have dural lesions had AV nidus in the low thoracic or lumbar segments of the cord
3. In approximately 15% of patients intercostal or lumbar arteries supplying the AVM also provide a medullary artery which supplies the spinal cord
4. The great majority of intradural AVMs are at the cervical and thoracic segments and have fast flow
5. AVMs may have associated saccular arterial or venous spinal aneurysms
6. No aneurysms occur with dural AV fistulas

Adult Ventriculus Terminalis

General Characteristics

1. A cavity within the conus medullaris
2. Rare in adults (less than 30 reported patients)
3. May be associated with AVM

Clinical Manifestations

1. Non-specific symptoms
2. Focal neurologic motor sensory deficits of the lower extremity
3. Bowel or bladder symptomatology

Neuropathology*Adults*

1. Ependymal lined cavity within the conus medullaris
 - a. Putative canalization and retrogressive differentiation during embryonic development
 - b. Putative acquired mechanisms in adults include:
 - i. Trauma
 - ii. Vascular alterations
 - iii. Inflammation
 - iv. Cord compress

Children

1. Associated with:
 - a. Tethered cord syndrome
 - b. Chiari Type I malformation
 - c. Lipomyelomeningocele
 - d. Lumbosacral lipoma

Neuroimaging*MRI*

1. Characteristic feature of VT
 - a. Cystic lesion of the distal central spinal cord canal
 - i. No cord signal alternation
 - b. Some patients demonstrate:
 - i. Septation with cord edema

*Venous Developmental Anomaly***General Characteristics**

1. Developmental venous anomalies (DVA) are congenital anomalies of venous drainage
2. DVA comprises 42 to 63% of all cerebrovascular malformations
3. Incidence is .05 to 3%

Clinical Manifestations

1. Usually asymptomatic
2. Surgical removal may be associated with:
 - a. Infarction of the territory they drain
 - b. DVA should be preserved if possible
3. Rare associations with:
 - a. Hydrocephalus (midbrain)
 - b. Spontaneous hemorrhages
 - i. Thrombosis of central draining vein
 - c. Other developmental anomalies
 - i. Cavernous malformations
 - d. Cerebral hemiatrophy
 - e. Aqueductal compression

Neuropathology

1. DVA is concomitant with cavernous malformations

a. Putative mechanisms include:

- i. Increased local venous pressure in the DVA that leads to recurrent petechial hemorrhage
 - ii. Ischemia that promotes new vessel growth which bleed
- b. Dilated venous channels
- i. Flattened endothelial cells
 - ii. Sparse smooth muscle cells
 - iii. Often connection to cavernous malformations (particularly in the cerebellum)

Neuroimaging*MRI*

1. Radically arranged venous complexes converging into a centrally located venous trunk that drains normal brain parenchyma
2. Linear tubular structure in the cerebellum with a connection to the IVth ventricle
3. Normal brain parenchyma around the malformation

Hereditary Hemorrhagic Lesions*Cerebral Cavernous and Venous Malformations***General Characteristics**

1. Cavernous malformations (CM)
 - a. Angiographically occult vascular malformation (vascular malformation that are not visible by angiography but are recognized by an MRI)
2. Venous malformations:
 - a. Present terminology is now developmental venous anomalies (DVAs)
 - b. Transitional forms between cavernous malformations and capillary telangiectasia have been described
 - c. Cavernous malformations and capillary telangiectasia may be a spectrum within a single entity
 - d. Both may occur in the same individual
3. CMs of the brain
 - a. Now defined as hamartomatous vascular lesions
 - b. Incidence in the general population is .47%
 - c. Constitute 8–15% of vascular malformations
 - d. Median age at presentation is 34; highest incidence is between 3rd and 5th decade; approximately 25% are children
 - e. Males and females are represented equally
 - f. Supratentorial lesions occur in 63–81% of patients
 - i. Frontal and temporal lobes; cortical or subcortical location in 50%
 - ii. Less frequent locations are:
 1. Paraventricular
 2. Basal ganglia
 3. Thalamus
 4. Lateral ventricle
4. Posterior fossa site:
 - a. 7.8–15.8% in the posterior fossa
 - i. Brainstem most frequent location

- ii. Pontine lesions are close to the IVth ventricle (50%); extend into cerebellar peduncles (30%); deep in the pons (20%)
- b. Mesencephalic lesions:
 - i. Greater than 60% are in the tectum
- 5. Spinal cord
 - a. 6%
- 6. Unusual locations of CM
 - a. IIIrd ventricle
 - b. Pineal area
 - c. Extraventricularly
 - i. Rare
 - ii. Middle cranial fossa adjacent to the cavernous sinus
 - iii. Tentorium of the cerebellum; dural vertex; Meckel's Cave; anterior cranial fossa; sella turcica optic chiasm; cranial nerves
 - d. Extension into the skull base
 - e. Interosseous
 - f. Multiple lesions 84.6% of familial and 25% of sporadic cases

Telangiectasia

General Characteristics

1. Approximately 16–20% of intracerebral vascular malformations
2. Most are asymptomatic
3. Grow very slowly by or not at all
4. Associated with:
 - a. DVA
 - b. Cavernous hemangioma
 - c. AVM (rarely)
5. Most often located in the brainstem (pons); rarely in the cerebral and cerebellar cortex

Clinical Manifestations

1. Most often asymptomatic
2. In many, if symptomatic, the associated malformation is responsible
3. Rare complications
 - a. VIth, VIIth and VIIIth cranial nerve palsy
 - b. Possible association with seizures (cortical)

Neuropathology

1. Numerous thin-walled capillary type ectatic vessels
2. Interspersed in a background of normal tissue
3. Devoid of calcification, gliosis, extra-luminal hemorrhage or hemosiderin-laden macrophages
4. May vary from a few millimeters to 2 cm

Neuroimaging

CT

1. Normal

MRI

1. No mass effect

2. Hypo- or isointense on T1-weighted images; slightly hyperintense in T2
3. Enhance with gadolinium
4. Gradient-echo demonstrates low signal intensity
5. Approximately 2/3 demonstrate an enlarged vessel, possibly a draining vein that suggests a transitional malformation

Familial Cavernous Malformations

General Characteristics

1. Autosomal dominant transmission
2. Chromosome 7q21-22 (Hispanic American kindred), CCM1 locus
 - a. Family mutation
 - b. Delayed and incomplete penetrance
3. CCM2 locus:
 - a. Chromosome 7p15-13
4. CCM3 locus:
 - a. Chromosome 3p25. 2-27
 - b. Non-Hispanic kindred
5. Genetic heterogeneity in non-Hispanic Caucasian patients
6. CCM1
 - a. Krev interaction trapped 1 (KRIT-1) gene
 - i. Encodes a 736 aa protein
 - ii. Interaction with RAP1A (GTPase) and ICAP α a modulator of β 1 integrin
 - b. KRIT-1 protein found in vascular endothelium and pyramidal cells
 - i. Important for arterial angiogenesis
 - ii. Endothelial cell morphology
 - c. Approximately 40% of kindreds with familial CM are limited to CCM3 locus on:
 - i. Chromosome 3q25. 2-27
 - ii. Programmed cell death
 1. Encodes 212 aa protein
 - d. CCM3:
 - i. Younger age at onset: less than 15 years old; higher in CCM3 than in CCM2 or CCM1
 - ii. Most common presentation is hemorrhage
 1. Possible role in vascular morphogenesis
 - e. Genotype – phenotype Correlations:
 - i. Penetrance of gene mutations
 1. CCM1 – 88%
 2. CCM2 – 100%
 3. CCM3 – 63%
 - f. Fewer lesions in CCM2 patients
 - g. Number of lesions increased more rapidly in CCM1 than CCM2 patients

Sporadic Cavernous Malformations

General Characteristics

1. Phenotype is similar to hereditary forms
2. Possible CCM1 mutations occur in patients with multiple CCMs

3. 75% of patients thought to have sporadic CCMs have multiple CCMs
 - a. Have an asymptomatic parent with documented lesion by MRI

Clinical Manifestations

1. Sporadic and hereditary forms demonstrate dynamic changes during the life of the CCMs
 - a. Change in size and signal intensity with MRI
 - i. May increase or decrease in volume
 - ii. Trend is for lesions to increase in size with time
2. De novo genesis of lesions:
 - a. Following X-RT
 - b. Along needle biopsy tracts
 - c. Spontaneous occurrence in approximately 30% of patients (.4%/patient/year)
 - d. Greater number of new lesions in familial forms (possibly 15%)
3. Familial CMs:
 - a. True CMs (Type I and II on MRI)
 - b. Related vascular malformation (Type III, IV) are a possible precursor state
4. Symptoms and signs may be acute or insidious and are related to:
 - a. Intrinsic growth
 - b. Bleeding and thrombosis
 - c. Perilesional iron deposition and atrophy
 - d. Siderosis
5. Clinical manifestations due to repeated episodes of exacerbation and remission
6. Seizure:
 - a. Most frequent presentation
 - b. Occurs in 40–50% of patients; incidence of epilepsy is 35–70%
7. Hemorrhage:
 - a. .8–3.1% per patient year in sporadic and mixed series
 - b. 4.3–16% per patient year in familial series
 - c. Rebleeding rate of approximately 4% (controversial)
 - d. Bleeding possibly higher in women and in brainstem lesions:
 - i. Infratentorial and deep lesions may have higher bleeding rate
 - ii. Bleeding incidence is increased in patients with prior hemorrhage
8. Focal neurological deficits:
 - a. Present in 10–40% in general series; higher in brainstem CCMs
 - b. Deficits may be transient, progressive, recurrent or permanent
 - c. Headache occurs in 6–52% of patients
 - d. 13–56% of patients present with symptomatic hemorrhage

Brainstem Cavernous Malformations

General Characteristics

1. Approximately 20% of intracranial CMs

2. No difference in age or gender from supratentorial lesions
3. Sudden onset of symptoms and neurologic deficits; >90% symptomatic at diagnosis
4. Bleeding rate of 4–6% per patient-year (controversial)
5. Rebleeding occurs more frequently than with supratentorial lesions (20–60%)

Neuropathology

1. Well circumscribed lesions
 - a. Closely packed enlarged capillary-like vessels
 - b. No intervening parenchyma
 - c. Multi-lobulated (“mulberry-like”)
 - d. Variation in size from a few millimeters to several centimeters
2. Microscopic examination:
 - a. Complex of dilated vascular channels arranged in a back to back pattern
 - b. Resemble dilated capillaries
 - i. Walls are composed of collagen
 - ii. Lined with a single layer of endothelial cells
 - iii. Contain macrophages that are filled with iron-pigment
 - c. Reticulin fibrils and cholesterol crystals are secondary to thrombosis
 - d. Collagenous stroma devoid of elastin and smooth muscle
 - e. Evidence of prior microhemorrhage and thrombosis
 - f. Gliotic scar in the surrounding parenchyma
 - g. May be associated with capillary telangiectasia

Dural Venous Anomalies (DVA)

General Characteristics

1. Definition of DVA
 - a. Congenital anomaly of normal venous drainage
 - b. Dilated radially arranged medullary veins that converge on a central draining vein – “caput medusa”
2. Surrounded by normal neural tissue
3. Approximately 60% of all intracranial vascular malformations; prevalence of 3% of the normal population
4. Associated with CCMs

Clinical Manifestations

1. Most are benign and asymptomatic
2. Bleeding risk of .22–.34%
3. Possibly more aggressive course if they are associated with CCMs (bleed more)
4. Surgical excision of the lesion during a procedure on the CCM may lead to venous infarction

Neuropathology

1. Lesions that are angiographically demonstrated
 - a. Dilated thin-walled vessels in white matter
2. Angiographically occult venous angioma
 - a. Compactly arranged venous channels with no smooth muscle layer

3. DVAs:
 - a. Congenital lesions
 - b. Lead to mixed and different intracranial formations

Radiation-Induced Lesions

General Characteristics

1. De novo formation of CMs occur after brain X-RT:
 - a. Most occur in pediatric patients
 - b. Males more frequently affected than females
 - c. Occur in medulloblastoma, glioma and acute lymphoblastic leukemia
2. Mean latency from time of X-RT approximately 9 years
3. Mean dose of X-RT 60.5GY
4. Most common presenting symptoms is seizure
5. Over time more than 50% of patients hemorrhage
6. New CMs may form following spinal cord X-RT
7. Cervical and thoracic levels more common than lumbar

Neuroimaging

Angiography

1. CCMs minimal or no findings on angiography
2. Abnormal angiograms demonstrate:
 - a. A vascular area (77%)
 - b. Venous pooling, capillary blush, or neo-vascularization in 20%

MRI

1. Gradient echo sequences are especially useful due to their ability to determine the stages of bleeding from the paramagnetic properties of hemoglobin, deoxyhemoglobin and hemosiderin

Classification of CCM Based on Their Pathological Constitution and MRI – Signal Characteristics

Type I Lesions

1. Hyperintense core on T1-weighted image (T1WI)
2. Methemoglobin
3. Visible on CT
4. T2-weighted image (T2WI)
 - a. Hyperintense core (if methemoglobin present)
 - b. Hypointense core if methemoglobin is broken down with a surrounding dark or hypointense rim (paramagnetic effects of iron and hemosiderin, also cancellation effects)
5. Pathologic correlation:
 - a. Subacute hemorrhage (4–8 days old)
 - b. Rim is composed of macrophages that have engulfed hemosiderin and gliosis

Type II Lesions

1. T1-Weighted Image sequence:
 - a. Reticulated mixed signal core with hypointense rim
2. T2-Weighted Image sequence:
 - a. Reticulated mixed signal core with hypointense rim

3. Pathologic correlate:

- a. Loculated areas of hemorrhage and thrombosis of different age surrounded by gliotic tissue and macrophages laden with hemosiderin
- b. Calcification may occur in large lesions

Type III Lesions

1. T1-Weighted Image sequences:
 - a. Iso- or hypointense signal in the core
2. T2-Weighted Image sequences:
 - a. Hypointense core and slightly darker rim; the lesion appears magnified
3. Gradient echo (more sensitive to blood products)
 - a. Hypointense signal
 - b. Greater magnification than T2WI
 - c. Correspond to chronic resolved hemorrhages (hemosiderin within and surrounding the lesion)

Type IV Lesions

1. Minimally visualized on T1 and T2-weighted images
2. Gradient – echo positive
3. Punctuate hypointense signal

Differential Diagnosis of CCMs

Radiologic Differential Diagnosis by MRI

1. Telangiectasia
2. Hemorrhage neoplasms
3. Cysticercosis
4. High grade glioma
5. Metastasis
6. Meningioma
7. Chronic granuloma
8. Lipoma
9. Hamartoma

Imaging Characteristics of Isolated Vergans Angioma

1. Linear on MRI
2. Frequently near a ventricle
3. Large prominent central draining vein
 - a. May be dilated into a varix
 - b. Hyalinized walls

Wyburn-Mason Syndrome

General Characteristics

1. Combination of retinal, orbital and midbrain AVM
 - a. Probably orbital facial and brainstem AVM without retinal lesions represent the same syndrome
2. Dysfunction at the seventh week of gestation in the vascular mesoform
 - a. Concurrent development of the anterior neural tube and the optic cup
 - i. Vascular plexus differentiates into the hyaloid vascular system and the midbrain vascular supply

Clinical Manifestations

1. Retinal AVM
 - a. Stable and cause no visual loss
 - b. Dilated tortuous arteriole and vein contiguous to the optic disc
 - i. Neovascular induced glaucoma from retinal shunting and ischemia
 - ii. Optic atrophy from orbitocranial AVM
2. Intracranial AVMs associated with:
 - a. Visual loss
 - b. Headache
 - c. Hemiparesis
 - d. Rare: seizures and loss of consciousness
3. Location:
 - a. Tends to be deeper in the brain than usual AVM

Cobb's Syndrome*Overview*

Cobb's syndrome (cutaneous meningospinal angiomatosis) is a somatic disorder characterized by vascular abnormalities of the spinal cord with associated skin, muscle and dura involvement at the same metameric level.

General Characteristics

1. Cutaneous nevus
2. Associated vascular lesion at the same dermatologic level
3. Vascular skin, muscle, bone and dural involvement at the same somite

Clinical Manifestations

1. Large AVM may be associated with congestive heart failure
2. Compression of the spinal cord, bleeding and deterioration of spinal cord function
3. May just have extradural and paraspinal components

Neuropathology

1. Progressive myelopathy
 - a. Venous congestion of an extradural nidus or fistula
 - b. May cause similar neurologic dysfunction as is seen with dural-based intradural lesions
 - c. Large epidural venous lakes

Neuroimaging

1. Type A – spinal extradural AVF:
 - a. Diffuse high signal intensity of the spinal cord on T2-weighted MR images
 - b. No mass effect
 - c. Primarily thoracolumbar and lumbar location
2. Type B – lesions:
 - a. Normal signal intensity of the cord
 - b. Severe mass effect due to enlarged extradural venous plexus
 - c. Cervical and upper thoracic locations

Sturge-Weber Syndrome*Overview*

Sturge-Weber syndrome, also called encephalotrigeminal angiomatosis, is a neurocutaneous disorder characterized by vascular lesions in the skin, eye, and brain.

General Characteristics

1. Facial port-wine stain (cutaneous nevus) in VI
2. Ipsilateral parietal-occipital leptomeningeal angioma

Genetics

1. Sporadic
2. Somatic mosaicism
3. Occurs in all ethnic groups; no gender preference

Clinical Manifestations

1. Cutaneous nevus
 - a. Usually involves the forehead and upper eyelid (VI distribution)
 - i. May involve the face bilaterally and extend to the trunk
 - ii. Trunk or V2 or V3 distribution lesions (without V1) rarely have an intracranial lesion
 - iii. Rarely patients have intracranial lesion without skin manifestations
2. Bilateral cerebral lesions occur in 15% of patients with unilateral facial nevus
 - a. The extent of the nevus increases the risk of a bilateral intracranial lesion
 - b. Similar cutaneous lesion with limb hypertrophy comprise the Klippel-Trénaunay-Weber syndrome
3. Ophthalmologic features
 - a. Glaucoma if the nevus is adjacent to the eyes
 - b. Newborns have buphthalmic amblyopia (rare)
 - i. Abnormal anterior chamber angle
4. Seizures and hemiparesis
 - a. Seizures develop acutely during the first or second year; often triggered by a febrile illness
 - b. Early onset and refractoriness of seizures are correlated with cognitive deficits
5. Adult patients with Sturge-Weber syndrome
 - a. Greater than 50% suffer contralateral motor deficits
 - b. Intracranial hemorrhage is rare
6. Intracranial hemorrhage is rare
7. Seizures occur in:
 - a. 72–80% of patient with unilateral lesions and greater than 90% of those with bilateral lesions
 - i. Early seizures are focal (infantile spasm, myoclonic and atonic seizures also occur)
 - ii. Adults have complex partial seizures or focal motor seizures
8. Patients may develop stroke-like episodes without seizures suggestive of TIA
9. Occipital lobe involvement

- a. Visual field deficits
- b. Cognitive deficit occurs in approximately 50% of patients; particularly severe if there is bilateral involvement

Neuropathology

1. Parietal and occipital lobe involvement is greater than in the frontal lobe
2. Leptomeninges:
 - a. Thickened
 - b. Angiomatous vessels may obliterate the subarachnoid space
 - c. Tortuous deep draining veins
 - i. Thin walled
 - ii. May extend into the parenchyma
 - iii. Ipsilateral choroid plexus may be involved
 - iv. Hyalinization and subependymal proliferation occurs in some vessels
 - d. Cerebral atrophy adjacent to the angioma
 - i. Neural loss and gliosis which may extend into normal appearing tissue
 - ii. Gyriform ("tram track") calcification is seen in outer cortical layers adjacent to blood vessels
 - e. Chronic venous stasis

Neuroimaging

1. Gyral calcification; bilateral calcification is common
2. Calcification more apparent with age; may be present at birth
3. Cerebral atrophy
4. Accelerated myelination in young patients
5. Hypoperfusion:
 - a. Impaired venous drainage
 - b. Several impaired regions demonstrate arterial perfusion deficits

PET

1. Decreased brain glucose utilization beyond the leptomeningeal lesion

SPECT

1. Decreased cerebral perfusion that may include areas with normal glucose uptake; often the deficit is larger than that noted by MRI

Angiography

1. Rare arterial occlusion; may see blush of the angioma
2. Decreased number of superficial cortical veins; enlarged and tortuous draining veins
 - a. Failure of opacification of the ipsilateral sagittal sinus due to occluded cortical veins

Von Hippel-Lindau Syndrome

Overview

Von Hippel-Lindau disease is a rare, autosomal dominant multisystem disorder associated with hemorrhagic blastomas

of the CNS, retinal angiomas as well as cysts and tumors of the viscera. The most common tumors are retinal and CNS hemangioblastomas, clear cell renal carcinoma, pheochromocytoma, pancreatic islet cell tumors and endolymphatic sac tumors.

General Characteristics

1. Autosomal dominant; 95% penetrance by age 60 with incomplete expression
 - a. Von Hippel-Lindau (vHL) suppressor gene on chromosome 3p25-26 is mutated
2. Development of benign and malignant tumors and cysts the include:
 - a. Hemangioblastoma (HB) in the CNS
 - b. Retinal hemangioblastoma (RA)
 - c. Pheochromocytoma (Pheo)
 - d. Clear cell renal carcinomas (RCC)
 - e. Renal cysts
 - f. Pancreatic cystadenoma
 - g. Pancreatic neuroendocrine tumors

Genetics

1. vHL protein mutations cause:
 - a. Decreased ubiquitination of hypoxia-inducible factor 1 α (HIF1 α)
 - b. Dysfunction of vascular endothelial growth factor in stromal cells
 - c. Upregulation of VEGFR1 and 2 in tumor endothelial cells
 - d. vHL protein regulates extracellular matrix formation and the ability of cells to exit the cell cycle
 - e. Major effect of vHL mutation:
 - i. Causes altered vHL protein and Elongin BC complex

Clinical Criteria for the Diagnosis of vHL Disease

1. Positive family history
2. Development of hemangioblastoma in the CNS, retinoblastomas, renal cell cancer, pheochromocytoma, pancreatic tumors or cysts
3. Patients who develop hemangioblastomas or retinal hemangioblastomas concomitant with renal cell carcinoma and the usual associated tumors
4. 80% of patients have a family history
 - a. Inter- and intrafamilial phenotypic variability
 - b. 20% are sporadic and require two manifestations: included requirements are CNS or retinal hemangioblastoma

Clinical Classification

1. vHL type I
 - a. No pheochromocytoma
2. vHL type II
 - a. Type 2A
 - i. Has pheochromocytoma

- ii. Associated hemangioblastoma in the CNS
- iii. No renal cell cancer
- iv. Low risk of renal cell cancer and neuroendocrine pancreatic tumor
- b. Type 2B
 - i. Has pheochromocytoma, renal cell cancer and other CNS tumors
 - ii. High risk of renal cell cancer and pancreatic endocrine tumor
- c. Type 2C
 - i. Has only pheochromocytoma

Clinical Manifestations

1. Isolated hemangioblastoma (HB) present in early adulthood (20 to 40 years of age)
 - a. Type 1 (no pheochromocytoma) or type 2A in 70% of vHL patients
 - b. Males 1.5:1 females
 - c. Location:
 - i. Cerebellum (83–95%)
 - ii. Spinal cord (3.2–13%)
 - iii. Medulla (2%)
 - d. Multiple spinal hemangioblastoma occur
 - e. In 40%, hemangioblastoma may be first manifestation of disease
2. Posterior fossa signs and symptoms
3. High hemoglobin occurs from overproduction of erythropoietin from hypoxia inducible factor (HIF)
4. Hemangioblastomas from vHL disease are 5–30% of cerebellar hemangioblastomas and 10% of spinal hemangioblastomas
5. Asymptomatic vHL gene carriers are approximately 4%
6. Intracranial or intramedullary subarachnoid or intraparenchymal hemorrhage is low (less than 5%)
 - a. Tumors size (1.5 to 5 cm); the average size that bled is 2.7 cm (larger than average HB)
 - b. Size of the tumor is associated with hemorrhage both spontaneous and following surgery
 - c. Subarachnoid hemorrhage occurs in a high percentage of patients that bleed
 - i. Superficial location of medullary HBs
 - ii. Cerebellar hemangioblastoma bleeds occur in the parenchyma
 - iii. Large solid hemangioblastoma have a higher risk of peri- and post-operative hemorrhage
7. Patients with complete deletion mutation of the vHL gene (as opposed to missense or protein-truncating mutations)
 - a. Better visual acuity
 - b. Decreased tumorigenesis incidence of hemangioblastomas
8. Higher levels of vascular endothelial growth factor VEGF, hypoxia-inducible factor (HIF) and ubiquitin have ocular hemangioblastomas

Neuropathology

1. Association with:

- a. Visceral cysts of the kidney, pancreas and epididymis
- b. Pheochromocytoma (type III, vHL)
- c. Pancreatic neuroendocrine tumors
- d. Endolymphatic carcinoma
- e. Head and neck paraganglioma
2. Stroma
 - a. Foamy vacuolated cells
 - b. Tumorlet dells (retinoblastoma) are poorly differentiated, small cells, prominent dark nuclei
3. Epithelial clear cell morphology
4. Increased expression (retinoblastoma) of erythropoietin (Epo); CD133; and the chemokine CXCR4

Neuroimaging

MRI

1. Should be of the entire neuraxis to rule out multiple hemangioma
2. Lesions are well circumscribed and are often associated with a cyst
3. Cystic lesions hypointense on T1-weighted images and hyperintense on T2-weighted images
4. Minimal or no edema
5. Enhancement of a mural nodule with gadolinium
6. May have vascular flow voids (MRA)
7. Solid HB enhance homogeneously with gadolinium

Differential Diagnosis

Neuroradiologic Differential Diagnosis

1. Pilocytic astrocytoma (children; spreads through the brainstem)
2. Astrocytoma (solid or cystic)
3. Metastasis (usually surrounding edema)
4. AVM (appear similar to large solid hemangioblastoma)

Angiography of Hemangioblastoma

1. May demonstrate a large vascular peduncle
2. Early draining vein (AV shunting)
3. Absence of a cystic component suggests metastatic renal cell carcinoma

Hereditary Hemorrhagic Telangiectasia (Osler-Weber-Rendu Disease)

Overview

Hereditary Hemorrhagic Telangiectasia (Osler-Weber-Rendu) is autosomal dominant, characteristic by epistaxis, cutaneous telangiectasia, visual and cerebral malformations. Epistaxis occurs in childhood, pulmonary AVMs at puberty, cutaneous and gastrointestinal telangiectasia in adulthood. Arteriovenous fistulas occur in childhood, small AVMs in adolescents and micro-AVMs in young adults.

General Characteristics

1. Autosomal dominant; high penetrance
2. Incidence of 1 in 5,000–8,000 persons

3. Telangiectasias are found:
 - a. Face
 - b. Nasal mucosa (nose bleeds)
 - c. Conjunctiva (30%)
 - d. Hands > legs and trunk
 - e. Anterior tongue
 - f. Retina (10%)
4. Telangiectasia – enlarge and multiply
5. Telangiectasia occur in internal organs
 - a. Lungs
 - b. GI tract
 - c. Genitourinary tract

International Diagnostic Criteria

1. Epitasis
 - a. Spontaneous
 - b. Recurrent
2. Multiple telangiectosis
 - a. Lips, oral cavity, fingers, nose
3. Visceral lesions
 - a. Gastro-intestinal telangiectosis
 - b. Pulmonary arteriovenous malformation; hepatic, cerebral and spinal AVM
4. Family history of a first degree relative with lesions
5. Clinical manifestations develop with age
6. Epitasis in childhood, pulmonary AVM from puberty, microcutaneous and gastrointestinal telangiectosis in adulthood
7. Approximately 2/3 of patients have some sign of HHT by 16 and 90% by 40 years of age
8. Neurologic symptoms occur in approximately 10–20% of patients

Genetics

1. Autosomal dominant; 2 genes described:
 - a. Endoglin – chromosome 9q24(CD105)
 - b. Activin – chromosome 12q HTT2
 - i. Proteins expressed are found in vascular endothelial cells
2. No definite relationship between the type of mutation and the phenotype of the disease
3. Protein levels from the mutated genes suggest haploinsufficiency
4. Endoglin and Activin receptor-like kinase 1(ALK1) involved in:
 - a. Transforming growth factor signaling pathway
 - b. Cell development
 - c. Vascular remodeling by control of the production of the extracellular matrix
 - d. Endoglin and ALK1 influence angiogenesis by binding with transforming growth factor β proteins
5. Some patients have HTT-juvenile polyposis overlap syndrome
6. HTT3 subgroup:
 - a. Chromosome 5 locus; SMAD-4
 - b. Prominent pulmonary involvement

Clinical Manifestations

1. Nasal and mucocutaneous telangiectosis
 - a. Epistaxis from nasal mucosa is the first complaint in about 50% of patients
 - i. Common in childhood
 - ii. Recurrent in 50 to 80% of patients
2. Skin telangiectasia
 - a. Later in life
 - b. Located on the face, lips, tongue, palate and finger tips
 - c. Size and number increase with age
3. Gastrointestinal telangiectasia
 - a. Recurrent hemorrhages occur in about 30% of patients usually starting in the fifth to sixth decade
 - b. Telangiectasia more prominent in stomach and duodenum than colon
 - i. Rarely AVM or aneurysms
 - c. Rare liver AVMs
 - i. Multiple AVMs may cause portal hypertension and biliary disease
 - ii. Cardiac failure from right to left shunt
 - iii. Hepatic encephalopathy (rare)

Pulmonary AVM (PAVM)

1. Occurs in 5–20%, possibly more are present in the 5HTT 3 subgroups
2. About 70% of all PAVMs occur in 5HTT patients
3. Location is primarily in the lower lobes
 - a. Enlarge with age and become symptomatic during the third or fourth decade
4. Associated with:
 - a. Decreased arterial oxygen saturation (right to left shunt)
 - b. Fatigue, dyspnea and cyanosis
 - c. Hemoptysis and hemothorax
 - d. Polycythemia
 - e. Clubbing, cyanosis
 - f. Platypnea-orthodeoxia (improved breathing with supine position; hypoxemia in sitting position)
5. Differential diagnosis of pathologic arteriovenous defects:
 - a. Patent ductus arteriosus
 - b. PFO
 - c. Right to left congenital heart defect
 - d. PAVM

Neurologic Manifestations

1. Occur at all ages; peak incidence is in 3rd–4th decade
2. Primary mechanisms:
 - a. PAVM (60%)
 - b. Brain vascular malformations (28%)
 - c. Spinal cord malformations (8%)
 - d. Hepatic encephalopathy (3%)
3. Neurologic complications from PAVM
 - a. Bland emboli to cerebral circulation
 - b. Septic emboli associated with SBE that cause cerebral abscess, meningitis and mycotic aneurysms

- c. Cerebral abscess is most frequently a septic complication:
 - i. Usually solitary
 - ii. Supratentorial (MCA territory most frequent)
 - iii. Incidence 3–5%; much higher if there is a recurrence
- d. Embolic patterns:
 - i. Paradoxical from peripheral sources such as DVT
 - ii. In a large ectatic PAVM a clot may develop in the wall of the malformation
 - iii. MCA territory most often affected (40 to 50% of CBF)
 - iv. Rarely CNS embolism is the initial symptom
 - v. Overall risk of emboli is related to the number of PAVMs
 - 1. Single PAVM infarction occurs in about 30%
 - 2. 60% of them are multiple PAVMs
 - vi. Other mechanisms of cerebral ischemia:
 - 1. Hyperviscosity from polycythemia
 - 2. An embolism

Differential Diagnosis of PAVM

1. Hepatopulmonary syndrome
2. Mitral stenosis
3. Trauma
4. Actinomycosis
5. Schistosomiasis
6. Metastatic thyroid cancer
7. Fanconi syndrome
8. Surgery in congenital heart case
9. Bronchiectasis
10. Venous atresia

Hemorrhagic CNS Complications

1. About 30% of HTT patients suffer hemorrhages from cerebral or spinal vascular malformation
 - a. Large malformations bleed at a rate of 1.4–2% per year
2. Prevalence of cerebrovascular malformations by MRI is about 20%
 - a. Large malformations bleed at a rate of 1.4–2% per year
3. Symptoms from malformations also occur due to
 - a. Thrombosis of the venous pouch
 - b. Venous ischemia
 - c. Rarely SAH from AVF or arterial aneurysm
4. Spinal malformations (AVFs):
 - a. Often large
 - b. High risk of hemorrhage
 - i. Progressive para- or tetraparesis the usual premonitory sign

Neuropathology

1. Telangiectasias are the most prominent lesions:
 - a. Focal dilatations of post-capillary venules
 - b. Some perivascular lymphocytic infiltration

- c. Enlargement of telangiectasias associated with excessive layers of smooth muscle without elastic fibers
- d. Connecting arterioles dilate and connect to venules by-passing a capillary bed

Neuroimaging

1. Associated arteriovenous malformation and arteriovenous fistula
 - a. Most often responsible for neurologic sequelae
 - b. Largest arteriovenous malformations occurs in the lungs, liver and CNS
 - c. Rare aneurysm
 - d. Multiple types of malformations may occur concomitantly
2. Three different malformations occur:
 - a. Large fistula
 - i. Direct arteriovenous shunt
 - ii. No nidus
 - iii. Ectatic draining vein
 - b. Small AVMs (1–3 cm)
 - i. Nidus
 - c. Micro-AVMs
 - i. Nidus smaller than 1 cm
3. Malformations most often are near the surface of the CNS
4. Venules are the initial component of the pathologic process
5. PAVM may enlarge during pregnancy (increased hemorrhagic risk)
6. Cerebral and spinal AVM's (16%)
7. No evidence of different features of AVMs among different genetic groups
8. Multiple brain AVMs (23%)
9. AVMs are of small size and tend to be cortical

Drug Abuse

General Characteristics

1. 25% of drug related strokes are ICH
2. 6% related to recreational drug abuse
3. Location
 - a. Subcortical
4. Hemorrhage in a first time user
 - a. Occurs in minutes to hours
5. ICH responsible for approximately 50% of cocaine related stroke

Cocaine Abuse

General Characteristics

1. Crack cocaine
 - a. Aqueous cocaine HCL with NH₃ and baking soda
 - b. Smoked or inhaled
 - i. Aseptic necrosis of the nasal septum
 - c. Reaches the brain 10 seconds after it is smoked (1 circulatory pass)
 - d. Most rapid "high"

Clinical Manifestations

1. Systemic effects of cocaine
 - a. Blood pressure increase
 - b. Increases temperature
 - c. Increases metabolism
 - i. Severe weight loss in chronic abusers
2. Signs and symptoms immediately after use:
 - a. Loss of consciousness
 - b. Headache
 - c. Focal neurological signs (vasospasm of specific blood vessels)
 - d. Frequent signs and symptoms due to concurrent alcohol use
 - e. Hemorrhages
 - f. Strokes occur shortly after use
 - g. Predilection for the brainstem
 - h. Bowel and myocardial ischemia may be associated

Neuropathology

1. Approximately 20% of patient with ICH after cocaine use have an underlying vascular lesion: AVM or aneurysm
 - a. SAH occurs in approximately 48–80% of patients with an underlying aneurysm after cocaine use
 - b. Rebleed may occur even with normal angiography
 - c. Vessels do not show signs of vasculitis
 - d. Deep hemorrhage is less likely to be caused by an underlying vascular lesion
 - e. Some patients present with hypertensive encephalopathy
 - i. Usual pressure is 210–240 mmHg systolic and 110–140 mmHg diastolic
 - ii. Multiple hemorrhages
 - iii. Cerebral edema

Heroin Abuse*General Characteristics*

1. Cerebral or spinal cord ischemic stroke
2. ICH from SBE (IV route); mycotic aneurysm rupture

Clinical Manifestations

1. Stroke occurs with use after a period of abstinence
2. Ischemia of cerebral vessels:
3. Stroke may occur immediately after use
4. Stroke may occur after a 6–24 hour delay
5. Pulmonary edema and transverse myelitis (IV heroin)
6. If hemorrhage occurs:
 - a. Heroin may be altered or used concomitantly with:
 - i. Cocaine or methamphetamine

Laboratory Evaluation

1. Eosinophilia
2. Comb's positive hemolytic anemia
3. Increased immune globulins
4. False positive serology
5. Antibodies to hepatitis C

Amphetamine Abuse*General Characteristics*

1. Hemorrhages occur a few minutes after drug use
2. Associated abuse of alcohol and other drugs
3. Focal ICH may be associated with:
 - a. Diffuse vasculopathy
 - b. Cerebral edema
 - c. Ischemic lesions

Clinical Manifestations

1. Thin patients (severe appetite suppression)
2. Characteristics of adult attention disorder (chronic abusers)
3. Alternate presentation:
 - a. Hypertension
 - b. Fever
 - c. Tachycardia
4. Fibrinoid necrosis of the media and intima of small and medium-sized arteries
5. Arteriographic evidence of segmental constriction and "beading" of intracranial arteries (superficial cortical arteries)
6. Amphetamine and methamphetamine more likely to cause hemorrhage than dextroamphetamine
7. Hemorrhage may occur with doses as small as 20 mg
8. Solid form of D-methamphetamine base that can be smoked
 - a. Street name is "ice"
 - b. May reach the brain in <20 seconds in one CBF pass

Clinical Signs and Symptoms

1. Clinical presentation:
 - a. Symptoms occur a few minutes after use
 - b. Headache
 - c. Seizures
 - d. Focal neurological signs from ICH
 - e. Average age of patients 25.4 years
 - f. Intracerebral lobar hemorrhage most common
 - i. <5% have underlying vascular lesion

Laboratory Evaluation

1. Comb's positive hemolytic anemia
2. Increased immune globulins
3. False positive serology
4. Antibodies to Hepatitis C

Phencyclidine (PCP)

1. Angel dust

*Clinical Manifestations**Signs and Symptoms*

1. ICH
2. Hypertensive encephalopathy
3. Self-destructive behavior
4. Dramatic nystagmus to all fields of gaze

LSD*Clinical Manifestations*

1. Hypertension
2. Hallucinations
3. Vasoconstriction but no ICH

Phenylpropanolamine (PPA)*General Characteristics*

1. May be combined with caffeine or antihistamine
2. Partial α -adrenergic agonist
3. Reactions to PPA are often idiosyncratic
4. Risk of hemorrhage with PPA use occurs with:
 - a. Post-partum use
 - b. Caffeine
 - c. Higher than recommended doses
 - d. Alcohol
 - e. Caffeine
 - f. Prior hypertension
 - g. Monoamine oxidase inhibitors
 - i. Multiple simultaneous hemorrhages

*Clinical Manifestations**Clinical Signs and Symptoms*

1. <30 years of age; female > male
2. SAH may occur
3. ICH
4. Blood pressure on admission
 - a. 160/104–210/110 mmHg

Neuroimaging

1. Segmental angiographic beading of intracranial vessels (similar to amphetamines)

Neuropathology

1. Location: lobar > basal ganglia > thalamic

Ethanol*General Characteristics*

1. Mechanisms predisposing to hemorrhage
 - a. Platelet abnormalities
 - b. Impaired production of clotting factors with concomitant liver disease
 - c. Hypertension associated with chronic alcoholism
 - d. Binge drinking
 - i. Acute elevations of blood pressure
 - e. Concomitant use of cocaine in face of liver dysfunction
 - i. May potentiate vasoconstrictor effects

Pentazocine and Pyribenzamine (“T’s” and “Blues”)*General Characteristics*

1. IV use: associated with: starch, methylcellulose crystals; taken I.V. can cause pulmonary emboli

Clinical Manifestations

1. Pulmonary hypertension:
 - a. Destruction of pulmonary arterioles with right-sided hypertension
 - b. Embolic material reaches the cerebral circulation
 - c. Damaged cerebral vessels result in ICH

Neuropathology

1. Crystals and talc may be noted in cerebral vessels

Methylphenidate

1. Associated with ICH

Metastatic Brain Tumors That Bleed*General Characteristics*

1. The most common hemorrhagic metastases are:
 - a. Melanoma
 - b. Hypernephroma
 - c. Papillary cancer of the thyroid
 - d. Choriocarcinoma
 - i. Often metastatic to the dura
 - e. Lung and breast
 - i. No specific proclivity to bleed but are very common tumors

Clinical Manifestations

1. Onset of brain metastasis is usually insidious
 - a. Sudden onset of neurologic deficits may occur from bleeding into the tumor or tumor embolism that causes vessel occlusion
 - b. Marantic emboli may cause sudden stroke with hemorrhage
 - c. New onset seizures
 - d. Headache
 - e. Focal neurologic deficits
 - f. Signs of increased pressure

Neuropathology

1. Multiple hemorrhagic metastases in several vascular territories
2. Histopathological features of the metastatic lesions are slightly less differentiated than the primary tumor
3. Micro-invasion occurs at the areas of demarcation of the tumor
4. Reactive astrogliosis occurs around the metastatic nodule
5. Microglial activation is noted around areas of necrosis
6. Neovascularization
7. Vascular endothelial/pericytic proliferation

Neuroimaging

1. Hemorrhagic lesions in multiple vascular territories
2. Cerebral edema often out of proportion to the size of the metastases
3. Petechial hemorrhages in many metastatic nodules without overt hemorrhage

Laboratory Evaluation

1. Increased growth factor production including:
 - a. Vascular endothelial growth factor (VEGF)
 - b. PDGF
 - c. EGF
 - d. $TGF\alpha$
 - e. $TGF\beta$
 - f. $FGF\alpha$
 - g. $FGF\beta$

Cerebral Congophilic Angiopathy as Cause of Non-Hypertensive Hemorrhage*General Characteristics*

1. Elderly non-hypertensive patients
2. Approximately 2–9% of ICH

Clinical Manifestations

1. Recurrent ICH or SAH
2. TISA presentation (rare)
3. Focal neurologic deficits depending on location
4. Seizure (rare)

Neuropathology

1. Various mutant amyloid peptides deposited into and weakening of arteriolar walls
2. Putatively accelerated atherosclerosis
3. Lobar superficial hemorrhages
4. Cortical microhemorrhages
5. Superficial cortical siderosis
6. Sulcal SAH
7. Location of CAA lobar hematomas:
 - a. Frontal 35%
 - b. Parietal 26%
 - c. Occipital 19%
 - d. Deep central gray 4%
 - e. Cerebellum 2%

*Neuroimaging***ECHO and MRI**

1. Gradient ECHO and susceptibility weighted MRI sequences
 - a. Cortical microbleeds
 - b. Superficial siderosis

MRI

1. Sulcal SAH
2. WMH
3. Leukoariosis
4. Dilated perivascular spaces

Rare Causes of Non-Hypertensive Parenchymal and SAH

1. Vasculopathy or Vasculitis
2. Sinus thrombosis
3. Post-partum coagulopathies

*Neuropathology***The Cerebrovascular Effects of Hypertension**

1. Arteries and arterioles
 - a. Have one or more layers of smooth muscle cells (myocytes) that are contractile and regulate vascular diameter
 - b. Bind with endothelial cells
2. In capillaries
 - a. Myocytes are replaced by pericytes
3. Innervation of cerebral arteries and arterioles
 - a. Nerve fibers that arise from autonomic and sensory ganglia
 - b. Smaller arterioles ($<100\ \mu\text{m}$) and capillaries are covered by the end feet processes of astrocytes
 - c. Extraparenchymal arteries and arterioles control 2/3 of vascular resistance; intracranial arterioles and capillaries control the other third

*The Adaptive Response of the Neurovascular Unit (NVU) to Changes in the Cerebral Circulation***Functional Hyperemia**

1. Local neuronal activity increases local cerebral blood flow:
 - a. Effected by the release of vasoconstrictive agents released by neurons, astrocytes and endothelial cells that include:
 - i. Nitric oxide
 - ii. Carbon monoxide
 - iii. Prostanoids
 - iv. Adenosine
 - v. P450 metabolite
 - vi. Potassium and hydrogen ions
 - b. Cause vasodilation of local arterioles and regional pial arterioles

Cerebral Autoregulation

1. Autoregulation maintains CBF independent of changes in arterial pressure between 60–150 mm Hg
 - a. Arterioles adjust their resistance according to intravascular pressure to maintain CBF during changes in peripheral arterial pressure
 - b. Arteriole myocytes contract when intravascular pressure rises
 - i. Intravascular pressure depolarizes arterial myocytes that induce Ca^{2+} influx and vasoconstriction by:
 1. Sensitization of the smooth muscle contractile process by activation of protein kinase C (PKC) and Rho-associated protein kinase (ROCK)
 2. Hypertension shifts the pressure-flow curve to the right so that higher blood pressure is needed to maintain the same level of CBF

Structural Alteration of Blood Vessels from Hypertension

1. Exacerbates atherosclerosis in pial arteries and arterioles

2. Induces fibrinoid necrosis of penetrating arteries and arterioles that supply the deep white matter that cause lacunar infarction and hemorrhage (basal ganglia microhemorrhages)
3. Remodeling:
 - a. Hypertrophic remodeling
 - i. Smooth muscle cells undergo hyperplasia and hypertrophy that encroaches into the lumen by increasing wall thickness
 - ii. Eutrophic remodeling:
 1. Smooth muscle cells undergo rearrangement that decreases the vessel lumen without an increase in the wall thickness
 - iii. Increased collagen deposition that decreased the compliance of the vessel wall
 - iv. Mechanisms for hypertrophy include:
 1. Sympathetic perivascular innervation
 2. Increased mechanical pressure on the vascular wall that induces:
 - a. Growth factors
 - b. Oxidative stress
 - c. Nitrogen oxide production decreased
 3. Nitrogen oxide has anti-proliferative smooth muscle activity
 4. Angiotensin II (AngII)
 - a. Pivotal in mechanisms of cerebrovascular remodeling through reactive oxygen species (ROS):
 - b. ROS:
 - i. Promote DMC proliferation
 - ii. Activate matrix metalloproteases (MMP)
 - iii. Extracellular matrix proteins are important for hypertrophy, remodeling and arterial compliance
 - c. Endothelial dysfunction
 - i. Hypertension alters endothelium dependent relaxation of cerebral blood vessels
 - d. Oxidative stress:
 - i. Systemic markers of oxidative stress are increased in:
 1. Essential hypertension
 2. Renovascular hypertension
 3. Malignant hypertension
 4. Pre-eclampsia
 - ii. Experimental models demonstrate:
 1. Reactive oxygen species (ROS) production is elevated in central autonomic nuclei
 - a. Putatively play a role in the neurohumoral changes that maintain hypertension
 2. Models of ANG-II-induced hypertension
 - a. There is an increase in ROS production in large and small cerebral blood vessels
 - b. Free radical scavengers decrease the effects of hypertension on functional hyperemia and endothelial function
 - e. Reactive oxygen species (ROS):
 - i. Cerebrovascular cells may produce ROS from:
 1. Mitochondrial enzymes
 - a. Mitochondrial respiratory chain dysfunction
 2. Xanthine/xanthine oxidase
 3. Lipo-oxygenase
 4. Nitric oxide synthases (NOS) uncoupling
 - a. NOS produces superoxide rather than nitric oxide
 5. Nicotinamides adenine dinucleotide phosphate (NADPH) oxidase:
 - a. A major source of ROS that mediate cerebrovascular dysfunction
 - i. Implication in effects of Ang-II activation
 6. ROS alters vascular regulation by:
 - a. The formation of peroxynitrite (sometimes called peroxonitrite) from the reaction between nitric oxide and superoxide
 - b. Peroxynitrite:
 - i. Damages DNA
 - ii. Induces lipid peroxidation
 - iii. Alters protein function by interaction with transition metal centers, tyrosine nitration and oxidation of cysteine
 - iv. May be pivotal for Ang-II effects
 - v. The main source of nitric oxide that is responsible for peroxynitrite formation is the vascular endothelium

Neuroimaging

1. Hypertensive hemorrhages occur in specific locations. The most significant locations are:
 - a. Basal ganglia (60%)
 - i. Caudate (10%)
 - ii. Putamen
 - iii. GPi (40%)
 - b. Thalamus (20%)
 - c. Cerebellum 15%
 - d. Lobar 10%
 - e. Pontine (5%)
 - f. Midbrain (<1%)
 - g. Medulla (<1%)
2. Cortical microbleeds

3. Superficial cortical siderosis
4. Dolichoectasia
5. Lacunar infarction
6. Leukoaraiosis
7. Increased perivascular spaces

Subarachnoid Hemorrhage

Overview

Subarachnoid hemorrhage is a devastating neurologic illness that carries a mortality of 30% with each bleed and very significant mortality in survivors.

The ictus is frequently characteristic as patients suffer a severe headache that reaches maximum intensity instantly. The headache is frequently basioccipital and then shifts to frontal areas. It is associated with vomiting in a significant number of patients with attendant loss of consciousness in approximately 30–50%. The neck is stiff; patients have positive Kernig's and Brudzinski's signs and focal deficits depending on the location of the bleed. The patients' eyes are sore and photophobia is present. Seizures occur in 20% of patients. A sentinel bleed prior to the rupture of an aneurysm occurs in a significant proportion of patients. There is controversy whether enlargement of the aneurysm with stretch of the dura can cause a sentinel headache. Clearly at surgery there are often signs of hemosiderin and a prior bleed.

Familial aneurysm, polycystic kidney disease, Turner's syndrome and associated AVMs are clear clinical settings for aneurysms. Acquired aneurysms have been noted both with trauma, atrial myxoma and SBE (mycotic) on peripheral arteries. Cigarette smoking and vasculitis may predispose at the circle of Willis. The role of hypertension in causation is controversial, but not in regard to rupture. Some autopsy series have demonstrated 0.9% of patients with a congenital aneurysm. An aneurysm of 7–10 mm is the most likely to bleed. Those less than 3 mm in general do not. An infundibulum at the take off of cerebral arteries is usually less than 2 mm and do not bleed.

The use of coiling and interventional neuro-radiographic techniques has made aneurysm care much safer and successful for many patients. Unfortunately, vasospasm is still a major problem. The differential diagnosis for subarachnoid hemorrhage is wide and includes vascular malformations as well as trauma, congophilic angiopathy, hemostasis dysfunction and diseases of the blood vessel wall.

Clinical Manifestations of SAH

1. Headache
 - a. Severe: 10/10 on a visual analogue scale
 - b. Reaches maximal intensity immediately ("worst headache of my life")
 - c. Cervical-occipital location with frontal radiation; primarily C2 distribution
 - d. Lasts 4–6 weeks
 - e. Associations:
 - i. Vomiting
 - ii. Loss of consciousness 30–50%
 - iii. Pain and soreness of the neck, shoulders and upper back
 1. Absence of head pain suggests spinal AVM
 - iv. Light sensitivity
 - v. Sore eyes
 - vi. Focal motor or sensory deficits depending upon the etiology of the bleed
 - vii. Seizures in 20%
2. Decreased level of consciousness
3. Vomiting: 30–50% of patients
4. Restlessness

Differential Diagnosis of SAH

1. Ruptured aneurysm
2. Arteriovenous malformation
3. Cavernous angioma
4. Congophilic angiopathy
5. Capillary, telangiectasia (very rare)
6. Dural arteriovenous malformation
7. Venous infarctions with hemorrhage
8. Sinus thrombosis
9. Head injury
10. Hemorrhagic metastasis
11. ICH with subarachnoid extension
12. Coagulopathies
13. Hemophilia
14. Amphetamines; cocaine; other sympathomimetic drugs
15. Migraine (extremely rare)
16. Intracranial arterial dissection

Specific Vascular Malformations

Congenital Aneurysms

General Characteristics

1. 0.9–6% of the general populations may have a congenital aneurysm autopsy series
2. 3.6% prospective autopsy series
3. 3.7% in retrospective angiography series
4. 6.0% in prospective angiography series in those undergoing arteriography

Incidentally Discovered Aneurysms by Artery

1. Internal carotid – post-communicating artery – 64%
 - a. Internal carotid ophthalmic artery 19.9%
 - b. IC – anterior choroidal – 12.8%
 - c. IC – cavernous portion – 10%
2. Anterior communicating artery – 12.2%
3. Middle cerebral artery – 6.3%
4. Basilar artery (rare)
5. PICA – vertebral (rare)
6. AICA – basilar (rare)

Meta-Analysis of 23 Studies of Prevalence

1. 0.4% in retrospective autopsy series

Incidence of Unruptured Aneurysms by Age

1. 1.1%: 0–29 years of age
2. 3–5%: 40–49 years of age
3. 5.7%: 50–59 years of age
4. 7.4%: 60–69 years of age
5. 6.1%: 70–79 years of age
6. 9.3%: 80–89 years of age
7. 37.5%: >90 years of age

Natural History of Unruptured Aneurysms

1. 1.4% annual rate of rupture; other studies 3% bleed/year (untreated)
2. 10% have ruptured at 10 years; 20% at 20 years and 32% at 30 years
3. Multiple Aneurysms
 - a. Risk of rupture universally proportional to age
4. Aneurysmal growth is not associated with:
 - a. Sex
 - b. Blood pressure
 - c. Patient's age
 - d. Initial size
5. Associations with Hereditary Diseases of Collagen
 - a. Ehlers–Danlos (type IV; COL 1A gene, type III collagen)
 - b. Pseudoxanthoma elasticum (COL2A gene)
 - c. Marfan's syndrome
 - d. Osteogenesis imperfecta
 - e. Polycystic kidney disease (PKD gene chromosome 12)
 - f. Tuberous sclerosis
 - g. Neurofibromatosis I (chromosome 17)
 - h. Fibromuscular dysplasia (FMD)

Associated Other Diseases

1. Coarctation of the aorta
2. Congenital anomalous blood vessels
3. Arteriovenous malformation (arteries feeding the malformation)
4. Moyamoya syndrome
5. Takayasu syndrome

Familial Aggregation of Congenital Aneurysms

1. 7–10% of patients with aneurysmal rupture have first or second degree relatives with an aneurysm
2. Among first degree relatives of those with ruptured aneurysms risk of SAH is four times that of the population at large
3. Risk highest among siblings of the index patient
4. Most families have 2–3 members that are affected if there is familial aggregation
5. Inheritance patterns are unclear; autosomal dominant most probable

Incidence of SAH with Aneurysms

1. 1/10,000 people
2. At risk for development of new aneurysm (after rupture of the first)

3. Each year: new aneurysms develop in 2% of patients with previously ruptured aneurysms, this group ruptures at an incidence of 6/10,000 in the general population
4. Morbidity and mortality
 - a. 12% die prior to medical attention
 - b. 40% die in the hospital within 1 month after the ictus
 - c. 1/3 of survivors suffer major neurologic deficits

*Clinical Manifestations***Associated Clinical Features of Aneurysms with Underlying Collagen Defects**

1. They are in typical locations
2. Bilateral
3. Associated with enlarged tortuous extracranial vessels
4. Occur at supra clinoid level
5. Associated with A-V fistulas
6. Associated with dural ectasia

Familial Aneurysms

1. Rupture at an earlier age than sporadic aneurysms
2. Smaller when they rupture
3. More often followed by the formation of new aneurysms

Multiple Aneurysms

1. Usually 2–3 in patients
2. Occur in 20–30% of patients
3. Rarely > 10
4. Occur with AVMs and other associated congenital anomalies of blood vessels

Factors Influencing Aneurysmal Rupture

1. Risk of rupture 1.9–3%/year
2. Aneurysms of <10 mm 0.7% rupture/year; usual size 7–10 mm at rupture
3. Aneurysms > 10 mm 5.5% risk of rupture
4. Risk of rupture > in women than men
5. Incidentally found aneurysms lower risk of rupture than those found in addition to one that has ruptured
6. Aneurysmal SAH; male > female
 - a. Premenopausal female low risk of rupture
 - b. Postmenopausal female with hormone replacement (intermediate risk)
 - c. Postmenopausal female without hormone replacement (highest risk)
 - d. Alcohol consumption
7. Cigarette smoking; 3–10× greater risk of aneurysm than nonsmoker
 - a. Smoking increases chance of developing a new aneurysm
 - b. Decreases alpha antitrypsin (inhibits proteases)
 - c. Inherited decrease of alpha antitrypsin causes increased risk of aneurysms
8. ADPKC disease (autosomal dominant polycystic kidney disease) 4.4% (2.7–7.2%) chance of aneurysm

- a. 9% risk in first degree relatives if 2 or more members have aneurysms
- b. Life time risk for SAH in persons with an affected first degree relative is 1% at age 50; 2% at age 70
9. Familial predisposition 4.0% (2.7–6%)
10. Atherosclerosis 2.3%
11. 8% of aneurysms detected >8 mm in size
12. Incidence of rupture increases after the third decade; average age of rupture is fifty years of age, increases with age until 80
 - a. Female > male risk of rupture after 40
 - b. Male > female risk of rupture < 40
 - i. Anterior communicating aneurysms female > male
13. 75% of unruptured aneurysms <10 mm; 80% < than 6 mm
 - a. Median time from diagnosis of unruptured aneurysms to rupture <2 years
 - b. Linear association of risk of rupture with increasing size
14. Younger patients at greater risk of rupture in the setting of multiple aneurysms
15. Aneurysms that were followed and found to have ruptured had grown in size
16. Multiple aneurysms female > males
17. Setting of hypertension
 - a. Rupture more common in older patients
 - b. Hemiparesis, hemihypesthesia, and hemianopsia have been described in:
 - i. 6–25% of unruptured aneurysms
- b. Minute tear of the aneurysm
 - i. Sudden onset: “thunderclap” headache
- c. Maximum intensity instantly
- d. Resolves in 48 hours usually, but may last for weeks
- e. Radiation to shoulder, neck and back, “flu-like” symptoms (with SAH)
2. 50% of patients lose consciousness or are stunned
3. Photophobia
4. 30–50% have suffered a sentinel headache days to weeks prior to the rupture
5. Neck stiffness
 - a. Kernig’s sign
 - b. Brudzinski’s sign
6. Subhyaloid hemorrhage (Torsten’s syndrome) of the retina
 - a. Side of the ruptured aneurysm (if there are multiple); sudden increased ICP with rupture of the preretinal veins
 - b. Shoulder, back or sciatic pain (associated)
 - c. Pain across the shoulders with “flu-like” symptoms (associated)
7. <5% pain is limited to the low back or neck without headache
8. Lethargy; inability to follow four part commands or perform visual praxis
9. Sore eyes to movement or palpation
10. Focal neurologic signs dependent on the specific aneurysm
11. Seizures may occur primarily with MCA and ACA aneurysms
12. A proportion have no neurologic signs but suffer meningeal irritation and altered mentation

Precipitating Factors Associated with Rupture

1. Valsalva maneuvers
2. Pregnancy (release of elastases)
3. Sleep (30% rupture during sleep)
4. Extreme sudden hypertension (amphetamines; cocaine, PPA)
5. Weight lifting
6. Coitus
7. Defecation
8. 30% rupture during normal activity

Neuropathology

The Defect Underlying Aneurysm Formation

1. Occur at branch points of arteries of the Circle of Willis
2. Decrease of type III collagen
3. Defect of the arterial media and localized loss of muscular elements
4. Loss or breakage of the internal elastic membrane

Clinical Presentation of SAH from a Ruptured Aneurysm

Clinical Manifestations

Severe Headache

1. Sentinel hemorrhage
 - a. Occurs in at least 30% of aneurysmal SAH

Specific Clinical Presentation of Congenital Aneurysms

P-COM (Posterior Communicating Carotid)

1. Pain in or behind the affected eye
2. Slowly reactive, oval or paralyzed pupil
 - a. Pressure sensitive parasympathetic fibers affected early or
 - b. Parasympathetic fibers localized to outer area 12–3 o’clock of the IIIrd nerve and are compressed early
3. Partial ptosis (lampshade ptosis secondary to infarction of the IIIrd nerve from medical diseases)
4. CT: Blood in the suprachiasmatic cisterns
 - a. Localized to the side of the bleed

A-COM Artery Complex (Anterior Communicating Artery Complex)

1. Mental status changes
 - a. Acutely: agitation (with no or minimal motor or sensory signs)
 - b. Several days following the ictus:
 - i. Abulia
 - ii. Akinetic mutism
 - iii. Amnesia

- iv. Decrease of executive function
- c. Slight contralateral leg weakness and sensory loss
- d. Dominant hemisphere
 - i. Broca's type aphasia (SMA involvement)
- 2. CT/MRI evaluation
 - a. Blood in medial frontal lobe
 - b. Intrahemispheric fissure anteriorly and extending posteriorly
 - c. Widening of A-Com

Middle Cerebral Artery Trifurcation Aneurysm

Clinical Manifestations

- 1. Anterior temporal headache
- 2. Contralateral hemiparesis and hemisensory defect
 - a. Embolus from giant aneurysm
 - b. Vasoconstriction
 - c. Mass effect from hematoma following rupture
- 3. Rare seizure (compression or irritation of the cortex)
- 4. Aphasia (DH)
- 5. Weakness arm and face > leg

Neuroimaging

- 1. Aneurysm may be > 2 cm (giant Aneurysm)
- 2. Large amount of blood in Sylvian fissure, vasoconstriction of MCA

Internal Carotid Artery Aneurysm

Clinical Manifestations

- 1. Pain behind the eye
- 2. Ptosis (partial) and pupillary paresis
- 3. Rare complete IIIrd nerve palsy
- 4. Contralateral hemiparesis and hemisensory deficits
- 5. Nasal visual field deficit
 - a. Homonymous
 - b. Compression of the lateral chiasm

Neuroimaging

- 1. MRI
- 2. May have giant aneurysm > 1 cm
- 3. MRI signals within the aneurysm may allow estimation of blood flow within the lesion

Ophthalmic Artery Aneurysm

Clinical Manifestations

- 1. Pain in or behind the eye
- 2. Painless loss of central vision
- 3. Rare bitemporal VF deficit
- 4. Chiasmatic syndrome (anterior)

Neuroimaging

- 1. May compress the optic nerve and chiasm

Anterior Choroidal Artery Aneurysm

Clinical Manifestations

- 1. Contralateral hemiparesis
- 2. Contralateral hemisensory defect

- 3. Central sector VF deficit
- 4. Transient focal ischemia of the internal capsule
- 5. Limb shaking (ischemia of internal capsule)
- 6. Tonic spasm (ischemia of internal capsule)
- 7. Rupture with:
 - a. Intracranial or intraventricular hemorrhage

Neuroimaging

- 1. Aneurysm may arise from the ICA adjacent to the AchA
- 2. May arise from the origin of the artery

Posterior Circulation Congenital Aneurysm

Clinical Manifestations

- 1. Vertebral Artery Aneurysm
 - a. PICA symptoms
 - b. Anterior spinal artery symptoms (VA-ASA)
 - i. Hemiparesis
 - ii. Proprioception and vibration loss
 - iii. Pain in the side of the neck
 - iv. Rarely pain radiates to lateral eyebrow
 - v. Acute blood in the IVth ventricle

Neuroimaging

- 1. Origin is close to the basilar artery
- 2. Dissecting aneurysms of the intracranial vertebral artery occurs in approximately 20% of VA aneurysms
- 3. Fusiform dilation of proximal and/or distal narrowing of the affected artery

PICA-Vertebral Artery Aneurysm

Clinical Manifestations

- 1. Dysphagia and hoarseness
- 2. Lateral pulsion (ipsilateral side)
- 3. Inability to stand
- 4. Nausea and vomiting
- 5. Pain in the basiocciput; lateral eyebrow or side of the face
- 6. Crossed hemisensory loss to pain and temperature
- 7. Oscillopsia
- 8. Acute rotary nystagmus (greatest ipsilaterally)
- 9. Ipsilateral Horner's syndrome
- 10. Blood in the IVth ventricle and the posterior fossa

Neuroimaging

- 1. Large proportion arise from the PICA branching sites

AICA-Basilar Artery Aneurysm

Clinical Manifestations

- 1. Sudden hearing loss or tinnitus
- 2. Peripheral ipsilateral facial weakness
- 3. Ipsilateral pain in the face
- 4. Contralateral pain and temperature loss (below the clavicle)
- 5. Contralateral hemiparesis
- 6. Blood in the posterior fossa

Neuroimaging

- 1. Blood in the IVth ventricle and posterior fossa

2. Usually at the junction with the basilar artery
3. Most project laterally; a small percentage are against the clivus

Superior Cerebellar-Basilar Artery Aneurysm

Clinical Manifestations

1. IIIrd nerve palsy
2. Ipsilateral dysmetria
3. Dysarthria
4. Blood in the perimesencephalic cistern

Neuroimaging

1. Blood in the perimesencephalic cisterns
2. A significant portion have other aneurysms associated
3. Mean size of 7.3 mm
4. At the basilar junction

Top of the Basilar-PCA Bifurcation

Clinical Manifestations

1. Pain in the back of the neck or basiocciput
2. IIIrd nerve palsy (peduncular)
3. Visual field deficit (embolus to PCA)
4. Hemiparesis or quadriparesis (emboli or pressure on the cerebral peduncles)
5. Movement disorder (emboli or vasoconstriction of the thalamoperforate artery)
6. Thalamic sensory deficit (emboli or vasoconstriction of the thalamogeniculate artery)
7. Blood in the perimesencephalic cisterns; intrapeduncular blood

Neuroimaging

1. Blood in the perimesencephalic and intrapeduncular arteries
2. Top of the basilar is a site of giant aneurysms

PCA-PI (Posterior Communicating Artery)

1. Similar to top of the basilar-PCA aneurysm

Specific Clinical Signs Denoting Specific Aneurysms

1. Giant MCA aneurysm
 - a. Seizure (focal motor)
 - b. Hemiparesis
 - c. Dysphasia
2. IIIrd nerve compression
 - a. AICA
 - b. ICA (hemiparesis often associated)
 - c. P-COM
 - d. Superior cerebellar artery
3. Isolated VIth nerve following aneurysmal SAH
 - a. Blood
 - b. Increased intracranial pressure
4. Cavernous sinus aneurysm
 - a. VIth nerve first sign
 - b. Severe Vth nerve facial pain
 - c. Late: IIIrd, IVth, VIth

5. Basilar tip
 - a. Forward pointing
 - i. Destroys the pituitary (endocrine failure)
 - ii. Visual field deficits
 - b. Vertical pointing
 - i. IIIrd, IVth nerve
 - ii. Compresses the IIIrd ventricle

Rare Clinical Signs of Aneurysms

1. Transient neurologic signs:
 - a. Ischemia of the parent vessel
 - b. Embolization:
 - i. Usually from giant aneurysms
 - ii. Cause strokes in the affected territory
2. Torsten's syndrome
 - a. Subhyaloid hemorrhage (preretinal)
 - b. Hemorrhage is moveable with changing head positions
 - c. Due to sudden increased pressure
 - d. Occurs on the side of the ruptured aneurysm (20% of patients harbor two or more aneurysms)
 - e. Secondary to rupture of a preretinal vein
3. Prognosis of SAH from an aneurysm is better if no aneurysm is demonstrated

Radiological Features of an Aneurysm That Has Ruptured if More than One Is Present by Arteriography

1. The largest aneurysm most often has bled
 - a. Most commonly between 7–10 mm
 - b. Giant aneurysm usually do not bleed
2. Aneurysm with the most excrescences
3. Local vasospasm
4. Local hemorrhage or hematoma

Aneurysmal Rebleeding

Clinical Manifestations

1. Sudden abrupt severe headache
2. Meningismus
3. Focal signs secondary to early hemorrhage
4. Late
 - a. Vasospasm of the parent vessel with focal expected signs and symptoms
5. Associated ICH leads to rapid coma
6. Aneurysms that cause neurologic symptoms rupture at a higher rate
 - a. 15% of rebleeding within 6 months
7. Fewer rebleeds in patients with Hunt grades I and II
8. Time of Aneurysmal rebleeding
 - a. 0.8–4% rebleed the first 24 hours
 - b. 20% rebleed the first 2 weeks
 - c. 30% rebleed by the end of the first month
 - d. 40% by the end of 6 months
 - e. >6 months 3%/year
9. Vasospasm concurrent with rebleeding
 - a. Occurs from day 3–5
 - b. Peaks between days 5–9

- c. Resolves after the second week
- d. Directly related to the amount of blood surrounding the artery
- e. Configuration of the arteries
 - i. Focal vasoconstriction approximate to area of the bleed
 - ii. Diffuse vasoconstriction of the artery
- f. Lumen of the affected artery <0.5 mm
- g. May occur at a distance from the rupture
- 10. Early clinical signs of vasospasm
 - a. Tachycardia
 - b. EKG changes
 - i. Inverted T-waves in leads V3–V6
 - ii. ST depression or elevation without q waves
 - iii. Atrial and ventricular arrhythmia
 - c. Decreased level of consciousness
 - d. Deficits corresponding to the affected artery
- 11. Early clinical signs of hydrocephalus
 - a. Decreased spontaneity
 - b. Constant headache (often frontal)
 - c. Lethargy
 - d. Incontinence
 - e. Increased reflexes legs > arms

Medical Complications of Aneurysmal Subarachnoid Hemorrhage

General Characteristics

1. Seen at 3 months
 - a. Symptomatic vasospasm – 46%
 - b. Rebleeding 7%
 - c. Total mortality 19%
2. Frequency of at least one severe (life threatening) medical complication
 - a. 40%
 - b. Death from medical complications 23% (of those that die)
 - i. Rebleeding 22% of these deaths
 - c. Vasospasm with stroke 23%

Cardiac Arrhythmia

1. 50% have an abnormal admission EKG
2. 25% have ST segment or T wave abnormalities
3. 15% have prolonged QT interval associated with at least one episode of moderate or severe arrhythmia
4. 35% of all aneurysms have one episode of cardiac arrhythmia on day 0–14; 66% of these are mild; 29% moderate and 5% are severe
5. Onset of arrhythmias usually first 7 days (peak day 2–3)
6. 17% of patients suffer moderate or severe arrhythmia on the day of rupture
7. Cardiac arrhythmia on the day after surgery
 - a. Life threatening 5% of patients
 - b. Less serious 30% of patients
8. Moderate arrhythmias
 - a. Sinus bradycardia

- b. Sinus tachycardia
- c. Atrial extrasystole
- d. Atrial fibrillation
- 9. Severe arrhythmia
 - a. Asystole
 - b. Ventricular tachycardia
 - c. Atrial fibrillation with hypotension
 - d. AV block
 - e. Supraventricular tachycardia
 - f. Ventricular extrasystole
- 10. EKG changes with SAH
 - a. ST depression or elevation without q waves
 - b. Deeply inverted T-waves (Pardee T-waves) V3–V6
 - c. U waves
 - d. Hyperpolarized T-waves
 - e. Pathogenesis
 - i. Myocytolysis
 1. Contraction band necrosis
 2. Myofibrillar degeneration
 3. Effects of increased sympathetic discharge

Pulmonary Edema

1. Occurs in 6% of patients (day 3 to 7)
2. Probable sudden increase in ICP
3. Water and electrolyte disturbance
4. Particularly with anterior communicating artery aneurysms
5. Increase of atrial natriuretic factor
6. Discharge of substance P containing afferents in lung capillaries

Hepatic Dysfunction

1. Occurs in 7% of patients
2. Usually 24% of patients have mild enzyme abnormalities
3. 4% severe hepatic impairment

Renal Dysfunction

1. Occurs in 7% of patients
2. 1.2% severe life threatening renal failure

Thrombocytopenia

1. Occurs in 4% of patients
 - a. Usually associated with sepsis

Sensitivity of Computed Tomography in Detecting SAH

1. Sensitivity of new generation CT scans for patients screened <24 hours from the ictus is 93%
2. Sensitivity of new generation CT scans in patients after 24 hours from the ictus is 90%
3. L.P. remains the gold standard to rule out SAH

Giant Aneurysms > 2 Centimeters

General Characteristics

1. Do bleed but rarely
2. Symptoms are caused by:
 - a. Pressure on local structures

- b. Emboli distally
- c. Seizure activity
- d. Endocrine dysfunction (erosion into the pituitary)

Clinical Manifestation

Giant Carotid Aneurysm

- 1. Pain behind or around the eye
- 2. May erode into the pituitary with endocrine failure
- 3. Compression of the optic chiasm with nasal VF deficit or chiasmal syndrome
- 4. IIIrd nerve palsy

Middle Cerebral Artery Giant Aneurysm

- 1. Anterior temporal or retroauricular headache
- 2. Seizure activity
- 3. Contralateral hemiparesis

Top of the Basilar Giant Aneurysm

- 1. Occipital headache
- 2. IIIrd, IVth nerve palsy (if extends dorsally)
- 3. Compression or invasion of the III ventricle
- 4. May cause obstructive hydrocephalus
- 5. Associated with emboli to the posterior cerebral artery territories with VF deficits
- 6. Hemiparesis (compression of the cerebral peduncle)

Acquired Aneurysms

General Characteristics

- 1. Peripheral arterial location (not at the Circle of Willis)
- 2. May be multiple on superficial conducting vessels
- 3. Cause of peripheral lobar hemorrhage

Differential Diagnosis

- 1. Fusiform
 - a. Secondary to hypertension
 - b. Dolichoectasia
 - c. Primarily Vertebrobasilar system
- 2. Subacute bacterial endocarditis
- 3. Trauma
- 4. Atrial myxoma
- 5. Collagen vascular disease
- 6. Cigarette smoking (women > men)

Basilar Fusiform Aneurysm

Clinical Manifestations

- 1. Occurs in elderly hypertensive patients with associated atherosclerosis
- 2. Dysarthria (pontine compression)
- 3. Hydrocephalus (blocks ventral CSF pathways)
- 4. Spastic gait (pressure on ventral pontine motor fibers)
- 5. XIIth nerve palsy (dysarthria)
- 6. Spastic quadriparesis (ventral pontine compression)

Closed Head Injury

- 1. Aneurysms of superficial subarachnoid conducting vessels

- 2. Rarely basilar artery is traumatized after cervical or basilar skull fracture with aneurysmal formation
- 3. May be multiple

Atrial Myxoma

Clinical Manifestations

- 1. Multiple peripheral aneurysms
- 2. MCA territory most common distribution
- 3. Myxomatous emboli may grow through the wall of the blood vessel

Traumatic Peripheral Carotid Artery Aneurysm (Pharyngeal Portion)

Clinical Manifestations

- 1. Knife or gunshot wound to the neck
- 2. Sympathetic ocular paralysis (complete Horner's syndrome)
- 3. Abnormal neck pulsation
- 4. Embolization in carotid territory
- 5. Pain in the side of the face
- 6. Carotodynia (pain in the artery itself)
- 7. Associated connective tissue disease:
 - a. Ehlers-Danlos type IV and VI
 - b. Marfan's disease
 - c. COLIA gene mutations
 - d. Fibromuscular dysplasia
 - e. May be bilateral

Traumatic Vertebral Artery Peripheral Aneurysm

Clinical Manifestations

- 1. Trauma to the neck
 - a. Often minimal and unrecognized when it occurs
- 2. Pain in the posterior or side of the neck
 - a. Mastoid pain
 - b. Occipital headache
- 3. Chiropractic manipulation (horizontal C2 portion most vulnerable)
- 4. Congenital connective tissue disorders (particularly if bilateral)
- 5. Signs and symptoms:
 - a. Distribution of the vertebral or basilar artery
 - b. Due to emboli at the site of the vessel tear
 - c. Rarely flow limiting pathogenesis for signs and symptoms
- 6. Cancer or cancer treatment (surgical trauma)

Subacute Bacterial Endocarditis

Clinical Manifestations

- 1. May be multiple
- 2. MCA territory most frequent locations
- 3. Hemorrhage is common
 - a. Cause of peripheral ICH
 - b. May be delayed after successful antibiotic treatment (destruction of the vessel wall)
- 4. Seizures are common

5. Focal motor deficits: the symptomatology depends on location
6. Streptococcus viridans; gram negative organisms most common
7. Following dental work
8. In association with deformed valves
 - a. Congenital bicuspid calcified valves
 - b. Rheumatic fever deformed valves
 - c. Rarely mitral valve prolapse

Differential Diagnosis of Subarachnoid Hemorrhage Without Detectable Aneurysm

General Characteristics

1. 15–20% of spontaneous SAH no aneurysm is detected by 4 vessel arteriography
2. There is a better prognosis in these patients than in those in which an aneurysm is found

Diseases

1. Idiopathic perimesencephalic hemorrhage
2. Venous trauma
3. Diffuse or anteriorly located hemorrhage in the basal cisterns
4. Incomplete visualization of the posterior circulation
5. Occult aneurysm
6. Carotid artery dissection
7. Vertebral artery dissection
8. Dural arteriovenous malformation
9. Spinal AVM
10. Parenchymal trauma
11. Mycotic aneurysm
12. Cocaine abuse (and other sympathomimetic drugs)
13. Sickle cell disease
14. Coagulopathies
15. Subarachnoid blood in the basal cisterns
 - a. Pituitary apoplexy
 - b. Cervical tumor
 - c. Rupture of circumferential artery (penetrators) in the pontine cisterns
 - d. Trauma
 - e. Mycotic aneurysm
 - f. Coagulopathies (rare)
 - g. Cocaine or sympathomimetic drug abuse

Idiopathic Perimesencephalic Hemorrhage

1. Approximately 10% of all SAH
2. Comprise 2/3 of patients with normal arteriograms
3. Occur in older patients (>6th decade)
4. Few patients with HCVD
5. Rarely concomitant with congenital aneurysm
6. 1/3 have history of strenuous exercise prior to the bleed
7. Headache reaches maximum intensity within minutes rather than seconds
8. No loss of consciousness with the ictus
9. No focal neurological deficits

10. No rebleeding or delayed ischemia
11. Normal on admission other than headache
12. 20% have hydrocephalus with no other clinical deficits
13. Excellent prognosis
14. Some evidence of capillary bleed as cause

Venous Trauma

1. Shearing head injury
2. Blood most often seen in the posterior part of the cisterna ambiens (superior cerebellar-quadrigenal cisterns) at the level of the tentorium
3. Vein is torn against the tentorium

Diffuse or Anteriorly Located Hemorrhage with Rupture into the Basal Cisterns

1. Patients are lethargic to stuporous
2. Focal neurologic deficits are present
3. Symptomatic hydrocephalus
4. Nidus of bleeding medial frontal lobe
 - a. Blood dissects into the interhemispheric fissure
 - b. May rebleed
5. Deterioration from associated ischemia

Incomplete Visualization of the Posterior Circulation

1. Ruptured aneurysm of the posterior circulation is suspected from the early CT scan
2. 85% of patients demonstrate blood in the IVth ventricle and to a lesser extent the IIIrd and lateral ventricles
3. IVH is the only abnormality on CT scan in 25% of posterior circulation aneurysms
4. Subarachnoid blood is noted in the midbrain cisterns with spread to the anterior basal cisterns

Occult Aneurysm

1. Approximately 20% of aneurysms are detected on the second arteriogram (after 2 weeks; vasospasm has cleared)
2. Aneurysmal rupture is likely if there is blood in the Sylvian or interhemispheric fissure

Carotid Artery Dissection

1. Rare cause of SAH
2. Clinical features:
 - a. Severe neck pain; subacute or acute onset
 - b. Facial pain
 - c. Oculosympathetic paralysis
 - d. MCA or carotid embolic stroke
 - e. May be associated with depressed level of consciousness
 - f. Rebleeding may occur within hours of the initial hemorrhage

Vertebral Artery Dissection

1. Autopsy series – comprises 4% of patients who died from SAH
2. Primarily middle aged patients

3. 1/3 have HCVD
4. Occurs after severe rotational neck movement or minor trauma
 - a. Patient may be going to a chiropractor because he has neck pain from the dissection; further manipulation exacerbates the dissection
5. Rarely associated with lower cranial nerve palsies; symptoms from occlusion or embolus of the PICA
6. May be bilateral if the cause is an underlying collagen defect
7. Rebleed occurs in 30% of patients; may occur within hours of the initial hemorrhage

Anticoagulation with Warfarin or Heparin

Risk Factors for ICH or Systemic Bleeding

1. Prolongation of prothrombin time beyond the therapeutic range
 - a. Hemorrhages occur occasionally in the therapeutic range
2. Large size of infarcted area (ischemic stroke)
3. Uncontrolled hypertension
4. Age related (relative risk); primarily for subdural hematoma

Clinical Features

1. Gradual and insidious onset
 - a. Hours to days
2. Predilection for the cerebellum with INR > 5
3. High morbidity and mortality

Patients Requiring Long Term Anticoagulation After Bleed; Reinstitution of Rx

1. 10–14 days possibly safe; 2–3 weeks heparin or warfarin probably safe
2. First year of anticoagulation most dangerous

Neuroimaging

MRI Evaluation

1. Inhomogeneous infarction mixed signal on T2-weighted images suggest acute bleeding and clots

Primary Tumors That Hemorrhage

1. Glioblastoma multiforme
 - a. In general petechial hemorrhage
 - b. Bleeding and edema may be initiated by minimal trauma
2. Pituitary apoplexy
 - a. Most often MRI demonstrates blood confined to the pituitary
3. Bleeding into tumors account for 5–10% of ICH
4. 1% of tumors bleed
5. Hemorrhagic metastatic tumors
 - a. Melanoma
 - b. Choriocarcinoma
 - c. Papillary Ca of the thyroid
 - d. Bronchogenic Ca
6. Tumors that bleed are overwhelmingly malignant

Clinical Characteristics Suggesting ICH Is Secondary to a Tumor

1. Underlying systemic cancer
2. Focal symptoms prior to hemorrhage
3. Unusual site:
 - a. Corpus callosum (glioma)
4. Multiple simultaneous hemorrhages

Bleeding Diathesis

General Characteristics

1. Platelet abnormalities
 - a. Associated with petechial hemorrhage in the lower extremities
 - b. Bleeding from the gums
 - c. Vaginal bleeding prior to cerebral hemorrhage may occur
 - i. Platelets < 30,000/mm³
 - d. Hemorrhage starts at <30–40 thousand/mm³
2. Waldenström's macroglobulinemia
 - a. Associated abnormalities of platelets with lower extremity petechiae
 - b. Bleeding from mucous membranes
3. Disseminated intravascular coagulation
 - a. Associated bleeding from all former venous puncture sites
 - b. Acrocyanosis
4. Hemophilias
 - a. Joint involvement
 - b. Associated subdural hematoma
 - c. Internal bleeding
 - d. Bleeding may develop gradually
 - e. Recurrent ICH less likely after 14 days
5. Liver transplantation

Differential Diagnosis of Coagulopathies

1. Coagulopathies (inherited and acquired)
2. Anticoagulation (INR > 5)
3. Thrombolytic treatment (TPA; urokinase)
4. Connective tissue disease
5. Sickle cell disease

Specific Diseases of Blood Vessels That Hemorrhage

1. Cerebral amyloid angiopathy
 - a. Autosomal dominant (Icelandic; Dutch variants)
 - b. Sporadic; incidence increases with age
 - c. Concomitant Alzheimer's disease and variants
2. Granulomatous angitis of the CNS
3. Lymphomatous granulomatosis
4. Benign appearing immunoproliferative vasculitis
5. Angiocentric lymphoma
6. Periarteritis nodosa
7. SLE (with and without lupus anticoagulant)
8. Connective tissue diseases
9. Sickle cell disease
 - a. 30% of sickle cell disease SAH occur in children

- b. Blood is in the superficial sulci
- c. Mechanisms
 - i. Distal branch occlusions
 - ii. Collateral leptomeningeal vessels
 - iii. Moyamoya disease (bilateral carotid occlusion)
- d. Adult patients may have:
 - i. Underlying aneurysm
 - ii. Blood in the basal cisterns

Thrombolysis Related Intracranial Hemorrhage

General Characteristics

1. Hemorrhages are large (approximate mean of 70 ml)
2. Solitary in 66%
3. Lobar 77%
4. Confluent 80%
5. Intraparenchymal 80%
6. Mortality 44–83%
7. Increased risk of subdural hematoma

Clinical Manifestations

1. 2/3 of hemorrhages are supratentorial and solitary
2. 1/3 subtentorial or multifocal
3. Perihemorrhage edema is minimal
 - a. Less in those hemorrhages with a blood fluid level
 - b. Mottling and a blood fluid level is indicative of continuing fibrinolysis

Thrombolysis Induced Hemorrhage Occur in 6% of Treated Patients

1. 7% may be asymptomatic; noted on follow-up CT scan
2. Main comorbidities associated with ICH:
 - a. History of diabetes mellitus and cardiac disease
 - b. Use of antiplatelet agents other than ASA prior to stroke related hemorrhage
 - c. Elevated pretreatment blood pressure
 - d. Age
3. Criteria that utilized CT findings and laboratory findings that predicts ICH thrombolysis after:
 - a. Ischemic changes on CT exceeding 1/3 of the MCA territory
 - b. Diabetes
 - c. Elevated serum glucose
 - d. Low platelet counts
4. Pretreatment diffusion-weighted MRI parameters and laboratory values predictive of ICH after thrombolysis
 - a. High systolic blood pressure
 - b. Severity of the stroke
 - c. Elevated serum glucose
 - d. Volume of initial DWI lesion
 - e. Voxels with decreased ADC value
5. Predictive CT findings for thrombolytic hemorrhage:
 - a. Large arterial territory involved
 - b. Obscuration of caudate nucleus (head)
 - c. Loss of the insular stripe
 - d. Sulcal effacement

Hemorrhage After an Acute Ischemic Stroke

1. All ischemic infarctions have petechial hemorrhages microscopically
2. Hemorrhagic transformation determinants:
 - a. Hypertension
 - b. Size of the ischemic area
 - c. Age of the patient
 - d. Embolic > thrombotic stroke
 - e. Endothelial cells of blood vessels are sensitive to hypoxia
3. Unfavorable prognostic signs
 - a. Intraparenchymal hemorrhage
 - b. Extraparenchymal bleeding (often occurs after streptokinase)
 - c. Cerebral edema
 - d. Size of the hematoma
 - i. Increased cerebral edema
 - e. Hemorrhagic transformation of an ischemic stroke has a better prognosis than a hematoma in ICH

Recurrent Intracerebral Hemorrhage

1. 1.8–5% of patients in Asia
2. 2–24% of European patients
3. 6% of ICH are recurrent in the USA; 2.4%/year for primary ICH
4. Mean age is 64.7 years
5. Interval between bleeds is 48 months
6. Recurrent hemorrhages occur at different locations
7. Patterns of recurrences
 - a. Basal ganglionic in hypertensive patients
 - b. Lobar in patients with congophilic angiopathy
8. Younger age and lobar hemorrhage increase the risk of recurrence of ICH
9. Recurrent ICH
 - a. Poor prognosis
 - b. Severe cognitive deficits
 - c. Risk is 4× higher in lobar hemorrhage

Post-Partum Cerebral Angiopathy

1. Cause of recurrent intracerebral hemorrhage in young women
2. Usually a vasospastic process
3. Usually benign and non-relapsing
4. Several intracranial vessels involved; often bilaterally
5. Similarities to benign isolated CNS angiitis:
 - a. Young women
 - b. Headache, seizures, neurologic deficits
 - c. Angiogram consistent with vasospasm

Differential Diagnosis of Multiple ICH

1. Underlying malignancy
2. Hypertension
3. Coagulopathies
4. Subacute bacterial endocarditis
5. Vasculitis of collagen disease
6. Congophilic angiopathy

7. Venous sinus occlusion
8. Multiple cardiac emboli
9. Artery to artery emboli
10. Multiple hemorrhages from thrombolysis therapy (after myocardial infarction)

Multiple Hemorrhages from Thrombolysis Therapy (After Myocardial Infarction)

1. Multiple hemorrhages are unusual in spontaneous ICH
2. Multiple hemorrhages occur earlier than solitary hemorrhages after thrombolytic therapy
3. Multiple hemorrhages
 - a. 0.47% for streptokinase (CSK) with sc. heparin
 - b. 0.57% for SK with iv heparin
 - c. 0.7% accelerated TPA with iv heparin
 - d. 0.95% for SK with both accelerated TPA and intravenous heparin
4. Time from thrombolytic treatment to ICH
 - a. Streptokinase – 17.5 hours
 - b. TPA – 10 hours
 - c. TPA + SK – 13 hours
5. Factors associated with increased risk of hemorrhage after thrombolysis for MI
 - a. Age
 - b. Congophilic angiopathy
 - c. Facial and head trauma
 - i. Risk increases if syncope had occurred <2 days prior to treatment

Clinical Manifestations of Aneurysm

Intracerebral Hemorrhage

General Characteristics

1. Significant parenchymal hemorrhage occurs in approximately 40% of patients
 - a. Associated with SAH
 - b. Origin most often is ruptured aneurysm
 - i. Temporal or frontal lobe hemorrhage whose origin appears in the Sylvian fissure
 1. MCA aneurysm
 - ii. Deep frontal hemorrhage that suggests top of the carotid bifurcation
 1. Ruptured carotid bifurcation aneurysm
 - iii. Basal frontal hemorrhage that extends to anterior communicating area
 1. A-Com Aneurysm rupture
 - iv. Bilateral medial frontal hemorrhage
 1. Pericallosal aneurysm rupture
2. Focal apoplectic deficits occur with aneurysmal intracerebral hemorrhage
 - a. Differential points:
 - i. Subarachnoid Hemorrhage (SAH) hemorrhage alone most often causes minimal focality, depressed consciousness, stiff neck
 - b. Hemiparesis most often with MCA aneurysms
 - i. If hemorrhage extends into the temporal lobe the patient may herniate

Intraventricular Hemorrhage from Aneurysmal Rupture

General Characteristics

1. IVH occurs in approximately 13–28% of aneurysmal ruptures
 - a. A-Com: 40%
 - b. Internal Carotid: 25%
 - c. MCA: 21%
 - d. Vertebrobasilar arteries: 14%
2. Patterns of rupture
 - a. A-Com and upper basilar artery aneurysms rupture into the IIIrd ventricle
 - i. Cardiac arrhythmia
 - ii. Hyperthermia
 - b. Distal PICA and vertebral aneurysms may rupture into the IVth ventricle
 - c. Acute subdural hematoma occurs in 2% of patients with SAH

Ischemic Vascular Disease Associated with Aneurysms

General Characteristics

1. Transient ischemia attacks and infarction may be aneurysm presentation in approximately 3 to 11% of patients
 - a. Most common arteries for this presentation are internal carotid and MCA
 - b. Emboli:
 - i. Most commonly occur from giant carotid and giant top of the basilar aneurysms
 1. Can occur with any size aneurysm (average size 12.5 mm)
 2. Source is thrombosis from inside the aneurysm

Mass Effect from Aneurysms

General Characteristics

1. Most common is compression of the IIIrd nerve:
 - a. May be painless and accompanied by partial or complete IIIrd nerve paralysis
2. Giant carotid aneurysm (greater than 25 mm)
 - a. Pituitary erosion and endocrine failure
 - b. Visual field deficit (lateral chiasm pressure)
 - i. Contralateral nasal deficit
3. Giant ophthalmic and anterior communicating artery aneurysms
 - a. Visual field deficits
 - b. Optic nerve compression
4. Giant MCA aneurysms
 - a. Contralateral hemiparesis
 - b. Seizures
5. Top of the basilar aneurysm
 - a. Emboli to occipital cortex
 - i. VF deficit
 - b. Obstruction of IIIrd ventricle
 - i. Hydrocephalus
6. Cavernous sinus aneurysms
 - a. CN-III, IV, VI and VI; (V2 outside of the sinus)

- b. Middle aged women
- c. Vth nerve often the first affected severe facial pain (may be retro-orbital)
- d. May be bilateral
- 7. Unruptured aneurysms presenting with mass affect rupture at 6% per year
- 8. Aneurysms with mass effect
 - a. Usually demonstrate insidious effects
 - b. Rare: stroke-like presentation:
 - i. Acute expansion from intramural hemorrhage or intra-aneurysmal thrombosis

Isolated Sulcal SAH

General Characteristics

1. Transient and recurrent focal neurological episodes; clinically stereotypical
2. High risk of intracranial hemorrhage
3. SAH is at the cerebral convexity
4. Most often in elderly patients and consistent with CAA

Vasospasm and Delayed Cerebral Infarction Following Aneurysmal Rupture

General Characteristics

1. The rupture of an intracranial aneurysm, causes:
 - a. Increased intracranial pressure
 - b. Decreased cerebral blood flow
 - c. An associated systemic stress reaction
 - d. Adverse effects of the systemic stress reaction
 - i. Myocardial dysfunction (noradrenergic contraction band deficits; cardiac ischemia)
 - ii. Increased levels of natriuretic peptides particularly brain natriuretic peptide (BNP)
 1. Causes renal sodium loss and hypovolemia
2. Approximately 70% of patients develop angiographic cerebral vasospasm between days 3 and 14 after SAH
 1. Delayed cerebral ischemia or infarction occur in 20 to 40% of patients
 2. The most important risk factor is the presence of thick clots in the basal cisterns
 3. Other risk factors include:
 - a. Poor clinical grade
 - b. Acute/chronic hypertension
 - c. Fever
 - d. Intravascular volume depletion
 - e. Cigarette smoking
 4. Focal aneurysm rupture may produce generalized vasospasm

Clinical Features of Vasospasm on Delayed Ischemic Stroke

General Characteristics

1. Pathophysiologic factors independent of angiographic vasospasm important for poor outcome after SAH

- a. Early brain injury before onset of delayed vasospasm
 - i. ICP
 - ii. Decreased CBF
 - iii. Global cerebral ischemia
- b. Above initiate BBB disruption, a proinflammatory state and detrimental oxidative cascades
- 2. Ameliorating of cerebral vasospasm is only partially effective in preventing delayed cerebral ischemia
- 3. Delayed cerebral neurologic deficits
 - a. Result from tissue ischemia in vascular territories in which CVS is documented angiographically
- 4. The clinical vasospasm syndrome
 - a. Manifests between the 4th and 12th day after ictus
 - b. Develops insidiously over several hours to 1–2 days (rarely rapidly simulating a stroke)
 - c. Slight febrile response and increase in leukocyte count 1–2 days prior to clinical deterioration
 - d. Hyponatremia may precede clinical symptoms
 - e. May develop increased headache severity
 - f. Decreased level of consciousness
 - g. Focal symptoms (distribution of the ischemic territory) develop insidiously but occasionally rapidly
 - h. Full syndrome in manifest is one to two days

Neuropathology

1. Aneurysms occur at branch points of arteries both at the circle of Willis and distally
2. Disease of type III collagen
3. Defect of arterial media and localized loss of smooth muscle elements
4. Loss or breakage of the internal elastic membrane

Neuroimaging

1. Determination which aneurysm ruptured (in case of multiple aneurysms):
 - a. Location of blood on CT
 - b. Irregular shape (Murphy's excrescences)
 - c. Larger size
 - d. Local vasospasm
 - e. Intra-aneurysmal thrombus
2. Ventricular and sulcal enlargement with:
 - a. Decrease in gray matter volume
 - i. Marker of general atrophy rather than hydrocephalus
 - ii. Correlates with decreased cognitive function
3. Delayed neurovascular imaging may be valuable in patients with diffuse SAH with negative initial CTA/DSA and DSA at 7 days

Differential Diagnosis of (SAH from Reversible Cerebral Vasoconstriction Syndrome) from Aneurysmal SAH and Convolutional SAH

Reversible Cerebral Vasoconstriction – SAH

General Characteristics

1. RVCS

- a. Recurrent thunderclap headache
- b. Reversible segmental multifocal cerebral artery narrowing
- c. Approximately 30% of patients develop SAH
2. Need to be differentiated from cryptogenic “angiogram negative” SAH (cSAH) versus aneurysmal SAH (aSAH)
3. Approximately 1/3 of RCVS develop ischemic stroke, lobar hemorrhage or convexity SAH
4. Thunderclap headache differential diagnosis:
 - a. Migraine headache with or without aura (common)
 - b. Cerebral artery dissection (rare)
 - c. Cerebral venous thrombosis (rare)
 - d. ICH (common)
 - e. Ruptured aneurysm (almost universal)
5. In approximately 15% of SAH the source is undetected following angiography and through imaging (cryptogenic SAH)
 - a. Perimesencephalic SAH (benign- some evidence of rupture of arteriole in the perimesencephalic venous plexus)
 - i. Headache
 - ii. No focality
 - iii. Usually only occurs once
 - b. Only evidence of blood by L.P.

Differential Clinical Features of RCVS-SAH Versus Cryptogenic SAH

RCVS-SAH

1. Independent risk factors
 - a. Younger age
 - b. History of hypertension
 - c. Chronic headache disorder
 - d. Prior antidepressant use
 - e. Lower Hunt-Hess grade
 - f. Lower Fisher group
 - g. Bilateral vasoconstriction (compared to unilateral or no vasoconstriction)

RCVS-SAH Versus “Non-Perimesencephalic” SAH

1. All patients with RCVS-SAH have convexity SAH
2. Bilateral arterial narrowing the only predictor of RCVS-SAH

Major Differential Feature for RCVS

1. Recurrent thunderclap headache (TCH)
 - a. 80% of a SAH have only one TCH
 - i. Less than 20% have sentinel headache
2. Approximately 80–100% of RCVS have 3–4 TCH
3. 30% of RCVS have convexity SAH
4. Association of chronic obstructive pulmonary disease (COPD) and RCVS-SAH (needs validation)
5. Prior antidepressant use:
 - a. Induces vasoconstriction (increased serotonin and noradrenergic monoamines)
 - b. Associated with both RCVS and vasospasm following SAH

Pathology of Aneurysms

The Arterial Wall and Aneurysms

The arterial blood vessel wall is composed of the tunica intima that is lined by endothelium, the media and the adventitia. The tunica media consists of smooth muscle cells and the extracellular matrix proteins collagen, elastin and glycosaminoglycans. The adventitia is made of connective tissue, nerve fibers and the vasa vasorum. The internal elastic membrane separates the tunica intima from the tunica media. There is no external elastic lamina in cerebral blood vessel walls.

Vessel wall inflammation may occur from several different mechanisms. The proinflammatory cytokine, tumor necrosis factor- α (TNF- α) is pivotal in many pathologic conditions. It damages structural components of the vessel wall that include the endothelium, smooth muscle cells and the internal elastic membrane. It induces inflammatory processes in the vessel wall that include migration of monocytes as well as inhibiting cell proliferation that inhibits cell repair. It also activates matrix metalloproteinases that degrade elastin and collagen which are major structural components of the arterial wall.

Vessel wall inflammation may also be induced by carbon monoxide. Carbon monoxide has a higher affinity for hemoglobin than oxygen which decreases the oxygen carrying capacity of blood which causes hypoxemia induced inflammation. The putative pivotal cause of inflammation of the vessel wall is hemodynamic stress (parameters of shear vessel stress that lead to degradation of the extracellular matrix and apoptosis of smooth muscle cells (the primary origin of the proteins of the extracellular matrix). Tissue infiltration of monocytes and macrophages release proinflammatory cytokines and chemokines (MCP-1) that amplify and recruit inflammatory cells as well as release MMPs. Macrophages are found in a high percentage of surgical aneurysms. M1 (proinflammatory macrophages) predominate in ruptured aneurysms.

In early stages of aneurysm formation, smooth muscle cells migrate into the intimal layer and proliferate which forms myointimal hyperplasia. Over time they undergo phenotypic differentiation from contracting cells to proinflammatory cells. In the process they change morphologically from compact bands to spider-like cells. They secrete less collagen and are a cause of a thinned media. There is evidence that the phenotypic switch noted in aneurysmal smooth muscle cells is induced by TNF- α which induces genes for MCP-1, MMPs, vascular cell adhesion molecule 1 and IL-1 β . Mast cells are found in aneurysm walls and contribute to arterial wall inflammation during aneurysm formation by the release of proinflammatory mediators.

Cytokine mediators of inflammation in the arterial wall are:

1. TNF- α effects:
 - a. Smooth muscle cells phenotype modulation
 - b. Activation of MMPs

- c. Decreases expression of tissue inhibitor metalloproteinase-1
 - d. Proapoptotic effect through FAS
2. IL-1 β effects:
- a. Induced in early stages of aneurysm formation
 - b. Smooth muscle cells apoptosis

Both chemokines (MCP-1 and others) as well as complement are involved in the inflammatory wall mechanisms of aneurysm formation. Reactive oxygen species are being studied in regard to their role in direct endothelial cell injury, SMC phenotype switch of SMC and up regulation of genes that control chemotactic cytokines, adhesion molecules and activation of metalloproteinases (MMPs).

Hemodynamic Stress

Hemodynamic stress is a major initiating factor for the arterial wall structural modulation that occurs with aneurysm formation. Hemodynamic stress is greater at arterial junctions, bifurcations or at areas of vascular angulation. Hypertension, loss of autoregulation and increased blood viscosity may also be synergistic with other factors that cause hemodynamic stress. It has been postulated that hypertension may compromise the vasa vasorum which supply the tunica media of the vascular wall. The effects of wall shear stress (WSS) are complicated and while there is evidence that high WSS may be important in the initiation of aneurysm formation, low WSS may be involved in aneurysm rupture by inducing apoptosis of endothelial cells and structural remodeling of the arterial wall. It has also been suggested that low WSS triggers the growth and rupture of large atherosclerotic aneurysms by an inflammatory mechanism while high WSS induces MMP activation, SMC apoptosis and medial thinning in small aneurysms. There is accumulating evidence that endothelial dysfunction and vessel wall remodeling and inflammation are induced by WSS.

The Effects of Wall Shear Stress

1. Occurs at bifurcation, junctions and areas of acute vessel angulation
2. Induction of inducible nitric oxygen synthase (iNOS) that produces peroxonitrate
3. Stimulation of endothelial production of matrix metalloproteinase
4. Smooth muscle cell injury in the tunica media from increased transmural flow gradients
5. WSS injuries are a component of:
 - a. Endothelial cell damage
 - b. Degradation of the internal elastic membrane
 - c. Thinning and phenotypic change of SMC in the tunica media

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Chapter 2

Epilepsy

Overview of Epilepsy

Introduction to Epilepsy

Seizures are now classified as localization-related (focal, local, partial) or generalized. Epilepsy syndromes (formerly classified according to type), neurologic features and EEG findings are now being categorized by their underlying genetic mutations.

In generalized epilepsy, the seizure begins simultaneously in both cerebral hemispheres. The neurologic examination is frequently normal. A great number of the partial epilepsies originate in a localized brain area and then may spread to involve the entire brain.

Generalized Epilepsies

Most generalized epilepsies have complex inheritance patterns, but there is now a rapidly expanding list of single gene mutations that cause the syndrome. They primarily code ion channel proteins (SCN1A, SCN2A, and GABRG2) are early examples. The mutations modify the gating and inactivation properties of the channels. In general, this leads to neuronal hyperexcitability of cortical neurons.

Mechanisms of Partial Epilepsies

Partial seizures are the most common seizure disorder in adults. The mesial temporal lobe that includes the hippocampal formation, amygdala, and adjacent parahippocampal cortex is the most common site of origin. Hippocampal sclerosis is a common pathology in which there is a loss of neurons in the dentate hilus, primarily of the hippocampal pyramidal-cell-layer, with relative preservation of dentate granule cells. Recent high resolution MRI studies demonstrate pathology in Sommer's sector of the hippocampal formation (HF). The amygdala and entorhinal cortex are often concomitantly involved. Hippocampal sclerosis may be caused by seizures in approximately 10% of patients with febrile induced status epileptics in children.

Voltage-Gated Ion Channels in Epilepsy

Cortical neurons have different distributions of voltage-gated ion channels in their functional somatodendritic and axonal domains. Dendritic spines of pyramidal neurons are the primary recipient of excitatory synapses while differential projections of GABA-ergic interneurons to specific domains of these neurons are inhibitory. Summation of excitatory and inhibitory synaptic input at the axon initial segment determines the membrane potential and probability of initiating an action potential.

Voltage-gated sodium (Na_v), potassium (K_v), calcium (Ca_v) and hyperpolarization-activated nucleotide-gated (HCN) channels are expressed differentially in specific neuronal domains and determine the physiology of the cortical neuron. These are transmembrane proteins that are a component of micro-molecular complexes with scaffolding proteins that initiate complex intracellular enzymatic cascades and inter-cellular communication. Cortical neurons, when depolarized, release the cytokine (fractalkine) that activates glia in the micro-environment. Cortical neurons are embedded in an astrocytic syncytium that can secrete proinflammatory cytokines as well as the excitatory transmitter glutamate. In total, the micro-environment of the cortical neuron is a dynamic complex and not fully understood. It may have a major bearing on the membrane potential of the dendritic neuron.

The differential distribution of ion channels on dendritic spines, the soma, and axonal components in conjunction with their scaffold proteins (ankyrin, PSD 93, 95, MAGs) determine the specificity of specific neuronal subtypes and their electrophysiological properties. These include: 1. neuronal excitability and action potential (AP) properties; 2. neurotransmitter release; 3. back propagation of the AP from the axon initial segment to the somatodendritic tree and aspects of activity-dependent neuroplasticity.

SCNA genes encode subunits of Na_v1 channels ($\text{Na}_v1.1$, $\text{Na}_v1.2$ and $\text{Na}_v1.6$) while their B-subunits (Na_v , B1–B4) are encoded by SCNB genes. Sodium channels are responsible for three forms of depolarizing currents; 1. fast inactivation or transient (I_{NaT}); 2. persistent (I_{NaP}) and 3. resurgent (I_{NaR}). Resurgent currents occur following APs and are a component of after depolarization and repetitive firing.

There are several superfamilies of potassium channels that include: 1. voltage-gated (K_v); 2. calcium-activated (K_{Ca}), 3. inward rectifying (K_{ir}) and 2-pore (K_{2p}). Functional KV channels are pivotal in the maintenance of the resting membrane potential, repolarization, and the firing frequency of neurons. KV1, KV2, and some KV3 channels contribute to repolarization. KV4 and some KV3 channels transmit a transient rapidly inactivating sub-threshold A current (A) which delays the initiation of the AP and decreases neuronal firing frequency. The molecular complex of KV 7.2 (KCNQ2) and KV 7.3 (KCNQ3) carry the M-current (I_m) that is important in setting sub-threshold neuronal excitation.

Calcium-activated K^+ channels (K_{Ca}) open in response to Ca^{2+} influx from different types of potassium channels. They include large conductance BK channels that function in the late stages of repolarization and after hyperpolarization and small conductance BK channels. These shape after hyperpolarization and are a feedback mechanism that reduces firing frequency (frequency adaptation) that limits Ca^{2+} influx after depolarization.

Inward rectifying K channels (Kir) whose inward current, active at negative resting potentials, as well as 2-pore K^+ channels that are open at rest are important in determining

the resting membrane potential. The adenosine triphosphate-gated K^+ channel (K-ATP) couples energy metabolism with membrane excitability. Guanine nucleotide binding protein-activated Kir channels mediate inhibitory effects of specific neurotransmitters. The $K_v4.1$ channels localized with aquaporin-4 on astrocytic end-feet processes buffer extracellular K^+ and are important for osmotic homeostasis.

HCN channels, active at hyperpolarization and are gated by cyclic adenosine monophosphate are partially open at rest (subthreshold potentials) and are permeable to Na^+ and K^+ . They also contribute to the maintenance of the membrane potential close to the resting membrane potential. HCN channels dampen the amplitude and duration of both EPSPs and IPSPs.

Calcium channels are classified into high-voltage activated (HVA) and low-voltage activated. L, N, P/Q and R channels are HVA while T channels are LVA. CACNA genes re-code pore forming $\alpha 1$ -subunits that are subdivided into Ca_v1 , Ca_v2 , and Ca_v3 families.

The Ca_v1 family comprises different L channels, the Ca_v2 the P/Q, N, and R channels and the Ca_v3 T-type channels. The HVA channel $\alpha 1$ -subunit forms a molecular complex with β , $\alpha 2$, and γ subunits while T channels only have $\alpha 1$ -subunits. Depolarization of calcium channels contribute to: 1. generation of dendritic spikes; 2. the shape and firing patterns of the AP; 3. neurotransmitter release and neural plasticity (primarily NMDA-mediated). Calcium channels are activated by glutamate release and back-propagating action potentials (APs) (that spreads through the dendritic tree). These calcium channels concomitant with Na channels augment EPSPs, which increases the response to glutamate. In a subset of cortical neurons, LVA $Ca_v3(T)$ channels generate low-threshold calcium spikes that trigger Na-dependent bursts of APs.

Voltage-Gated Channel Integration

Glutamatergic synapses on dendritic spines contain AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) and NMDA receptors. AMPA receptor activation causes fast synaptic depolarization of the dendritic arbor while NMDA receptors contribute to the intracellular calcium concentration. Back propagation of the AP activates Na_v , K_v and Ca_v channels of the somatodendritic spine arbor. Na and Ca influx augment EPSPs and initiate dendritic spikes (regenerative APs). $Ca_v3(T)$ channels may induce burst firing by producing low threshold spikes. Potassium channels decrease the amplitude, propagation, and duration of back-propagated APs and maintain an inhibitory effect on dendritic spines. Potassium channels also control interspike interval, spine depolarization and intercellular calcium influx. Distal dendritic HCN channels also contribute to the inhibition of both EPSPs and IPSPs.

Mutations of specific voltage-gated channels or their subunits alter the balance of excitation and inhibition of cortical networks that lead to hyper-synchronization that is the basic mechanism underlying seizures.

SCN1A Mutations

In general, SCN1A mutations cause loss of function of the Na 1.1 channel which result in 1. generalized epilepsy with febrile seizures plus (GEFS+) and 2. severe myoclonic epilepsy of infancy (Dravet's syndrome). The mechanism may involve failure of fast-spiking inhibitory interneuron GABA projections from loss of their $Na_v1.1$ currents. The mutation may also cause cognitive impairment, ataxia and increased cardiac myocyte excitability.

SCN1B mutations that encode the Na_vB subunit cause GEFS+, Dravet syndrome, temporal lobe epilepsy and absence seizures from failure to modulate Na_v1 gating that promotes neuronal hyperexcitability.

Mutation of the SCN2A gene that encodes the $Na_v1.2$ channel cause benign familial neonatal-infantile seizures as well as intractable childhood partial and generalized epilepsy. The mutation may cause shifts in activation and inactivation thresholds or reduced channels in the plasma membrane.

Potassium Channel Mutations

Mutations in the KCNQ2 or KCNQ3 genes (encode $K_v7.2$ and $K_v7.3$ channel subunits respectively) cause benign familial neonatal convulsions which usually remit by four months. Mutations in these genes are linked to: 1. Rolandic epilepsy without neonatal seizures; 2. and early onset epileptic encephalopathy responsive to adrenocorticotrophic hormone; 3. approximately 10 to 15% develop seizures later in life.

KCNA1 mutations are linked to seizures in association with movement disorders. KCNA1 encodes $K_v1.1$ and is associated with episodic ataxia type1, neuromyotonia, and seizures. KCNA1 gene mutations (encodes the $\alpha 1$ subunit of the BK channels) which also causes generalized epilepsy and paroxysmal dyskinesia. The mechanism of action is a gain of channel function that causes rapid repolarization and a faster neuronal firing rate.

Mutations in other K^+ genes cause a wide spectrum of seizures that are associated with varying medical manifestations:

1. Mutation in the KCNJ11 gene that encodes $K_v6.2$ or in the ABCC8 gene (encodes the sulfonylurea receptor 1 subunit) cause:
 - a. Developmental delay
 - b. Seizures
 - c. Neonatal diabetes
2. Mutations in the KCNJ10 gene:
 - a. Encodes the $K_v4.1$ channel in glia
 - b. Loss of function
 - c. Expressed in astrocytic end-foot processes
 - d. Extracellular K^+ buffering
 - e. Cause seizures, ataxia, sensory-neural deafness, and tubulopathy
3. KCTD7 (potassium channel tetramerization domain-containing protein 7):

- a. Failure of maintenance of the resting membrane potential causes
- b. Progressive myoclonic epilepsy
- c. Opsoclonus/myoclonus/ataxia syndrome
- d. Infantile neuronal ceroid lipofuscinoses

Calcium Channel Mutations

1. Mutations in $Ca_v2.1$ (P/Q) channels:
 - a. Affect the $\alpha 1$ -subunit (pore-forming) and the B4, $\alpha 2 L$ and r2 subunits of the P/Q channel
 - b. Cause absence seizure with ataxia
 - c. Decreased neurotransmitter release in cortical neurons
 - d. Decreased evoked excitatory potentials in thalamic neurons
 - e. Absence epilepsy (spike-and-wave) from T channel triggered burst firing and synchronization of thalamo-cortical neurons
2. Mutation in CACN1A Gene:
 - a. Encoding $Ca_v2.1$
 - b. Associated with idiopathic generalized epilepsy
 - c. Absence seizures alone or with ataxia
3. Mutations in CACNB4 gene:
 - a. Encodes auxiliary B4 subunit of $Ca_v2.1$
 - b. Idiopathic generalized epilepsy and episodic generalized epilepsy and episodic ataxia
4. Mutation in Ca_v3 (T-channels):
 - a. CACNA1H mutations
 - i. Encodes Ca 3.2 channels
 - ii. Associated with childhood absence seizures

Epilepsy Mechanisms

Juvenile absence and myoclonic epilepsy, febrile seizures, and temporal lobe epilepsy.

A loss of function in HCN2 channels linked to generalized epilepsy.

Electrophysiology

Absence Seizures

1. Thalamocortical circuitry governs:
 - a. Rhythms of cortical excitation
 - b. Physiologic patterns of sleep
2. Thalamic relay neurons respond to excitatory afferents by a burst or tonic mode of discharge
3. The response mode depends on voltage-dependent inward calcium currents through T-type channels of the soma and dendritic arbor
4. Burst mode:
 - a. Occurs with deactivation of T-channels in hyperpolarized neurons

- b. Results in a low Ca^{2+} spike current whose upper limit is 12 Hz
- c. Occurs during non-REM sleep and the abnormal thalamocortical oscillations of spike-and-wave discharges of absence epilepsy
- d. Spike-and-wave discharges emerge from 5–9 Hz oscillations in the cortical circuits
- e. Reciprocal discharge between cortical pyramidal cells, thalamic reticular neurons, and thalamic relay neurons generates the oscillations of the thalamocortical circuits
- f. The oscillatory pattern is determined by:
 - i. The balance between T and P/Q channel activity
 - ii. Thalamic GABA-ergic inhibition
- g. Ascending monoaminergic thalamic inputs:
 - i. Modulate the thalamocortical circuitry increasing or decreasing the likelihood of a burst mode of cell firing
- h. The anterior and centromedian/parafascicular nuclei (cm/pf) are activated during spike-and-wave seizures
5. EEG/fMRI evaluation of genetic generalized epilepsies:
 - a. Enables the study of electrophysiology of genetic generalized epilepsies *in vivo*
 - b. Present information supports the concept that:
 - i. Genetic generalized epilepsies (GGE) are a network disorder that includes multiple nodes in the thalamus and cortex
 - ii. Clinical presentation is dependent on which node of a participating network is affected
6. Voxel-based morphometric studies demonstrate thalamic gray matter (GM) reduction in a portion of patients with idiopathic generalized epilepsy:
 - a. The anteromedial thalamic nuclei demonstrated reduced GM
 - b. Functional connectivity (FC) analysis seeding at the anteromedial nucleus revealed:
 - i. Decreased thalamocortical FC in the bilateral medial prefrontal cortex
 - ii. Decreased precuneus and posterior cingulate cortex
 - c. Thalamo prefrontal network abnormality underlies some of the pathophysiologies of IGE

Basic Electrophysiological Mechanisms Underlying Seizures and Epilepsy

Seizure Initiation:

1. High-frequency bursts of action potentials
2. Hyper-synchronization of a neuronal population
3. A paroxysmal depolarizing shift is the cellular manifestation of epilepsy
 - a. Initiated by Ca^{2+} mediated depolarization
 - b. Opens voltage-gated Na^+ channels that initiate action potentials
 - c. Depolarization is followed by:
 - i. Hyperpolarization mediated by Ca^{2+} -dependent K^+ channels

- ii. GABA-activated CL ion influx
- d. Several million neurons are required to discharge simultaneously to produce a focal interictal epileptiform spike

Seizure Propagation

1. Sufficient activation of the seizure onset zone is required to recruit surrounding neurons due to loss of surround inhibition
2. Different lobes are activated via long association pathways:
 - a. Corpus callosum (bi-hemispheric activation)
 - b. Superior longitudinal fasciculus (parietal to frontal lobes)
 - c. Inferior longitudinal fasciculus (occipital to temporal lobe)
 - d. Anterior commissure (connects the temporal lobes)
 - e. Uncinate fasciculus (temporal to frontal lobe)

Control of Burst Firing

1. Intact hyperpolarization
2. Surround inhibition effected by GABA-ergic inhibitory interneurons

Recruitment of Surrounding Neurons During Seizures

1. Repetitive discharge (burst firing):
 - a. An increase in extracellular K^+ which decreases hyperpolarizing outward K^+ currents and depolarizes contiguous neurons
 - b. Increased Ca^{2+} in presynaptic terminals that enhances neurotransmitter release
 - c. Activation of NMDA receptors that further increase intracellular calcium concentration

Network Level Excitation and Inhibition

1. Increased network excitability
 - a. Loss of GABA-ergic interneurons that cause decreased feed forward and backward inhibition of dentate granule cells (in the HF)
 - b. Recurrent excitatory connections from axonal "sprouting":
 - i. May be due to loss of excitatory input to inhibitory interneurons
 - ii. Development of reverberating self-reinforcing circuits from axonal collaterals

Physiological Mechanisms That Underlie Partial Epilepsies

Mesial Temporal Sclerosis

1. Ictal onset in the hippocampus, amygdala, and parahippocampal cortex
2. Selective loss of neurons in the dentate hilus and hippocampal pyramidal cell layers

3. Relative preservation of:
 - a. Dentate granule cells
4. Pyramidal cell loss of cornu ammonis field 2 of the hippocampal formation
5. Neuronal loss in the amygdala and entorhinal cortex
6. Epileptogenesis from hippocampal sclerosis:
 - a. Sprouting of many fibers from dentate granule cells to:
 - i. Inner molecular layer
 - ii. Aberrant mossy fibers may synapse on dendrites of granule cells
 - iii. Initiate a recurrent excitatory circuit
 - b. Excitatory neurons that activate $Na_v 1.1$ receptors on inhibitory interneurons are lost:
 - i. Decreased inhibition of dentate granule cells
 - c. Abnormal integration of newly generated dentate granule cells into hippocampal circuits that causes:
 - i. An imbalance between excitation and inhibition
 - d. Alterations in the composition and expansion of GABA-A receptors in dentate granule cells
 - e. Hippocampal sclerosis demonstrates:
 - i. Structural reorganization
 - ii. Selective neuronal loss
 - iii. Aberrant neurogenesis that causes circuit alterations
 - iv. Change in neurotransmitter receptors
 - v. Development of focal hyperexcitability

Some Aspects of Electrophysiology in Focal Epilepsy

1. Long term intracranial recording in intractable partial epilepsy reveals:
 - a. Slow modulation of high-frequency activity (40–140 Hz) is a measure of pre-ictal activity
 - b. High-frequency oscillations (80–500 Hz)
 - i. More frequent in the seizure-onset zone (SOZ)
 - ii. Linked to seizure genesis
 - iii. More reliable for localization of seizure onset areas than prediction of seizures
2. Immune Mechanisms in Epilepsy
 - a. Inflammatory processes have been associated with seizures:
 - i. Neuro-inflammation has been demonstrated in epileptic brain autopsy material
 - ii. Systemic inflammation may increase discharge in epileptic neurons by loss of potassium or glutamatergic homeostasis
 - b. Effects of systemic inflammation may be mediated by loss of blood-brain barrier (BBB) function:
 - i. Vascular endothelial cell dysfunction
 - ii. Activation of circulating leukocytes
 - iii. Release of mediators that increase vascular permeability

Immune Seizures

1. Rasmussen's Encephalitis
 - a. Pathology demonstrates hemispheric inflammation

- i. CD4⁺ T-cells
 - ii. Microglial activation and nodules
 - iii. Progressive neuronal loss and gliosis secondary to apoptosis
- 2. Seizures from autoimmune disorders:
 - a. SLE
 - b. Celiac disease
 - c. Associated with autoantibodies and increased inflammatory markers
 - d. Response of seizures to immunosuppressive treatment
- 3. Immune-Mediated Seizures:
 - a. Autoantibodies:
 - i. Against neuronal surface proteins on the NMDA receptor
 - ii. The potassium channel complex protein leucine-rich, glioma inactivated 1 (LGI1) protein
 - iii. Glutamic acid decarboxylase (intracellular)
 - iv. Respond to immunosuppressive therapy to some degree

Secondarily Generalized Tonic-Clonic Seizures (SPECT Imaging) Mechanisms

- 1. Single photon emission computed tomography:
 - a. Images cerebral blood flow (CBF)
 - b. CBF is linked to metabolic activity generated by neuronal firing
 - c. SPECT tracer is taken up rapidly after injection (approximately 30 seconds) and does not redistribute

Cortical and Subcortical Network Analysis

- 1. Secondarily generalized tonic-clonic seizures:
 - a. Early increase of tracer in seizure onset zone (SOZ)
 - b. Progressing to bilateral cortical and subcortical network activity
- 2. Pre-generalization phase:
 - a. Focal CBF increase depending on anatomical area involved
 - i. Primarily in the temporal lobe
 - b. Generalization stage:
 - i. CBF increase in the thalamus, basal ganglia, medial cerebellum
 - c. Post-ictal stage:
 - i. Progressive increase of CBF in the cerebellar hemispheres and midbrain
 - d. Cerebellar increased blood flow correlates with:
 - i. Increases of CBF in the midbrain and thalamus
 - ii. Decrease of CBF in the frontoparietal association cortices during and following seizures
- 3. The thalamus and upper brainstem are critical for:
 - a. Synchronization of abnormal cortical and subcortical electrical discharges

- b. Generation of tonic motor firing
 - c. Impaired consciousness
 - d. Seizure generalization
- 4. Cerebellar CBF increases:
 - a. Contribute to seizure termination and suppression
 - b. Purkinje cell output is inhibitory
 - c. Projects via the deep cerebellar nuclei and thalamus to the cortex
 - d. Decreased CBF of the lateral frontoparietal association cortex cingulate gyrus and precuneus comprise:
 - i. Default mode network that is involved with decreased consciousness

Malformations of Cortical Development

Approximately 20% of adult patients that undergo surgical resection for intractable epilepsy have histopathology proven focal cortical dysplasia. This number rises to approximately 50% of children undergoing seizure surgery. Polymicrogyria, heterotopias, and focal cortical dysplasia manifest as discrete areas of abnormal neuronal migration and disruption of anatomical cortical lamination. Intracortical EEG, SPECT, PET, Doppler studies have demonstrated complex cortical and subcortical networks that intake and maintain seizure disorders. Visible MPI, cortical lesions may be just an indicator of the epileptogenic zone rather than its complete substrate.

The recent classification of patients with malformations of cortical developments is based on deficits of normal development and mutations in genes that control the complex patterns of neuronal circuit generation and maintenance. An outline of this classification follows.

Group Ia: Abnormal Neuronal and Glial Proliferation or Apoptosis

- a. Reduced proliferation or accelerated apoptosis
 - i. Congenital microcephaly
 - ii. Increased proliferation or decreased apoptosis (megalencephaly)
 - iii. Abnormal proliferation:
 - 1. Focal and diffuse dysgenesis and dysplasia

Group Ib: Cortical Dysgenesis with Abnormal Cell Proliferation

This component of Group 1 is particularly important for normal cortical development and seizures:

- 1. The mammalian target of rapamycin (mTOR)
 - a. Causes increased cell growth, ribosome biogenesis, and messenger RNA translation. This occurs in tuberous sclerosis complex gene mutations in which mTOR is activated
- 2. Focal cortical dysplasia I (FCD I)
- 3. FCD II
 - a. Similar to protein phenotype of the tuberous sclerosis complex

- b. Progenitor proteins of early development are found in the dysplastic tissue
- c. Similar to multipotent or pluripotent stem cells
- d. Evidence that seen balloon cells may originate from glioneuronal progenitor cells (radial glial cells)

Group II: Malformations due to abnormal neuronal migration

1. Subcategories:

- a. Neuro ependymal (ventricular epithelium)
 - 1. Periventricular nodular heterotopia
 - 2. Defects in the initiation of migration
- b. Abnormalities of transmantle migration:
 - 1. Lissencephaly
 - 2. Subcortical heterotopia
 - 3. Defects in terminal migration/pial limiting membrane (cobblestone malformations)

Group II A: Heterotopias

Major Forms:

- 1. Periventricular nodular heterotopia
 - a. Most common
- 2. Periventricular linear heterotopia
 - a. Gray matter (smooth) lining the ventricular wall
- 3. Columnar heterotopia
 - a. Linear aggregation of neurons (ependymal to pia)
- 4. Subcortical heterotopia
 - a. Curvilinear aggregation of neurons from deep sulci through the cortical mantle

Group II B: Lissencephaly

- 1. Malformations due to abnormal transmantle migration
 - a. Agyria
 - b. Pachygyria
 - c. Subcortical band heterotopia
- 2. Mutations in the TUBA1A gene
 - a. Dysgenesis involves the cortex, corpus callosum, basal ganglia/white matter, and midbrain
 - b. Specific mutations of the gene are identical to LIS mutations
 - 1. Frontal pachygyria and posterior agyria
 - 2. Complete agyria

Group II C: Subcortical Heterotopia and Sub-Lobar Dysplasia

- 1. Malformations in which aggregates of neurons accrue in deep cerebral white matter
- 2. They include:
 - a. Transmantle (columnar heterotopia)
 - b. Curvilinear aggregates of neurons
 - c. Multiple nodules in deep white matter
 - d. Sublobar dysplasia

Group II D: Cobblestone Malformations

- 1. Mutations in genes involved in:
 - a. O-glycosylation of dystroglycan
 - b. Phenotypic variations of eye, muscle, brain disease
- 2. Defective formation of basement membranes of skeletal muscle, retina, cerebrum and the cerebellum
 - a. Impaired linkage of radial glia to the pial basement membrane

- b. Deficiency of cerebral basement membrane (BM) that causes:

- 1. Abnormal lamination
- 2. Over migration of neurons through the BM

Group III A: Polymicrogyria and Schizencephaly

- 1. The cause is heterogeneous
- 2. Four subcategories:
 - a. Schizencephalic clefts or calcification
 - 1. Infection or vascular etiology
 - b. Group III b:
 - 1. Genetic and vasculature disruption
 - c. Group III c:
 - 1. Genetically defined multiple congenital anomaly syndromes
 - d. Group III d:
 - 1. In conjunction with in-born errors of metabolism

Group III C: Focal Cortical Dysplasia

- 1. Malformations of abnormal postmigrational development
- 2. Associated with prenatal and perinatal insults
- 3. Focal cortical dysplasias III (FCD III) are associated with:
 - a. Injuries
 - b. Vascular malformations
 - c. Tumors

There are many other causes of epilepsy not reviewed in this brief outline that include:

- 1. Specific genetic syndromes
- 2. Glia buffering defects that are pivotal for ion and glutamate hemostasis
- 3. Neuroplasticity of neuronal circuits
- 4. Network imbalance of excitation and inhibition
- 5. The role of epigenetics

Introduction to Epileptic Seizures

Definition of Seizure by Gordon Holmes

A seizure as defined by the eminent British neurologist Gordon Holmes is a sudden involuntary time limited attenuation in function, secondary to an abnormal discharge of neurons in the central nervous system. Seizures may be congenital (genetic mutations in ion channels and subunits or migrational defects) or to an acute systemic process or focal neurologic lesions. Idiopathic seizures have no known underlying definitive cause. Genetic sequencing advances and high strength MRI magnets are rapidly revealing mutations and various migrational defects which are rapidly shrinking the percentage of truly idiopathic patients. The study of epigenetics (gene regulation) will certainly further our understanding of many epilepsies.

Epileptic Seizures

- 1. Discrete epileptic events due to transient hypersynchronous abnormal neuronal discharges
- 2. Epilepsy: Recurrent unprovoked seizures

General Epidemiology

1. Overall incidence:
 - a. 40–70 patients per 100,000 people in developed countries
2. Single seizure:
 - a. 0.5%–3% of the population over a lifetime
3. Greatest incidence occurs during the first year of life
4. Western Europe and the USA:
 - a. By the age of 20, 1–3% of children may have had a seizure. Approximately 25% of these patients will develop epilepsy
 - b. 80% of these children are seizure free within five years; often by one year
 - c. Approximately 20–30% of newly diagnosed epilepsy patients will develop medically refractory seizures (most often partial complex seizures from the temporal lobe)
 - d. There is a secondary rise in seizure incidence after 60 years (primarily due to vascular diseases)
5. Risk factors for the development of epilepsy:
 - a. Genetic predisposition
 - b. Specific syndrome
 - c. Cognitive impairment
 - d. Perinatal disorders
 - e. Cerebral palsy (intrauterine stroke, infection, malformation)
 - f. Cerebrovascular disease
 - g. Neoplasm
 - h. Infection of the CNS
 - i. Neurodegenerative disease
 - j. Drug abuse

The major problems in the epilepsies suffered by adult patients are complex partial seizures and major motor seizures. Occasionally, primary childhood seizure types extend into adolescence and adulthood and will be discussed. Congenital and primarily pediatric seizures will not be discussed in detail, but may be mentioned for completeness.

International Classification of Epilepsies, Epileptic Syndromes, and Related Seizures Disorders

1. Localization-related (focal, local, partial)
 - a. Idiopathic (primary)
 - i. Benign childhood epilepsy with centrotemporal spike
 - ii. Childhood epilepsy with occipital paroxysms
 - iii. Primary reading epilepsy
 - b. Cryptogenic defined by:
 - i. Seizure type
 - ii. Clinical features
 - iii. Etiology
 - iv. Anatomical localization
 - c. Symptomatic (Secondary)
 - i. Temporal lobe epilepsies
 - ii. Frontal lobe epilepsies

- iii. Parietal lobe epilepsies
 - iv. Occipital lobe epilepsies
 - v. Chronic progressive epilepsies partials continua of childhood
 - vi. Syndromes characterized by seizures with specific modes of precipitation
- d. Undetermined epilepsies both generalized and focal seizures
 - i. Neonatal seizures
 - ii. Severe myoclonic epilepsy in infancy
 - iii. Epilepsy with continuous spike-waves during slow-wave sleep
 - iv. Acquired epileptic aphasia (Landau Kleffner syndrome)
 - v. Other undetermined epilepsies without unequivocal generalized or focal features

Generalized Epilepsies

1. Benign neonatal familial convulsions
2. Benign neonatal convulsions
3. Benign myoclonic epilepsy in infancy
4. Childhood absence epilepsy
5. Juvenile absence epilepsy
6. Juvenile myoclonic epilepsy
7. Epilepsies with grand mal seizure on awakening
8. Other generalized idiopathic epilepsies
9. Epilepsies with seizures precipitated by specific modes of activation
10. Cryogenic or Symptomatic:
 - a. West syndrome (infantile spasms)
 - b. Lennox-Gestaut syndrome
 - c. Epilepsy with myoclonic-astatic seizures
 - d. Epilepsy with myoclonic absences
11. Non-specific Etiology
 - a. Early myoclonic encephalopathy
 - b. Early infantile epileptic encephalopathy with suppression burst
 - c. Other symptomatic generalized epilepsies
 - d. Specific Syndromes:
 - i. Epileptic seizures many complicate many disease states
12. Special Syndromes-Situation-related Seizures
 - a. Febrile convulsions
 - b. Isolated seizures or isolated status epilepticus
 - c. Seizures occurring only when there is an acute or episodic event due to alcohol, drugs, eclampsia or non-ketotic hypoglycemia

Definitions

1. Partial Seizure
 - a. The first clinical and/or EEG changes indicate initial involvement of one hemisphere
 - b. Classification depends on impairment of consciousness:
 - i. Simple partial: no impairment of consciousness

- ii. Complex partial: impairment of consciousness
- iii. Partial with secondary generalization
- 2. Generalized Seizure
 - a. The first clinical and/or EEG changes indicate initial involvement of both hemispheres
 - b. Conscious is impaired (rare exceptions) with the following seizure categories:
 - i. Tonic-clonic
 - ii. Absence
 - iii. Clonic
 - iv. Myoclonic
 - v. Tonic
 - vi. Ataxic
- 3. Unclassified
 - a. Some neonatal syndromes
- 4. Epileptic Syndromes
 - a. Heterogeneous groups of disorders with specific manifestations. The classification is based on:
 - i. Cluster of signs and symptoms
 - ii. Seizure type
 - iii. Age at onset
 - iv. EEG evaluation
 - v. Prognosis
 - vi. Response to medications

Video EEG Monitoring of Refractory Seizures

Information that correlates EEG evaluations with clinical signs and symptoms has been determined primarily by prolonged video EEG. Utilization of the technique for guidance in seizure surgery, demonstrate that the ictal onset zone, which at time was found to be distinct from the cortical areas that produce clinical signs and symptoms (symptomatogenic zone).

Semiology of Generalized Tonic-Clonic Seizures

- 1. Phase I
 - a. Simple partial seizure with preserved consciousness; the initial cortical activation and produces the aura
 - b. Generalized idiopathic seizures may have auras (correlated with focal cortical hyperexcitability)
- 2. Phase II
 - a. Four alternative semiology's dependent on whether the seizure was localization-related or primary generalized
 - i. Complex partial pattern
 - ii. Tonic
 - iii. Clonic
 - iv. Absence
- 3. Time course of phase I and II varied between 10 seconds to 4 minutes
- 4. Phase III
 - a. Brief period between antecedent 2 phases is the induction of the generalized seizure
 - b. Clinical manifestations include:

- i. Vocalization
- ii. Head version (may also be seen variably with IGE) a marker of contralateral BA10 eye field activation

Phase IV

- a. Brief period of irregular and asymmetric irregular clonic jerking

Phase V

- a. Sustained contraction of all voluntary musculature (tonic posture) with minimal clonic jerking

Phase VI

- a. Tremulousness or the "vibratory" clonic phase

Phase VII

- a. Main clonic phase
 - i. In localization-related epilepsy the clonic jerking may end asymmetrically on the ipsilesional hemispheric side

Duration of phases

- 1. Phase III – 9.5 seconds
- 2. Phase IV – 8.5 seconds
- 3. Phase V – 18.5 seconds
- 4. Combined phase VI and VII – 43.5
- 5. Almost all seizures end before 2 minutes; rarely all 5 phases were noted, but phases VI and VII are most consistent

Additional Characteristics of Generalized Tonic-Clonic Seizures (Localization Related with Secondary Generalization)

- 1. Prodrome (prior to phase I)
 - a. Extreme fatigue several days to one week prior to seizure onset
 - b. Increase of nocturnal myoclonic jerks
 - c. Mood change (usually depression)
 - d. Increased irritability
- 2. Phase II (tonic phase)
 - a. Tonic contraction of axial musculature and limbs
 - b. Upward eye deviation
 - c. Pupillary dilatation
 - d. "Epileptic cry":
 - i. Sudden contraction of intercostal muscles forcing air through the larynx
 - e. Tongue and jaw contracture:
 - i. Lateral tongue biting (side opposite a focal lesion)
- 3. Phase II (clonic phase)
 - a. Gradual onset
 - b. Low amplitude of clonic activity
 - c. Builds to frequency of 8 jerks per second with increasing amplitude that then decreases to four jerks/second
 - d. Atonic inhibition
 - i. Loss of continence
 - ii. Atonia of somatic muscle
- 4. Post-ictal events
 - a. Post-ictal sleep (variable; minutes to one hour)
 - b. Confusion on awakening (minutes to one hour; may last far longer)

- c. Dull pounding headache (occipital predominant)
- d. Todd's paralysis (may be due to an underlying structural lesion)
- e. Lateral tongue biting (side opposite the lesion)
- f. Soreness of the paraspinal and leg extension muscles
- g. Rare bilateral posterior dislocation of the shoulders (younger patients)
- h. Fracture of thoracic vertebrae (older patients)
- i. Increased blood pressure (during the seizure)
- j. Hyperhidrosis for minutes to hours (ANS activation)
- k. Temperature to 101 degrees F (sustained seizure; induced muscular activity)
- l. CSF up to 100 neutrophils/mm³ (dural movement/irritation)
- m. Post-ictal psychosis (fighting constraints)
- n. Myoglobinuria and renal failure (prolonged seizure)
- o. Briefly arouseable and then falls back to sleep
- p. Rare maintenance of trismus and opisthotonus
- q. Increased prolactin levels (temporal lobe seizures)

Rare Sequela:

- 1. Neurogenic pulmonary edema
- 2. Cardiac arrhythmias (EKG abnormalities)
- 3. Bleeding from the first portion of the duodenum (through and through penetrating ulcer)
- 4. Myoglobinuria with renal failure
- 5. Severe acidosis (pH < 7.0)
- 6. Posterior shoulder dislocation
- 7. Sudden unexplained death (SUDEP)

Progression of Signs and Symptoms of GTC Seizures (localization-related with secondary generalization):

- 1. Aura or focal motor signs signal seizure onset at a cerebral locus
- 2. Loss of awareness with automatisms (limbic involvement)
- 3. Contralateral extremity posturing (centripetal spread to basal ganglia)
- 4. Generalization to clonic-tonic activity:
 - a. Initially contralateral face or extremities are involved followed by ipsilateral involvement

Differential Diagnosis of Causes of GTCS

Monogenetic Causes

General Principals

- 1. Ion channelopathies may disrupt the balance between excitatory glutamatergic and inhibitory GABA-ergic transmission:
 - a. Leads to hyper-synchronization of cortical networks
 - b. Mutations primarily affect the principal or auxiliary subunits
 - c. Axonal initial segment may be involved and contain Na, K, and GABA receptors
 - d. Mutations may affect:
 - i. Developmental regulation of expression of the ion channel

- ii. Subunit composition
- iii. Auxiliary subunit interactions
- iv. Membrane compartmentalization

SCN1A Mutations

- 1. Most common epileptogenic ion channel mutation
- 2. Encodes the Na α 1 subunit
- 3. Loss of function, decreased excitability of fast-spiking GABA-ergic neurons
- 4. Febrile seizure plus (GEF+) as well as severe myoclonic epilepsy of infancy (Dravet's syndrome)
- 5. Missense mutation is most common
- 6. Reduced fast-spiking in GABA-A neurons and, therefore, loss of inhibition

SCN1B Mutation

- 1. Encodes the Na β , subunit
- 2. Associated with:
 - a. GEF+
 - b. Dravet's syndrome (DS)
 - c. Temporal lobe epilepsy
 - d. None-febrile absence seizures
- 3. Decreased ability to modulate Na v 1.1 channel gating

SCN2A Mutations

- 1. Encode Na v 1.2 channel
- 2. Expressed in excitatory pyramidal neurons
- 3. Associated with a spectrum of epilepsies
 - a. Benign familial neonatal, infantile seizures
 - b. Intractable childhood partial and generalized epilepsies
 - c. Dravet's syndrome (DS)
 - d. Infantile spasms
 - e. Mechanisms include:
 - i. Shift of activation and inactivation thresholds of involved neurons
 - ii. Reduced levels of channel proteins in the plasma membrane

Potassium Channel Mutations

- 1. Mutations of KCN Q2 (encoding K v 7.2) or KCNQ3 (encoding K v 7.3)
 - a. Linked to AD benign familial neonatal convulsion
 - b. Generalized epileptic syndromes
 - c. Clinical remission within weeks or months
 - d. Sequence variations of KCNQ2 and KCNQ3 genes are associated with:
 - i. Rolandic epilepsy without neonatal seizures
 - ii. Idiopathic generalized epilepsy
 - iii. Early onset epileptic encephalopathy with multifocal drug-resistant seizures responsive to adrenocorticotrophic hormone
- 2. KCNA1 Mutations
 - a. Encodes the K v 1.1 channel
 - b. Associated with:
 - i. Episodic ataxia type 1

- ii. Neuromyotonia and seizures
- iii. KCMNA1 gene mutations:
 - 1. Linked to generalized epilepsy
 - 2. Paroxysmal dyskinesia
 - 3. Rapid repolarization of action potentials that allow faster neuronal firing
- iv. KCNJ1 gene mutations
 - 1. Encodes K_v (involved trafficking)
 - 2. ABCC8 gene mutation:
 - a. Encodes its regulatory sulfonylurea receptor 1 subunit
 - b. Linked to a syndrome that includes:
 - i. Developmental delay
 - ii. Epilepsy
 - iii. Neonatal diabetes
- v. KCNF10 mutations:
 - 1. Encodes the glial K_r 4.1 channel
 - 2. Expressed in astrocytic end-feet
 - 3. Decreased extracellular K^+ buffering
 - 4. Linked to syndrome that includes:
 - a. Epilepsy
 - b. Ataxia
 - c. Sensorineural deafness
 - d. Tubulopathy
- vi. KCTD7 (potassium channel tetramerization domain-containing protein)
 - 1. Maintains the resting membrane potential; reduces cell excitability
 - 2. Syndrome that includes:
 - a. Progressive myoclonic epilepsy
 - b. Opsoclonus/myoclonus/ataxia syndrome
 - c. Infantile-onset neuronal ceroid lipofuscinoses subtype (CLN14)

Calcium Channelopathies

- 1. Associated with epilepsy mediated by:
 - a. Loss of function of $Ca_v2.1$ (P/Q) channels
 - b. Gain of function of $Ca_v3(T)$ channels
 - c. Linked to generalized epilepsy
 - d. Generalized spiked and wave absence epilepsy

CACNA1 Gene Mutation

- 1. Mutation affects the pore-forming $\alpha 1$ subunit or auxiliary B4 subunits
- 2. Absence epilepsy phenotype with spike-and-wave EEG pattern:
 - a. Reflects enhanced T channel triggered burst firing and synchronization of thalamocortical projection neurons
 - b. Or loss of $Ca_v2.1$ channels in fast-spiking GABA-ergic neuron that would increase excitability of cortical neurons

CACNB4 Mutations

- 1. Linked to idiopathic generalized epilepsy and episodic ataxia

$Ca_v3(T)$ Channel Mutations

- 1. Linked to absence (“spike-and-wave”) epilepsy

CACNA1H Variants

- 1. Encodes $Ca_v3.2$ channels
- 2. Linked to:
 - a. Childhood absence epilepsy
 - b. Juvenile absence epilepsy
 - c. Juvenile myoclonus
 - d. Febrile seizures
 - e. Temporal lobe epilepsy

HCN Channel Mutations

- 1. HCN2 mutation
- 2. Linked to generalized epilepsy
- 3. Dendritic HCN channels reduces EPSP and IPSP amplitudes
 - a. Stabilizes the membrane potential

Metabolic Causes of (Generalized Tonic-Clonic Seizures) GTCS

- 1. Hypoglycemia
 - a. Cerebral spinal fluid sugar is approximately 2/3 of blood sugar. In general, patients may have seizures when the CSF sugar is less than 30 mg/dl. This usually occurs when the peripheral blood sugar is 40–60 mg/dl. The rate at which the sugar falls may also be a determinant if a seizure will be provoked. As the blood sugar decreases, a noradrenergic response causes hunger, piloerection, hyperhidrosis, tremulousness and abnormal behavior. If the peripheral sugar falls to below 30 mg/dl, a parasympathetic discharge occurs that may be associated with salivation, bradycardia and coldness (97 degree F)
- 2. Hypocalcaemia:
 - a. The usual setting is renal failure with secondary hypoparathyroidism or renal tubular acidosis
 - b. Muscle fasciculations occur spontaneously or may be evoked by mechanical stimuli
 - c. Peripheral nerves may discharge to mechanical stimuli Chovstek’s sign (VIIth nerve percussion) or to ischemia (Trousseau’s sign).
 - d. Long QT interval; non-specific T wave change on EKG (may also occur from seizures)
- 3. Hypomagnesia
 - a. Often occurs concomitantly with hypocalcaemia
 - b. Secondary to prolonged enteral feeding
 - c. Burn patients
 - d. Clinically similar to hypocalcaemia
 - e. EKG changes; long AT interval and non-specific T wave changes
- 4. Uremia
 - a. Blood urea nitrogen (BUN) between 90–120 mg/dl but very variable

- b. Following rapid osmotic shifts (post dialysis)
 - c. Need to r/o cerebral vascular disease:
 - i. Ischemic stroke of large and small blood vessels; calcification of large blood vessels occurs with renal failure
 - ii. Embolic stroke; higher incidence of infective endocarditis (lines and shunts)
 - iii. Intracranial hemorrhage:
 1. Uremic thrombocytopenia
 2. Hypertensive hemorrhage
 3. Incomplete reversal of anticoagulation (following hemodialysis; with protamine sulfate)
 4. Subarachnoid hemorrhage (platelet dysfunction; combination of pathologies)
 5. tPA for thrombolysis of blocked shunt
 6. Infection (Staph aureus, gram-negative bacilli, HIV)
 7. Seizures are often short
 8. Pupillary abnormalities (dilated) and often associated with ischemic optic neuritis, (pallor with loss of the optic cup)
5. Hepatic Failure
- a. Usual clinical features are confusion, asterixis, hyperactive reflexes
 - b. Rarely focal neurologic signs
 - c. Seizures often from underlying illness or hypoglycemia
 - d. Hepatic encephalopathy and seizures:
 - i. From many anticonvulsants
 - ii. Dilantin (Steven Johnson's syndrome, arteritis with lobar hepatic infarction)
 - iii. Carbamazepine
 1. Seizures may occur from inappropriate antidiuretic hormone secretion; exacerbation of sodium channelopathies
 - iv. Valproic Acid (VPA)
 1. May induce hyperammonemia without hepatic failure
 2. Combination antiepileptic drugs (AEDs) exacerbate and induce hepatic encephalopathy
 3. Clinical features of VPA-induced encephalopathy:
 - a. Acute onset of impaired consciousness
 - b. Focal neurologic signs
 - c. Increased seizure frequency (in an epileptic patient)
 - d. EEG; pronounced slowing and increased epileptiform discharges
6. Hypernatremia
- a. Seizures are dependent on the rate at which serum sodium decreases
 - b. Seizures occur at levels less than 110 meq/ml
 - c. Hyperreflexia and generalized weakness
 - d. "Finger print sign" (intracellular edema); pressure elicits finger print when tissue compressed against bone
7. Acute intermittent porphyria
- a. Major motor seizure occurs from:
 - i. Porphyrins
 - ii. Concomitant inappropriate ADH (low serum sodium)
 - iii. Abdominal pain, motor neuropathy with wasting, hyperactive ankle jerks in the face of general hyperreflexia and PRES
8. Inappropriate ADH
- a. Usual serum sodium is between 120–130 meq/dl
 - b. Initiated by:
 - i. Head trauma
 - ii. Metabolic abnormalities (AIP, hypothyroidism)
 - iii. Drugs (carbamazepine)
 - iv. Paraneoplastic (squamous cell of the lung)
 - v. Intracranial surgery
 - c. Confusion, generalized seizures, hyperreflexia
9. Hyperosmotic states:
- a. Non-ketotic diabetic coma:
 - i. Blood sugar often between 2000–3000 mg/dl
 - ii. Occurs in type II diabetes following infection (frequently)
 - iii. Associated with confusion, segmental myoclonus, generalized seizures, asterixis
 - b. Renal failure
 - c. Hyperlipidemia
 - d. Insufficient free water with PEG or other internal feeding methods
10. Pulmonary failure:
- a. $p\text{CO}_2 > 70$ torr; $p\text{O}_2 < 80$ torr
 - b. Clinical manifestations:
 - i. Dilated optic veins, suffused optic disc with papilledema
 - c. Asterixis (failure to maintain extensor posture)
 - d. Fasciculation and muscle hyperexcitability
 - e. Generalized seizures

Drugs/Toxin-Associated Features with GTCS

1. Specific features of different drugs and toxins:
 - a. Methanol: hemorrhagic optic neuritis
 - b. INH: hyperthermia, hyperglycemia
 - c. Phenothiazine; hyper or hypothermia, small pupils
 - d. Insulin: severe hypoglycemia
 - i. Used by medical personnel for malingering
 - e. Anesthetics
 - i. Propofol
 - ii. Halothane
 - iii. Enflurane
 - iv. Sevoflurane
 - f. Theophylline (jitteriness)
 - g. Amphetamines: psychosis, wasting
 - h. Tricyclic antidepressants: parasynpathomimetic effects, hyperthermia, cardiac arrhythmia
 - i. Lithium: tremor, myoclonus

- j. Cocaine:
 - i. Hypertension with cerebral hemorrhage
 - ii. Cerebral and coronary vasospasm (may be delayed)
 - iii. 20% of hemorrhages due to underlying vascular malformation
- k. Heroin:
 - i. Pulmonary edema
 - ii. Transverse myelitis
 - iii. SBE with mycotic aneurysm (IV administration)
- l. PCP:
 - i. Hallucinations
 - ii. Dilated pupils
 - iii. Severe rotary and up beating nystagmus
 - iv. Self-destructive behavior
- m. Anticonvulsants:
 - i. Liver failure
 - ii. Ophthalmoplegia (phenytoin)
 - iii. Focal neurological signs (Phenobarbital)
- n. Penicillin
 - i. Large IV doses in a setting of renal failure
- o. Alcohol withdrawal:
 - i. Hypothalamic disinhibition with primarily adrenergic manifestations
 - ii. Delirium tremens

Infections Associated with GTCS

1. Cortex must be involved to initiate GTCS
2. Diffuse inflammation of the meninges and spread of infection to the arachnoid, pia mater and through Virchow-Robin spaces
3. Cortical strokes with GTCS occur with:
 - a. Tuberculosis (endarteritis, meningeal involvement)
 - b. Cryptococcosis (meningeal; spreads through Virchow-Robin spaces; cysts in the basal ganglia)
 - c. Mucormycosis (sinus spread), ophthalmoplegia, black palate; immunosuppressed patients
 - d. Aspergillus: (venous spread); lung abscess; head and neck surgery
 - e. Listeria: pregnant women; lesions in the dorsal pons
 - f. HIV: direct endothelial involvement; opportunistic organisms (when CD4 count < 200 cells/mm³)
 - g. Syphilis (proliferative endarteritis; often with brainstem involvement; associated with HIV (has telescoped pattern-all three stages overlap)
 - h. Subacute bacterial endocarditis (SBE): mycotic aneurysms, arteritis and late focal cortical hemorrhage
 - i. Cysticercosis: multiple cortical calcified cysts; partial and secondarily generalized seizures
 - j. Toxicaria (toxocara canis): primarily seizures in children
 - k. Malaria (microvascular cortical vascular damage)
 - l. Chagas disease (myocardial failure with emboli; esophageal echolalia)

Common Causes of GTCS

1. Often are acute symptomatic without reoccurrence:
 - a. Vascular (infarction, hemorrhage, malformation)
 - b. Head injury (acute or remote)
 - c. Venous infarction (post-partum)
 - d. Tumor (primary and metastatic)
 - e. Prior cortical scar (in the setting of sleep deprivation or metabolic dysfunction)
 - f. Prior stroke (occur in at least 10% of stroke patients)
 - g. Anticonvulsant withdrawal
 - h. Alcohol withdrawal

Precipitating Factors for GTCS

1. Failure of drug compliance
2. Sleep deprivation
3. Metabolic dysfunction
4. Cortical scars
5. Specific drugs that cause seizures
 - a. Cocaine
 - b. Amphetamines
 - c. High doses of penicillin (setting of renal failure)
 - d. Phenothiazine (particularly if there is a structured lesion)
 - e. Antidepressants
 - f. Phosphodiesterase inhibitors (asthma)
 - g. Antihistamines
6. Hypoglycemia (missing breakfast then administering insulin in a diabetic)

Differential Diagnosis of GTCS by Age

1. Adolescent:
 - a. Genetic (channelopathy; Na, K, Calcium, HCN-rare)
 - b. GTCS upon awakening
 - c. Syndrome (tuberous sclerosis complex)
 - d. Noncompliance with drug therapy for localization-related seizures
 - e. Metabolic (hypoglycemia)
 - f. Drugs (cocaine, amphetamine, PCP, barbiturates, alcohol)
 - g. Vascular (infarction, embolus, hemorrhage, malformations)
 - h. Component of autoimmune diseases (vasculitis)
 - i. Encephalitis (herpes simplex)
 - j. Head injury
 - k. Hippocampal sclerosis with secondary generalization
 - l. Mitochondrial disease (MERRF); Kearns-Sayre syndrome
 - m. Migration disorders (nodular and band heterotopias; cortical micro-dysgenesis)

Adult Under 40 Years Old

1. Epilepsy with grand mal on awakening:
 - a. Occurs shortly after awakening regardless of the time of day

- b. Triggered by sleep deprivation
- c. Manifests in the second decade
- d. At 40 years after onset >50% are seizure free for >5 years
- e. Age at presentation determines prognosis; younger the patient at onset worse prognosis
- f. Risk-taking behavior and frontal lobe dysfunction undetermined as different or similar to juvenile myoclonic epilepsy
- 2. Lack of AED compliance
- 3. Illicit drugs (cocaine and amphetamines)
- 4. Vascular (ischemic, embolic hemorrhagic stroke)
- 5. Tumor (primary > than metastatic)
- 6. Metabolic
- 7. Medications
- 8. Alcohol withdrawal
- 9. HIV (associated opportunistic infection)
- 10. Encephalitis (herpes simplex)
- 11. Complication of autoimmune disease (SLE)
- 12. Head injury
- 13. Cardiac arrhythmia (global cerebral ischemia)
- 14. Migrational disorders
- 15. Syndrome

Adults over 40 Years of Age

- 1. Lack of drug compliance
- 2. Localization-related with secondary generalization (partial complex seizure)
- 3. Vascular: embolus > infarction > hemorrhage
- 4. Metabolic causes
- 5. Tumor (metastatic > primary)
- 6. Drugs (illicit; hypnotic sedatives, withdrawal)
- 7. HIV (associated opportunistic infection)
- 8. Herpes simplex infection (temporal and frontal lobe involvement with secondary generalization)
- 9. Migrational disorders

Adult over 60 Years of Age

- 1. Vascular: ischemic > embolic > hemorrhagic
- 2. Cardiac arrhythmia
- 3. Metabolic dysfunction
- 4. Prior CNS structural lesion
- 5. Tumor (meningioma > metastatic > glioma or lymphoma)
- 6. Herpes simplex encephalitis
- 7. Migrational disorder (rarely)

Absence Seizure

- 1. Reciprocal connections between neocortical pyramidal neurons, thalamus reticular neurons, and the thalamocortical projection neurons are the anatomical basis
- 2. Patterns of oscillatory activity of this circuitry determine absence seizures or normal wakefulness
- 3. The pattern of thalamocortical activity is determined by the balance between T and P/Q activation and GABA-ergic discharge within the thalamus

- 4. General Clinical Features:
 - a. Onset between 3–6 years of age
 - b. Most prevalent in first ten years of life
 - c. Rarely persist into adulthood
 - d. Seizures are less than 30 seconds
 - e. Not associated with aura or post-ictal confusion
- 5. Clinical Types:
 - a. Simple typical absence:
 - i. Sudden onset of impaired consciousness associated with absence of facial expressions and without motor or behavioral manifestation
 - ii. Approximately 10% of absence seizure patients
 - b. Complex absence seizure:
 - i. Associated motor or behavioral change
- 6. Clinical Manifestations:
 - a. Sudden onset of a blank stare
 - b. Onset of motor activity
 - c. Clonic components: eye blinking, nystagmus, rapid arm jerking
 - d. Tonic postural contraction causing flexion or hyper-tonic extension postures
 - e. Loss of tone causes head nodding or dropping of objects
 - f. Patients rarely fall
 - g. Automatism:
 - i. These are semi-purposeful moments and behaviors which the patient cannot recall. They are perservative or de novo:
 - 1. De novo: Simple acts such as hand rubbing, licking the lips, chewing, scratching, picking at clothes
 - 2. Perservative: dealing cards, handling an object or playing a hand game
 - 3. Speech is usually dysarthric, but may be normal or preservative
 - h. Autonomic manifestations:
 - i. Pupillary dilatation
 - ii. Hyperhidrosis
 - iii. Salivation
 - iv. Piloerection
 - v. Urinary incontinence

EEG

- 1. Generalized 3 Hz spike-and-wave pattern

Atypical Absence Seizures

- 1. Onset prior to age 5
- 2. Associated with other seizure types, GTCS, myoclonic, tonic and typical absence and cognitive impairment
- 3. Average seizure is longer than typical absence; onset is less abrupt
- 4. Diminished postural tone
- 5. Automatisms are more often perseverative
- 6. Postural tone changes frequently
- 7. Blank stare or change of facial expression greater than typical absence seizure
- 8. Smiling automatism is frequent

EEG Evaluation

1. 1.4–2.5 Hz spike-and-wave discharges
2. Multiple spike-and-wave discharge that are irregular or asymmetrical
3. Interictal EEG is often slow and demonstrates multifocal epileptiform features

Absence Syndromes

1. Epileptic encephalopathy:
 - a. Severe brain disorders of early age
 - b. Manifest electrographic EEG paroxysmal activity
 - c. Multiform and intractable seizures
 - d. Progressive cognitive, behavioral and neurological dysfunction
 - e. Assumption that epileptic activity during maturation may be causative of neurological deficits
 - f. Tendency to abate in adolescence but with severe residual neurologic deficits
2. Classification of the International League Against Epilepsy of the following syndromes have been designated:
 - a. Early myoclonic epilepsy (neonatal)
 - b. Ohtahara syndrome (neonatal)
 - c. West syndrome (infancy)
 - d. Dravet syndrome (infancy)
 - e. Myoclonic status in non-progressive encephalopathy (childhood)
 - f. Lennox-Gastaut syndrome (childhood)
 - g. Landau-Kleffner syndrome (childhood)
 - h. Epilepsy with continuous spike-and-wave during slow-wave sleep in childhood and adolescence

Other Syndromes That Are Similar Include

1. Migrating partial seizures in infancy
 2. Severe epilepsy with multiple independent spike foci
- The infantile and childhood forms of primarily absence and myoclonic seizures will not be discussed further.

Juvenile Myoclonic Epilepsy

1. Seizure onset is in adolescence
2. All have myoclonus; 90% have GTCS and approximately 1/3 absence status
3. Myoclonic jerks frequently the earliest sign
4. GTCS and myoclonic seizures occur upon awakening
5. Fewer retropulsive movements
6. May be features of focal epilepsy in the seizure semiology
7. EEG features:
 - a. Predominance of 4–6 Hz polyspike waves
 - b. In approximately 30% of patients, there are focal abnormalities
8. Mutations in CACN1A; CACNB4; CACNA1H genes

Juvenile Myoclonic Epilepsy of Teens

1. Starts between 12–18 years of age (few patients start in the late 20's)

2. Genetics: associated genes are: CACNB4, CASR, GABRA1, GABRD and Myoclonin 1/EFHC1
3. Early morning: mild to moderate myoclonic jerks of the neck, shoulders and arms
4. Myoclonic jerks may culminate in GTCS; 1/3 of patients suffer absence attacks
5. Seizures are precipitated or increased by awakening, fatigue, alcohol or recreational drugs, reading, writing or cognitive activities
6. EEG evaluation:
 - a. Interictal 3.5–6 Hz irregular spike-and-wave complexes
 - b. Rapid 10–16 Hz spikes followed by irregular slow waves are noted during the myoclonic seizures
 - c. JME persists for life
 - d. Drinking on the weekend in adults may initiate myoclonic seizures with GTCS on Monday morning

Pathology of Juvenile Myoclonic Epilepsy

1. Alterations of mesial frontal connectivity by fMRI and diffusion tensor imaging (DTI)
2. Morphometric abnormalities of medial frontal gray matter; micro-dysgenesis or regional neuronal loss
3. Increased measure of microstructural connectivity between the prefrontal cognitive network (pre-SMA) and the motor system appear pivotal
4. Three mutation-harboring genes for myoclonic epilepsy (JME)
 - a. GABA receptor alpha1 (GABARA1) on chromosome 5q 34–q35 (French Canadian family)
 - b. Chloride channel gene
 - i. Chromosome 3q26
 - ii. German family
 - iii. EFHC1
 1. Hispanic family of native American and European ancestry from California and Mexico
5. Patients with HLA-B 1502 who have taken Tegretol have suffered:
 - a. Stevens-Johnson syndrome
 - b. Primarily Indian and Asian patients

Neuroimaging

1. Routine MRI and CT are negative
2. PET reveals metabolic and neurotransmitter changes in the dorsolateral prefrontal cortex (DLPFC)
3. H-magnetic resonance spectroscopy reveals:
 - a. Thalamic dysfunction
4. Quantitative MRI:
 - a. Cortical gray matter abnormalities in medial frontal areas near SMA

Epilepsy with Generalized Tonic-Clonic Seizure on Awakening

1. Onset in the second decade
2. 90% of seizures occur on awakening at any time of the day
3. May occur with relaxation at night
4. Associated with absence and myoclonic seizures
5. Mutations found in CLCN2 gene

Absence Status Epilepticus*Clinical Manifestations*

1. Sustained impairment of consciousness
2. Patients are confused
3. Partially responsive and able to perform activities of daily living
4. Facial twitching
5. Eye blinking
6. Staring
7. Automatisms
8. Arm, neck, and facial muscles are involved
9. Rare in adults

Electrical Status During Slow Wave Sleep

1. General Features:
 - a. Present between 1–12 years of age
 - b. Cognitive regression
 - c. Patient may not have clinical seizures
2. EEG Manifestations
 - a. Continuous spike-and-wave during non-REM sleep
 - b. Seizures and EEG abnormalities may disappear during the second decade

Progressive Myoclonic Epilepsy

1. General Features:
 - a. Consist of a group of diseases with myoclonic seizures and progressive neurologic degeneration
 - b. Onset in childhood or adolescence
 - c. Major clinical manifestations:
 - i. Myoclonus
 - ii. Seizures
 - iii. Cognitive decline
 - iv. Progressive neurologic deficit

Epileptic Encephalopathy with a Component of Myoclonic Epilepsy

1. Dravet syndrome
2. Channelopathies
 - a. SCN1A and SCN1B
 - b. CACNA1A, CACNB4, CACNA1H
 - c. GABA, GABRD, GABRG2
3. Severe myoclonic epilepsy in infancy (SMEI)
4. GEFS

Specific Myoclonic Epilepsies*Lafora Body Disease*

1. Genetics:
 - a. AR
 - b. Mutations in the EPM2A or EPM2B genes
 - i. Encode Laforin phosphatase
 - ii. Malin ubiquitin ligase
 - iii. Cytoplasmically active enzymes that regulate glycogen construction

1. The normal is symmetric expansion into a spherical shape (soluble)
- c. Early onset Lafora body disease
 - i. Maps to chromosome 4q 21.21
 - ii. Gene is PRDM8
 1. Encoded protein interacts with Laforin and malin and causes translocation of these two proteins to the nucleus
2. Clinical Manifestations:
 - a. Onset in teenage years; death between 17–24 years in 90% of patients
 - b. Myoclonus:
 - i. Affects any area of the body
 - ii. Startle sensitive
 - iii. Absent during sleep
 - c. Visual hallucinations
 - d. Dysarthria
 - e. Rigidity
 - f. Spasticity
 - g. Generalized tonic-clonic seizures often the presenting features; status epilepticus in terminal stage
 - h. Visual seizures occur in 50% of patients
 - i. Scotoma
 - ii. Simple hallucinations
 - iii. Occipital complex seizures
 - i. Dementia follows seizures in 2–3 years
 - j. Fluctuating course associated with episodes of cortical pseudo-blindness
 - k. Myoclonus becomes increasingly frequent:
 - i. Associated with alteration of consciousness
 - ii. Disinhibited dementia
 - l. Terminally a vegetative state in status myoclonus

Pathology

1. Increased glycogen content in tissue
2. Malformed glycogen molecules (Lafora bodies) accumulate in skeletal muscles, heart, liver, skin and brain
3. Accumulation of polygons is primarily in dendrites in the cerebral cortex, substantia nigra, thalamus, and globus pallidus

EEG

1. Bilaterally synchronous spike-and-wave complexes in association with myoclonic jerks

Clinical Features of Early Onset Lafora Body Disease

1. AD; PRDM8 gene; chromosome 21q 21.21
2. Encoded protein interacts with Laforin and malin; translocates these proteins to the nucleus
3. Present at 5 years with dysarthria, myoclonus, and ataxia
4. Course is typical progressive myoclonic epilepsy; more protracted than infantile neuronal ceroid lipofuscinoses
5. Intermediate in severity between Unverricht-Lundborg disease and Lafora body disease

Unverricht-Lundborg Disease (Progressive Myoclonic Epilepsy Type 1; EPM1)

1. Genetics:
 - a. Mutation in a cysteine protease inhibitor cystatin B (CSTB) gene
 - b. Inhibits cathepsins
2. Clinical manifestations:
 - a. Onset at 6–16 years of age
 - b. Begins insidiously
 - c. Stimulus-sensitive myoclonus
 - d. Tonic-clonic seizures
 - e. Overtime ataxia, incoordination, intention tremor, dysarthria, dysphagia develop
 - f. Neuropsychologic evaluation reveals:
 - i. Emotional lability
 - ii. Depression
 - iii. Cognitive decline
 - g. Skeletal abnormalities include:
 - i. Thickening of cranial bones
 - ii. Thoracic and lumbar spine scoliosis
 - iii. Large paranasal sinuses
 - iv. Arachnodactyly
 - v. Accessory ossicles of the foot

Neuroimaging

1. Alterations in:
 - a. Subcortical white matter
 - b. Thalamocortical projections
 - c. Cerebellum

Pathology

1. Atrophy of medulla, pons and cerebellum
2. Loss of Purkinje cells, dentate and olivary neurons

Neuronal Ceroid Lipofuscinoses

1. Genetics
 - a. A family of AR lysosomal storage disorders
 - b. Disease mutations in 13 gene cause approximately eleven variants
2. Mutation in CLN6; chromosome 15q23
 - a. Results in a variant late infantile form
 - b. Adult-onset form
 - c. Encoded protein (CLN6) is a non-glycosylated membrane protein localized to the endoplasmic reticulum
 - d. Animal models suggest CLN6 protein is involved in extracellular matrix modulation, signal transduction, apoptosis and immune/inflammatory response pathways
3. Autosomal recessive adult NCL is linked to childhood CLN1, CLN5, and CLN6
4. Autosomal dominant
 - a. DNAJC5 gene
5. Accumulation of subunit C of mitochondrial ATP synthase or SAPs A and D in lysosome-derived organelles
6. Interference in intracellular vesicle trafficking and lysosomal function

Clinical Features of Juvenile Variant

1. Onset 5–10 years of age
2. Begins with progressive visual loss
3. Pigmentary degeneration of the retina
4. Death by the end of the second decade

Adult Variant (Kuf's Disease)

1. Onset in third or fourth decades
2. Progressive dementia
3. Seizures
4. Myoclonus
5. Ataxia
6. No blindness or retinal degeneration

Pathology

1. Loss of neurons in the cerebral and cerebellar cortices with associated atrophy
2. Accumulation of lipopigments in nerve cells
3. CLN1 and CLN10 demonstrate granular lipopigments
4. CLN2 have curvilinear profiles
5. CLN3 have fingerprint profiles
6. Other forms have a combination of these features
7. Specific profile may be seen in lymphocytes, skin, rectum, conjunctiva and skeletal muscles

Mitochondrial Disease and Epilepsy

1. Mitochondrial DNA mutations are major causes of epilepsy
2. Mitochondrial DNA maintenance disorders
3. Complex I deficiency
4. Disorders of coenzyme Q(10) biosynthesis
5. Disorder of mitochondrial translation (RARS2 mutations)

General Features of Mitochondrial Disease

1. Short stature
2. Sensorineuronal hearing loss
3. Proximal muscle weakness
4. Cardiomyopathy
5. Migraine headache
6. Diabetes mellitus

Specific Mitochondrial Diseases with Myoclonic Epilepsy

1. MELAS
2. MERRF
3. POLG (Alpers syndrome)
4. Spinocerebellar ataxia with epilepsy
5. Myoclonus, epilepsy, myopathy and sensory ataxia (MEM-SA)
6. Sialidosis with Myoclonic Epilepsy
 - a. Mutations in the sialidase gene located on chromosome 6p21.3; AR
 - b. Encodes lysosomal sialidase
 - c. Two clinical forms:
 - i. Type II (severe)

1. Early onset at 6 months
2. Dysostosis multiplex
3. Hepatosplenomegaly
4. Cognitive impairment
5. Myoclonic epilepsy
- ii. Type I (milder)
 1. Late onset
 2. Visual loss
 3. Myoclonus syndrome
 4. Cherry red macular spot
 5. Ataxia
 6. Hyperreflexia
 7. Seizures

Neuroimaging

1. MRI
 - a. Diffuse progressive brain atrophy

Action Myoclonus-Renal Failure Syndrome

General Features

1. AR; French Canadian
2. Mutation in SCARB2
 - a. Loss of function
 - b. Encodes a lysosomal membrane type 2 protein

Clinical Manifestations

1. Progressive action myoclonus
2. Dysarthria
3. Ataxia
4. Generalized seizures
5. End stage renal failure
6. Phenotype is variable
7. Some patients have progressive myoclonus epilepsy without renal failure

Rare Causes of Autosomal Recessive Myoclonic Epilepsy

1. Neuropathic Gaucher's disease
2. Ataxia-PME
3. Type III Gaucher's disease
4. All lysosomal diseases

Rare Causes of Myoclonus with Seizures

1. Gaucher's disease (type III) (also categorized as neurodegenerative myoclonus)
2. GM gangliosidosis
3. Biotin-responsive encephalopathy
4. Dentatorubral-pallidoluysian atrophy (DRPLA)
5. SCA6
6. Atypical inclusion body disease
7. Action myoclonus renal failure syndrome
8. Neuroaxonal dystrophy
9. Pantothenic kinase deficiency

10. Celiac disease
11. Dutch mt-DNA deficiency
12. HARP syndrome (hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration)
13. Perioral myoclonia with absences
14. Familial cortical myoclonic tremor with epilepsy (FCMTE)
15. Adult onset polyglucosan disease

Myoclonic Seizures with Perioral Myoclonia

1. Generalized electrographic seizures presenting as perioral myoclonus
 - a. Chin twitching while awake
 - b. Video-EEG
 - i. Paroxysms of polyspike and slow wave activity maximal over frontocentral regions
 - ii. Correlates with chin myoclonus
 - c. Rarely juvenile myoclonic epilepsy and other idiopathic epilepsies are associated with perioral myoclonus

Familial Cortical Myoclonic Tremor with Epilepsy and Cerebellar Changes

General Features

1. Approximately 60 families have been described worldwide
2. AD inheritance; 8q23.3-q24.4; 2p11.1-q12.2 and 5p15.31-p15 are chromosomal localizations

Clinical Manifestations

1. Distal tremulous movements
2. Generalized seizures that manifest after the onset of movements
3. Dutch pedigrees have cerebellar signs and pathology
4. Age at onset ranged from 3 to 70 years
5. Symptoms may differ between pedigrees:
 - a. 8q (Japanese)
 - b. 2p (Italian)
 - c. 5p (French)
6. Japanese pedigrees:
 - a. Age of onset 3rd decade
 - b. Tremor followed by seizure
 - c. Photosensitivity
 - d. No cognitive impairment
7. European pedigrees:
 - a. Onset is earlier
 - b. Widespread cortical/subcortical involvement
 - c. Cerebellar involvement
 - d. Greater progression with cognitive decline
 - e. Complex partial seizures
 - f. Night blindness, migraine, visuospatial deficits, glucose deprivation and exercise as triggers
 - g. Gait disorder

Neurophysiology

1. Tremulous movements:
 - a. Cortical origin
 - b. Stimulus-sensitive
 - c. Cortical hyperexcitability
 - d. fMRI tremulous movements correlate with activity of sensorimotor cortex
 - e. Deficits in GABA-ergic inhibition

Neuropathology

1. Dutch pedigrees demonstrate cerebellar degeneration
 - a. Purkinje cell changes similar to SCA6

Differential Points Between Progressive Myoclonic Epilepsies and Genetic Generalized Epilepsy, Progressive Encephalopathies with Seizures and Progressive Myoclonic Ataxias

PME core features:

1. Increasing action myoclonus; also, present at rest
2. Activates with noise, light and touch
3. Coexistence of other seizures, progressive ataxia, and dementia
4. Presentation in late childhood or adolescence

Juvenile myoclonic epilepsy does not demonstrate:

1. Progressive neurologic disability
2. Failure to respond to AED
3. Background EEG slowing

Progressive Encephalopathy with Seizures

1. GM2 gangliosidosis
2. Non-kenotic hyperglycemia
3. Niemann-Pick type C
4. Juvenile Huntington's disease
5. Alzheimer disease

Progressive myoclonic ataxias:

1. Affects adults
2. Progressive ataxia and myoclonus
3. Few tonic-clonic seizures
4. No dementia
5. Mutation in the MRE11 gene
 - a. Cause an ataxia-telangiectasia-like (ATLD) disorder (causes myoclonic ataxia)
6. Mutations in NBS1
 - a. Cause Nijmegen breakage syndrome (NBS) with myoclonic ataxia

Unusual Features Associated with the Myoclonic Epilepsies

1. Hyperostosis frontalis interna with Unverricht-Lundborg disease
2. Myoclonic jerks – misdiagnosed as focal seizures
3. Focal or lateralized EEG findings as local epilepsy
4. Myoclonus may be triggered by muscular contraction or interruption of muscular activity
5. Bilateral massive proximal myoclonic seizures and GTCS occur concomitantly

6. Severe myoclonic epilepsy of infancy (Dravet syndrome) in adults
 - a. Convulsive seizures persisted from infancy to adulthood
 - b. Often nocturnal
 - c. Less frequent than in childhood
 - d. Loss of cognitive function
 - e. Ataxia and extrapyramidal features in approximately 30% of patients
 - f. Majority have SCNA1 mutations
7. Hepatic signs as the first manifestation of Lafora body disease
8. PME with demyelinating peripheral neuropathy
9. Three mutation-harboring genes for myoclonic epilepsy (JME)
 - a. GABA receptor alpha1 (GABARA1) on chromosome 5q 34-q35 (French Canadian family)
 - b. Chloride channel gene
 - i. Chromosome 3q26
 - ii. German family
 - iii. EFHC1
 1. Hispanic family of Native American and European ancestry from California and Mexico
10. Patients with HLA-B 1502 who have taken Tegretol have suffered:
 - a. Stevens-Johnson syndrome
 - b. Primarily Indian and Asian patients

Tonic Seizures**General Features**

1. Sustained muscle contraction that leads to posturing
2. Last several seconds
3. Tonic seizure with focal epilepsy
 - a. Preferentially affects proximal muscles
 - b. Uni- or bilateral (asymmetric)
 - c. Consciousness not clouded at the onset of asymmetric movements
 - d. Consciousness with bilateral activity (localized to SMA)
 - e. Most common in frontal lobe epilepsy (very rare in TLE)
 - f. Unilateral tonic seizure localize to contralateral side
 - g. 1/3 of frontal lobe origin have bilateral tonic activity

Tonic Seizures from the Supplementary Motor Area

1. Bilateral from onset (usual)
2. May be asymmetric with rapid bilateral spread
3. Posturing may be unilateral or restricted to a single limb
4. Proximal limb and axial involvement is prominent
5. Most often all 4 limbs are involved:
 - a. Abduction of the upper limbs
 - b. Asymmetric flexion of the elbows (fencer posture)
 - c. Abduction of the hips; extended or semiflexed knees

Pattern of Tonic Seizures as a Component of a Generalized Seizure (GTCS)

1. Initiated with tonic flexion of the body with shoulder and arm elevation
2. Semiflexion of the elbows
3. Opisthotonus posture:
 - a. Elbows semiflexed in front of the chest (may be extended)
 - b. Forearm pronation and wrist flexion and finger extension or wrist extension and fist clenching
4. Epileptiform scream from contraction of thoracic and abdominal muscles forcing air through the larynx

Pattern of Secondarily Generalized Seizure

1. Demonstrate a motor sequence
 - a. Version and pulling of the face contralateral to seizure focus
 - b. Progresses to M2e position
 - c. Asymmetric tonic limb posturing “sign of four”
2. Lateralizing significance:
 - a. Tonic force and version-contralateral focus
 - b. Fencing posture (M2e) – lateralizes to the hemisphere contralateral to the extended arm

Epileptic Spasms

1. Usually seen with generalized epilepsies
2. May be seen with focal epilepsies
 - a. Parieto-occipital lobes most common foci
3. Symmetric muscle contractions:
 - a. Tonic or myoclonic features
 - b. Predominantly affect proximal axial musculature
 - c. Flexion of the trunk with extension and abduction of the arms
 - d. Variable length from seizure to seizure
 - e. Generalized EEG pattern
 - f. Possible involvement of the brainstem raphe

Seminal Clinical Seizure Patterns

Clonic Seizures

1. Myoclonic contractions at 2–5 Hz
2. Originate in the primary motor strip
3. Progression:
 - a. Face, frontal eye fields, and hands are affected prior to the legs
4. Clonus without alteration of consciousness as first sign of seizure:
 - a. Contralateral primary motor area
5. Secondary generalized tonic-clonic seizure
 - a. Clonic activity may last longer on ipsilesional side at the end of seizure (paradoxical clonus)
6. Asymmetric seizure end is unusual in generalized epilepsies

Versive Seizures

1. Forced and involuntary turning of the head and eyes

- a. Frontal eye field locus is in the contralateral hemisphere
- b. Version occurs earlier in FEF focus than from temporal lobe focus
- c. Lateralization reinforced if the version occurs within 10 seconds of secondary generalization

Complex Motor Seizures

1. Movements that involve several joints and resemble normal activity:
 - a. Running
 - b. Pedaling
 - c. Automatisms with sexual overtones (writhing, pelvic thrusting, touching the genitalia)
2. Proximal muscle involvement with large movements
3. Occur during sleep
4. Origin is primarily orbital or medial frontal lobe; may occur with insular or temporal lobe epilepsy

Automotor Seizures

1. Manifest as automatisms that involve the mouth, hands, feet and tongue
2. Primarily seen with TLE but can occur from the frontal lobe
3. Clinical features:
 - a. Bilateral or unilateral automatisms
 - b. Frontal lobe in origin is shorter than those from the temporal lobe
 - c. Unilateral automatism suggests an ipsilateral origin
 - d. Greater than 90% are associated with altered consciousness; if consciousness preserved the focus tend to be non-dominant mesial temporal lobe

Gelastic Seizures

1. Primarily from hypothalamic hamartomas
2. Also have been described from lesions in the anterior cingulate gyrus, frontal, parietal and temporal lobes
3. Non-modulated laughter

Atonic Seizures

1. Loss of postural tone with falls or head drop
2. Occur in generalized epilepsies (Lennox-Gastaut syndrome)
3. Preceded by generalized proximal myoclonic seizures
4. May be seen in frontal and temporal lobe focal epilepsies
 - a. Not associated with myoclonic seizures

Astatic Seizures

1. Seizure that consist of epileptic falls
2. A myoclonic seizure followed by an atonic seizure

Motor Seizures

Hypomotor Seizure

1. A decrease or total absence of motor activity
2. Occur concomitantly most frequently with temporal and parietal lobe seizures

Akinetic Seizures

1. Inability to perform voluntary movements
2. Activation of inhibitory motor areas of the mesial frontal and inferior frontal gyri

Negative Myoclonic Seizures

1. A brief movement of less than 400 msec duration (similar to asterixis)
2. Due to loss of muscle tone
3. Reported from the postcentral cerebral cortex

Dystonic Posturing

1. Sustained (>10 sec) unnatural position of an upper extremity with a rotational component
 - a. TLE-lateralizes to the contralateral side
2. Due to activation of the basal ganglia
3. May occur from extratemporal lobe foci

Localization Related Epilepsy**Overview**

In the past, focal seizures were thought to be caused by a paroxysmal depolarization shift of neurons in a focal epileptogenic zone with spread of abnormal electrical activity to other brain regions. Structural lesions were correlated with ictal signs and symptoms. Recent advances in both multimodal neuroimaging and electrophysiological techniques exemplified by functional MRI and magnetoencephalography have demonstrated that focal seizures are caused by abnormalities in functional networks of cortical and subcortical neurons rather than a single epileptogenic focus. The new terminology proposes that “focal” indicates a seizure that arises “within networks limited to one hemisphere that may be discrete or more widely distributed.”

It is clear that seizures interact with functional MRI determined (fMRI) “resting state networks”. Resting spontaneous brain activity continuously interacts with brain networks that underlie salience, sensorimotor, visual, auditory and executive functions.

Focal Motor

1. General characteristics
 - a. The most common type originates in the supplementary motor area (SMA)
2. Clinical manifestations
 - a. Version of the head and eye contralaterally to the seizure focus
 - b. Tonic extension of the limbs opposite the focus (“fencer posture”) which may constitute the entire seizure or it may evolve into clonic movement
 - c. Extension of the limbs may occur prior to simultaneously with loss of consciousness

- d. A unilateral frontal lobe lesion may cause a GTCS without the initial version of the head and eyes
- e. Loss of consciousness is postulated to arise from the spread of the ictal discharge to the thalamic and high midbrain reticular formation
- f. Other clinical presentations include:
 - i. Hyperkinetic complex movements (SMA)
 - ii. Dystonic postures (SMA)
 - iii. Speech arrest (Broca’s area; BA44)
 - iv. Frontal absence
- g. Jacksonian seizures
 - i. Initiated with forceful sustained deviation of the head and eyes, most often contralateral to the epileptic zone but rarely to the ipsilesional zone
 - ii. The seizure focus is usually in Brodmann area BA8
- h. Jacksonian “march”
 - i. Patterns of spread within the primary motor cortex (BA4) are:
 1. Partially dependent on the innervation density, size of the cortical representation of the body part and the activation threshold of neurons that control that body part
 2. The seizure may be initiated with tonic contracting of the fingers, face or foot. If it is initiated in the hand, the thumb may demonstrate clonic movements followed by twitching of the corner of the mouth (cortical representations are contiguous). The tonic contraction of the affected body part transforms into the clonic contractions
 3. The typical spread is from the hand up the arm to the face. The shoulder often is minimally affected; it then spreads down the leg.
 4. If the onset is in the foot, it spreads up the leg, down the arm and to the face
 5. The length of time of the “march” is usually 20–30 seconds
 6. Rarely the first muscles affected can be in the abdomen, thorax or neck
 7. Todd’s paralysis may follow contractions of the affected part:
 - a. The paralysis usually lasts for minutes to hours
 - b. May signify an underlying structural lesion
 - c. The length of the paralysis often bears a relationship to the duration of the seizure
 - d. The cause of the paralysis putatively is:
 - i. Overinhibition of the affected area by mechanisms that terminate the seizure
 - ii. A continuing ictal discharge
 - iii. Possibly metabolic failure of the affected area
 8. If there is a sensory component to the focal motor seizure:

- a. The lesion may be post Rolandic
- 9. Brodmann's area 4 lesions:
 - a. Clonic contractions
- 10. Area 6 lesions cause:
 - a. Tonic contractions contralateral to the focus
- 11. Supplementary motor lesions are associated with:
 - a. "Fencing posture"
- 12. High medial frontal lesions (area 8) are associated with:
 - a. Choreoathetosis
 - b. Dystonic postures
 - c. Complex motor movements
- 13. Involved body parts may demonstrate piloerection and hyperhidrosis
- 14. Ictal aphasia may occur in isolation. Post-ictal aphasia causes complete speech arrest; verbalization at the onset of a seizure is often initiated from the non-dominant hemisphere
- 15. A simple partial motor seizure (no spread), particularly of the upper extremity may last for days to weeks:
 - a. Known as Menschikoff's syndrome
 - b. Usually is due to an old vascular lesion or cortical scar
 - c. Difficult to treat

Simple Sensory Partial Seizure

- 1. The abnormal sensations described are usually as numbness, tingling, "pins and needles", formication (crawling), electricity or movement of a part
- 2. Pain and thermal sensations are rare. Pain sensation can be evoked from insular cortex stimulation and in a few instances from SI
- 3. Bilateral and widespread somatic sensations can occur from lesions of the secondary sensory area SII (at the foot of SI) or the supplementary sensorimotor area (SSMA) and the posterior insular cortex
- 4. SII activation may cause pain or a rising heat sensation
- 5. A Jacksonian sensory march is very similar in sequence to that noted for its motor equivalent
- 6. The face and hand are particularly involved (low neuronal activation threshold; high innervation density)
- 7. The trunk may be involved
- 8. The areas of origin of a sensory march is usually the primary sensory homunculus of SI or the posterior parietal sensory BA5 or BA7
- 9. Occasionally sensory seizures may begin in the proprioceptive component of the sensory cortex (SIa) with consequent posturing of the affected extremity; abnormal kinesthetic sensations may be initiated by a specific passive posture
- 10. Posterior parietal sensory seizures may induce a feeling of tingling in a parietal sensory distribution. Patients may feel unduly tired

- 11. SII activation or its spread to the temporal, parietal occipital junction may induce a sensation of heat that spreads from the feet and envelops the body bilaterally

Frontal Lobe Epilepsy

- 1. General characteristic
 - a. The frontal lobe comprises 1/3 of the human brain
 - b. It is the second most common seizure type
 - c. It can be subdivided into three major regions:
 - i. Dorsolateral
 - ii. Medial
 - iii. Inferior orbital
- 2. Lateralizing signs may not be present; EEG, functional imaging may not be localizing
- 3. The clinical features of frontal lobe seizures depend on the area of the frontal lobe affected and the seizure propagation pathways
- 4. Its semiology is diverse due to its major functions that include:
 - a. The planning and execution of movement
 - b. Primary expressive speech
 - c. Higher cortical executive function
 - d. Memory
- 5. Semiology of frontal lobe seizures by stereoelectroencephalography
 - a. Group 1
 - i. Elementary motor signs (precentral and premotor cortex)
 - b. Group 2
 - i. Elementary motor signs and non-integrated gestural movements (premotor and prefrontal cortex)
 - c. Group 3
 - i. Integrated gestural motor behavior with distal stereotypies (anterior lateral and medial prefrontal areas)
 - d. Group 4
 - i. Seizures with fearful behavior (ventromedial prefrontal cortex with spread to the anterior (oral areas)
- 6. The anatomical organization of frontal lobe semiology
 - a. Organized along a rostrocaudal axis
 - b. Bands within a spectrum (anatomical areas with concordant signs and symptoms) rather than a rigid anatomical area
 - c. The more anterior the seizure focus in the frontal lobe the greater integrated behavior during seizures
 - d. Distal stereotypies (repetitive, impulsive, rhythmic, purposeless movements that follow an individual repertoire) are seen with the most anterior prefrontal seizure foci
 - e. Proximal stereotypies are more common with posterior prefrontal areas
 - f. Somatosensory and Jacksonian clonic signs are highly correlated with a periorolandic localization
 - g. General motor agitation are most commonly localized to frontopolar and orbitofrontal localizations

Dorsolateral Frontal Lobe Epilepsy

1. General Characteristics
 - a. Anatomy
 - i. The dorsolateral frontal lobe is classically divided into:
 1. Brodmann's area 4 (BA4) of the precentral gyrus
 2. Premotor cortex
 3. Prefrontal cortex
2. Clinical Manifestations
 - a. Seizures arising from the primary motor cortex (BA4)
 - i. Partial motor seizures: Jacksonian March
 - ii. Rapid secondary generalization particularly if the focus is M1 or S1
 - iii. Often arise out of sleep
3. Propagate into the second inferior frontal convolution (Broca's area; BA44) which causes speech arrest, stammering or stuttering during the seizure
4. May occur in clusters
5. Seizures are often brief, less than 15 seconds
6. Short ictal state
7. Unilateral or bilateral automatisms
8. Motor arrest
 - a. Activation of the suppressor strip of Marion Hines
9. May maintain consciousness

Premotor Cortex (PMC)

1. Versive seizures with involuntary forced head deviation
2. Sustained and unnatural position of the head; more extreme than that which may be seen from a temporal or occipital lobe focus
3. Forced head deviation occurs contralaterally to the seizure focus occurs in 90% of patients
4. Broca's Area Seizure (BA44)
 - a. Aphasia (speech ignition failure; stuttering)
 - b. Patients may suffer prolonged ictal phenomena if the seizure spreads into the dominant temporal lobe by means of the uncinate fasciculus

Prefrontal Cortex

1. Hypermotor seizures:
 - a. Involve both premotor and prefrontal regions
 - b. They may be preceded by a somatosensory aura that is followed by gestures, coughing, bicycling, pedaling movements, running and thrashing
 - c. Arise out of sleep
 - d. Brief duration
 - e. Short post-ictal state
 - f. May be associated with "stereotypies":
 - i. Motor and Verbal
 - ii. Distal motor stereotypies are associated with an anterior prefrontal localization
 - iii. Proximal stereotypies are localized more posteriorly
 - iv. These movements suggest activation of a frontostriatal loop

Supplementary Motor Area Seizures (SMA)

1. Anatomic localization to SMA (BA8)
2. Brief
3. Preservation of consciousness
4. Sudden paratonic rigidity contralateral to the seizure focus
5. Speech arrest
 - a. Involvement of projections to Broca's area (BA44)
6. Vocalization
7. Cluster at night
8. Fencing posture; extended contralateral arm; flexed ipsilateral arm; contraversive head and eye movements

Orbitofrontal Cortex Seizures

1. Present with either frontal lobe type seizures or temporal lobe semiology
2. There may be no aura until the discharge spreads into the cingulate or insular cortex
3. After propagation:
 - a. Autonomic signs
 - b. Olfactory hallucinations and illusions
 - c. Oroalimentary auras
 - d. Persistent vocalization
 - e. Violent dramatic automatisms
 - f. Motor and gestural automatisms

Cingulate Cortex Seizures*General Characteristics*

1. Anatomical subdivisions
 - a. Affective component
 - i. Connected to the periaqueductal gray, amygdala, anterior insula and the nucleus accumbens
 - ii. A functional component of endocrine and autonomic control
2. Cognitive Component
 - a. Connected to the parietal cortex, lateral prefrontal cortex, premotor and supplementary motor cortices
3. Propagation from ictal posterior cortex
 - a. Motor manifestations from spread to:
 - i. Lateral premotor, orbitofrontal, SMA, precuneus and inferior parietal lobule
 - b. Dialectic seizures (alteration of consciousness (unresponsiveness during the seizure)) and amnesia post-ictally:
 - i. Spread to the medial temporal, intraparietal lobe, mesial occipital and mesial frontal areas

Clinical Manifestations

1. Anterior cingulate focus
 - a. Hyperkinetic seizures
 - b. Associated with fear, laughter or interictal personality change
 - c. Early onset but may start in adulthood
 - d. May occur during sleep

- e. Associated with emotional outbursts (aggressive behavior and psychotic symptoms)
- f. Autonomic symptoms (increased sympathetic tone)
- 2. Posterior cingulate focus:
 - a. Semiology suggestive of a temporal lobe origin
 - b. Surgical resection of the supra cingulate gyrus has caused SMA deficits

Frontal Opercular Seizures

- 1. Ipsilesional clonic facial movements
- 2. Mastication, salivation and swallowing movements
- 3. Choking at night:
 - a. Occurs frequently
 - b. Has extrapyramidal features
 - c. Stereotypy of attacks
- 4. Gustatory hallucinations
- 5. Rare epigastric auras, fear and autonomic signs (tachycardia)

Frontopolar Cortex Seizures

- 1. Vocalization
- 2. Truncal flexion
- 3. Complex gestural automatisms
- 4. Hyperventilation
- 5. Sudden awakening after a seizure
- 6. Bimanual and bipedal automatisms
- 7. Forced thinking
- 8. Axial clonic jerks (may cause falling)

Differential Diagnosis of Hyperkinetic Frontal Lobe Seizures

- 1. Location of the seizure focus:
 - a. Orbitofrontal cortex (OFC)
 - b. Dorsolateral prefrontal cortex (DLPFC)
 - c. Frontomesial cortex
 - d. Frontopolar cortex
- 2. Clinical manifestations
 - a. Complex bimanual and bipedal movements
 - b. Kicking, thrashing, clapping and hand rubbing
 - c. Sexual automatisms

Nocturnal Frontal Lobe Epilepsy

- 1. General Characteristics
 - a. Mutations in CHRNA4, CHRNA2, CHRNB2 and KCNT1 genes that encode:
 - i. alpha4, alpha2, and Beta2 subunits of the neuronal nicotinic acetylcholine receptor
 - ii. A potassium channel subunit
 - b. DEPDCD (DEP domain-containing proteins) has been linked to ADNFLE as well as familial temporal lobe epilepsy (FTLE) and familial focal epilepsy with variable foci (FFEVF)
 - c. Wide spectrum of stereotyped motor manifestations

- d. There is a family history of possible nocturnal frontal lobe epilepsy in approximately 25% of patients with nocturnal frontal lobe seizures
- 2. Clinical Manifestations
 - a. Several attacks per night; multiple episodes occur within hours; often within 30 minutes of sleep onset
 - b. Occur during non-rapid eye movement sleep (stages 1 and 2 of non-REM sleep)
 - c. Stereotyped motor pattern
 - d. Drug resistant forms exist
 - e. Brief duration of attacks (<2 minutes)
 - f. Onset is from infancy to adolescence; the seizures tend to persist into adulthood
 - g. Patients with nocturnal frontal lobe epilepsy (NFLE) have a strong family history of parasomnias
 - h. Often patients are aware of their surroundings and can recall much of the event
 - i. There are no cognitive or behavioral alterations
 - j. Excessive daytime sleepiness
 - k. There are rare spontaneous remissions

Clinical Variants of Nocturnal Frontal Lobe Epilepsy

- 1. Paroxysmal arousals of abrupt and brief episodes of stereotypical motor activity
- 2. Nocturnal paroxysmal dystonic seizures:
 - a. Complex movement and dystonic motor attacks lasting <2 minutes
 - b. Episodic nocturnal stereotyped agitated somnambulism

Differential Diagnosis of NFLE (Nocturnal Frontal Lobe Epilepsy)

Non-REM Arousal Parasomnias

- 1. General Characteristics:
 - a. Arise from stage 3 or 4 NREM sleep
 - b. There is no conscious awareness
 - c. There are three major categories:
 - i. Confusional arousals:
 - 1. Little motor or autonomic involvement
 - ii. Somnambulism:
 - 1. Motor activity but little autonomic symptomatology
 - iii. Sleep terrors:
 - 1. Prominent autonomic involvement and variable motor activity

Differential Clinical Signs Distinguishing NREM Parasomnias from NFLE

- 1. Clinical features supporting the diagnosis of parasomnias
 - a. Crying
 - b. Waxing and waning of the episode
 - c. Physical or verbal interaction with bystanders
 - d. Modification of the event by bystanders
 - e. Coherent speech in sentences
 - f. Normal arousal behaviors
 - i. Scratching and face rubbing

2. Clinical features supporting NFLE

- a. Bicycling movements
- b. Thrashing
- c. Grimacing and grunting
- d. Dystonia

Onset

1. Parasomnias begin with arousal behavior (approximately 80% of events)
 - a. Eye opening, staring and head elevation
 - b. Lasts from seconds to several minutes
 - c. In approximately 20% of patients:
 - i. Explosive motor onset (sitting forwards, frightened and agitated behavior)
 - d. The episode may be triggered by an external event such as a noise or an internal stimulus (cough)
 - e. Tachycardia is invariably associated with the episode
 - f. This pattern at onset is seen in approximately 40% of parasomnias
2. NFTLE Onset:
 - a. Brief arousal behavior similar to parasomnias are seen in approximately 50% of patients (median time of the episode is 7 seconds)
 - b. In approximately 50% of patients, there is abrupt onset with no preceding arousal, associated tachycardia is seen in all events
 - c. Triggers for seizures occur in less than 10% of patients

Differential Diagnosis in Offset Between Parasomnias and NFLE

1. Parasomnias terminate with complete wakefulness in 25% of patients or light NREM sleep in 75%
2. Tapering of effects in those that did not awaken completely
3. Clear distinct offset was seen in <20% of patients

Differential Diagnosis in Offset Between Offset Is in NFLE Patients

1. Approximately 90% end with full consciousness
2. 75% demonstrate distinct offset
3. A small percentage of patients demonstrate dystonic posturing

Behavior Patterns in Parasomnias vs NFLE

1. Behaviors are short
2. Less elaborated than NFLE
3. Parasomnia arousal behavior:
 - a. Is seen at some point during all events; usually at onset or offset
 - i. Hypnotic jerks can precipitate events
 - ii. Trembling and shivering can occur throughout the episode
 - b. Non agitated motor behavior
 - i. Sitting forward, manipulating objects, searching

- ii. Perplexed expression
- iii. Speech is coherent
- iv. Interactive speech and behaviors
- v. This behavioral pattern occurs in 70% of patients
- c. Distressed emotional behavior:
 - i. Occurs in approximately 50% of patients
 - ii. Fearful expression, behavior and speech
 - iii. Sitting, standing, screaming and frantic searching, sobbing and anguish
 - iv. Behavior patterns occur in various combinations

EEG Evaluation

1. Parasomnias and seizures arise out of NREM sleep
2. Most seizures occur during light NREM sleep
3. In parasomnia, there is a light sleep pattern with vertex waves; sleep spindles can occur during episodes
4. Some patients demonstrate a posterior dominant alpha rhythm

AD Frontal Lobe Epilepsy

1. Genetics:
 - a. Mutation in DEPDC5 (Dishevelled, Egl-10 and Pleckstrin)
2. Domain containing protein 5
 - a. Reported in families with familial focal epilepsy with variable foci (FFEVF) linked to chromosome 22q12
 - b. DEPBC5 mutations also found in:
 - i. Familial TLE
 - ii. ADNFLE
 - c. Emode a GTPase-activating protein that is part of a complex that negatively regulates mTORC1
3. Seminal clinical features
 - a. Onset in childhood
 - b. Clusters of brief motor seizures with hyperkinetic, tonic or dystonic features
 - c. Rare GTCS
 - d. Breathless feeling (some patients)
 - e. Cognitive/psychiatric features in some patients
 - f. Association with somnambulism
4. EEG: minimal ictal or interictal abnormalities
5. High rate of drug resistances
6. Overlap between ADNFLE and FFEVF

Temporal Lobe Epilepsy

Overview

The major seizure problem in adults and the source of a major component of intractable epilepsy are complex partial seizures of temporal lobes origin. The spectrum of symptomatology is wide and the semiology varies from patient to patient. The symptoms reported may be the only ones remembered and may be due to propagation patterns.

MRI techniques magnetoencephalography, PET, SPECT, video-EEG with concomitant functional MRI and intracranial recordings have allowed a great deal of insight into the localization of temporal lobe auras and consequent semiology. Often the clinical evaluation allows localization of the symptomatogenic zone which may overlap or is in close proximity to the epileptogenic zone. This is particularly important in MRI-negative focal epilepsy which is shrinking as Tesla strength increases. An increasing share of intractable TLE is due to migrational disorders and focal cortical dysplasia (abnormal lamination) which will be detected by 7 Tesla magnets. Careful evaluation of seizure semiology is a major component of determining the epileptogenic zone. The focal epilepsies that often mimic TLE arise from the insula cortex, temporal-plus (extratemporal areas) and parieto-occipital lobes.

General Characteristics

Definition of Semiology

Semiology is the clinical manifestation of epilepsy:

1. Dependent upon electrical activity from seizures that are initiated and organized within existing neural networks
2. The epileptic discharges spread both temporally and spatially which generate the clinical symptomatology
3. Signs emerge after seizure onset
 - a. Temporal lobe seizures propagate more slowly than those from the frontal lobe
4. The “early spread network” is closely related to the epileptogenic zone
5. Clinical features vary according to the degree of involvement of either the primary or associative cortex (more complex symptoms)

Definition of Primary Cortex Semiology

1. Visual or auditory hallucinations
2. Elementary sensorimotor signs
 - a. May occur as a march (Jacksonian)

Definition of Associative Cortex Semiology

1. Involves more widely distributed networks
2. Altered cognitive function
3. Behavioral abnormalities

Definition of Frequency of the Seizure Discharge

1. Fast gamma discharge deactivates normal function
2. Theta discharge may mimic physiologic function

Definition of Synchronization

1. Interaction between nodes of specific networks (determined by functional MRI)
2. Ictal fear:
 - a. Associated with decorrelation between network nodes that induces “release phenomena”
 - b. Increased synchronization as exemplified by increased synchronization between behavioral nodes

- c. A specific semiology during a seizure is dependent on:
 - i. Anatomical origin of the ictal discharge
 - ii. Propagation
 - iii. Activation and dynamic interplay of nodes within specific distributed networks

Definition of Electrocorcography

1. The measurement of electrical brain signals from electrodes implanted subdurally on the surface of the brain and have:
 - a. High signal to noise ratio
 - b. Are less susceptible to artifacts than scalp EEG
 - c. Have high spatial and temporal resolution
 - i. Less than 1 cm of brain surface
 - ii. Less than 1 millisecond in duration
 - d. Electrocochleography (ECOG) amplitudes in specific frequency bands give insight into:
 - i. Motor execution and planning
 - ii. Auditory processing
 - iii. Visual-spatial attention
 - iv. Information is thought to be relayed in the gamma band (70–110 Hz)
 - v. ECOG identifies functional connectivity and task related spatial-temporal dynamics
 - vi. Most often used in pre-surgical evaluation of refractory TLE patients
 - vii. Aura: an ictal event that occurs at the onset of a seizure
 - viii. Prodrome:
 1. An awareness of an impending seizure days in advance; prodromes may cause:
 - a. Headache
 - b. Irritability
 - c. Fatigue
 - d. Insomnia
 - e. Personality change
 - f. Depression
 - g. Increase in nocturnal myoclonic jerks

Automatisms

General Features of Automatisms

1. Involuntary motor activity often during impaired consciousness
2. Patient is partially or totally amnesic for the behavior
3. May continue or begin in the post-ictal period
4. May be a continuation of movements that occurred prior to the seizure (perserverative) or may be a new (de novo) movement
5. Motor activity is usually fragmentary rarely are there sequential coordinated movements
6. Automatisms vary from patient to patient but are stereotypical for an individual patient; increasingly complex with age
7. May occur with absence, frontal lobe and temporal lobe seizure as well as in the post-ictal phase of a GTCS

8. Temporal lobe automatisms:
 - a. Most often are initiated from the hippocampal formation-amygdala complex; meso orbital frontal lobe and cingulate gyrus. They may be the site of origin of motor automatisms. Oral buccal automatisms most often originate from the amygdala and frontal operculum
 - iii. Failure to perceive one's body
 - iv. Seeing a double of the whole body or body part
 - d. Time distortion (usually too slow)
 - e. Feeling of unreality
 - f. Forced thinking (continued thinking of a specific thought or phrase)

Clinical Manifestations

Patterns of Clinical Automatisms (TLE)

1. Oro-buccal lingual automatisms:
 - a. Smacking of the lips, chewing and swallowing, choking, eating, spitting, abnormal tongue movements and water drinking (amygdala; frontal operculum)
2. Gestural: repetitive movements of the hands and fingers may be semi-purposeful (drawing, playing cards) rubbing the nose or face (most often are post-ictal with an ipsilateral focus)
3. Sexual; masturbation, pelvic thrusting (may also be from a frontal focus)
4. Expressional: facial expression of fear, anxiety, confusion or anger (central amygdala nucleus)
5. Motor automatisms:
 - a. May be unilateral or bilateral
 - b. Unilateral (Ipsilateral epileptogenic zone)
 - c. Ictal frontal lobe motor automatisms, in general, are shorter than those from the temporal lobe
6. Upper limb automatisms differ quantitatively in temporal and frontal lobe seizures
 4. Affective symptoms:
 - a. Ictal fear; poorly localized, may be associated with abdominal sensation impending doom, an overwhelming quality (amygdala or medial hippocampal formation (HF))
 - b. Sadness (common)
 - c. Depression (common)
 - d. Embarrassment (usually medial frontal lobe)
 - e. Joy (rare)
 - f. Crying (dacrystic)
 - g. Sexual feelings
 - h. Gelastic (laughing) is more common with hypothalamic hamartoma; laughing without mirth; not modified correctly; patient may be fearful while laughing
 5. Distortion of memory:
 - a. Déjà vu: as if the experience had occurred before
 - b. Entendu: auditory experience
 - c. Jamais-vu: prior experience or place is experienced as new or unfamiliar
 - d. Vivid "flashbacks" of past events
 6. Special Sensory Symptoms:
 - a. Alterations of perception:
 - i. Unusual clearness
 - ii. Heightened sensitivity
 - iii. Poorly formed hallucinations (primary visual and auditory reception areas)
 - iv. Auditory auras – a "buzz" or "a noise" or distortion of a sound (too far away or too near); Herschel's gyrus; Brodmann's Area 22
 - v. Visual auras and visual hallucinations:
 1. Flashing lights of different colors; the patient blinks and they move in the visual field (usually BA17, BA18, BA19)
 2. Hallucination in front of both eyes (not lateralizing); if in one visual field (VF)-lateralized contralaterally
 3. Blindness during the seizure or post-ictally; flashing lights may be perceived above the blind VF
 4. Complex visual hallucinations and visual illusions (parietotemporal function; limbic cortex)

A Common Sequence Preceding Motor Automatisms

1. Arrest phenomena
 - a. The patient stops activity and maintains a posture for a few seconds
2. Autonomic phenomena
 - a. Loss of facial expression associated with pallor
3. Onset of motor phenomena

Psychic Auras

1. Often preceded by alterations in consciousness
2. General anatomical locations:
 - a. Severe anxiety (anterior temporal lobe)
 - b. Complex phenomena (neocortical) lateral temporal lobe
 - c. Fear, impending doom (medial temporal lobe (central and basolateral amygdala complex))
3. Complex cognitive emotional states (neocortical lateral temporal lobe; right side greater than left)
 - a. Dream state
 - b. Detachment and strangeness
 - c. Autoscopic phenomena:
 - i. Feeling of presence without an optical image
 - ii. Observing oneself from above (out of body experience; autoscopia)

Differential Diagnostic Points Between Fear as an Ictal Event vs a Panic Attack

Clinical Features of a Panic Attack (Psychiatry)

1. Sudden spontaneous onset
2. Intense fear and discomfort
3. Impending doom; thoughts of dread

4. Feeling of being trapped; loss of control
5. Event lasts for a few minutes
6. Full recognition and remembrance of the attack

Fear as a Seizure Aura

1. Anticipating anxiety
2. Expression of impending doom
3. Buccal automatism
4. Autonomic disturbance
5. Complex behavioral automatisms
6. Incomplete recall for the event

Abdominal Auras

General Characteristics

1. Occur in 20–60% of patients with TLE
2. Originate primarily in the temporal lobe but have been described from the insula and frontal lobe (about 20% of patients)
 - a. Approximately 65% from the medial temporal lobe; 35% with neocortical origin
3. Extratemporal locations:
 - a. 5% perirolandic
 - b. 17–20% parieto-occipital
 - c. 3% frontal
 - d. Posterior insular cortex
4. Specific simple sensations:
 - a. Nausea
 - b. Squeezing
 - c. Rolling
 - d. Turning in the abdomen
 - e. Electric shock
 - f. Pain
 - g. Butterflies
 - h. Hunger
 - i. Warmth
 - j. Sudden descent in an elevator; flip-flop; feeling of defecation
5. Auras begin in the epigastrium or stomach in the midline:
 - a. May remain localized
 - b. Rise to the chest, throat or face
 - c. Neck or face involvement is associated with loss of consciousness
6. Associated symptoms with abdominal auras:
 - a. Ictal vomiting
 - b. Subjective fear
 - c. Oro-alimentary symptoms
7. May evolve into clonic seizures
 - a. Occurs in 2/3 of patients with frontal seizures
8. Abdominal pain with abdominal auras
 - a. Pain occurs in 5% of abdominal auras
 - b. Pain occurs in 5% of auras initiated from the frontal lobe
 - c. Painful areas may originate from the parietal lobe
 - d. Direct stimulation of the insula cortex may elicit pain
 - i. There is rare pain from stimulation from SI (somatosensory I)

Olfactory Auras

1. Amygdala is the most common location; also described from the uncus of the hippocampal gyrus (“uncinate fits”)
 - a. Unpleasant smells, burning rubber, garbage, feces; rarely pleasant (usually an exaggeration of the pleasant quality)
 - b. May be produced by cortical stimulation of:
 - i. Amygdala
 - ii. Olfactory bulb
 - iii. Uncus of the hippocampal gyrus
 - iv. Posterior orbital cortex
 - v. Medial temporal lobe
 - c. Olfactory auras may be associated with:
 - i. Gustatory, visual and auditory auras
 - ii. Neoplasms of the amygdala

Gustatory Auras

1. Unpleasant tastes: blood, bitter, chemical, rotting, metallic
2. Insula is the symptomatogenic zone (not lateralizing)

Autonomic Auras

1. Palpitations, sweating, piloerection
2. Symptomatogenic zone (anterior insular cortex)
3. Piloerection map spread similar to a Jacksonian march

Rare Visceral Auras

1. Burning, tingling, growing, choking throat sensations
2. Ictal hunger
3. Ictal thirst (common)
4. Severe pain or unusual genital sensations
5. Severe vomiting
6. Goose bumps (piloerection)
7. Coldness-shivering
8. Spitting (expectoration)

Cardiac and Chest Aura (Insular Cortex)

1. Heart racing or pounding
2. Pain in the central chest (no true cardiac radiations)
3. Cardiac arrhythmias (atrial or ventricular) may be associated

Common Visual Auras

1. Blurred vision
2. Micropsia (objects too small)
3. Macropsia (object too large)
4. Perceptual illusions: objects too far or too close
5. Distorted objects
6. Rare: clear visual hallucination (evergreen true in a temporal visual field)
7. Kinesigenic: aura illusion of movement

Common Auditory Auras

1. Sound or voices not clearly perceived

2. A1 (primary auditory receiving area: clicking, roaring, wind blowing, rumbling sounds)
3. Receptive (Wernicke's) aphasia; BA22, BA23
4. Distorted or muffled sounds
5. Sounds too loud or too soft
6. Auditory hallucination (most often a psychiatric or drug withdrawal phenomenon)

Vestibular Aura

1. Non-specific dizziness or light-headedness. One of the most frequent TLE auras (superior temporal gyrus or intraparietal sulcus)

Cephalic Auras

1. Head is perceived as too big or too small
2. Head is off of the body
3. Ice pick (stabbing) headache (also occurs with migraine)
4. Squeezing compression of the head

Medial Temporal Lobe Seizure Localizing Auras

1. Uncinate auras
2. Impending doom
3. Automatism
4. Arrest response
5. Searching head movements
6. Contralateral dystonia
7. Cough or sigh
8. Amnesia
9. Gustatory auras

Lateral Temporal Lobe Localizing Auras

1. Wernicke's aphasia: speech arrest left side
2. Psychical auras (temporal cortex associated areas R > L)
3. Autosomal dominant lateral temporal epilepsy (ADLTE)

Anterior Temporal Lobe Cortex Aura Localization

1. Panic attacks; anxiety
2. No precipitating cause
3. Stereotypical and associated with autonomic features
 - a. Hyperhidrosis
 - b. Piloerection
 - c. Mydriosis

Medial Temporal Lobe Syndrome

Clinical Manifestations of Hippocampal Sclerosis

1. Early age at onset of seizures
2. Prolonged febrile convulsions important in etiology; seizure free interval after initial febrile convulsion
3. Material specific memory deficit
4. Executive and attention attributes are intact
5. Deficits in:
 - a. Verbal comprehension

- b. Perceptual organization
- c. Verbal memory
- d. Some visual spatial abilities
- e. No generalized cognitive impairment
- f. Impairments in access to an array of cognitive functions rather than restricted pattern of memory loss
- g. Post-ictal psychosis
- h. Autonomic auras
- i. Automatism (oro-buccal-pharyngeal)
- j. Ictal fear
- k. Limbic seizure occurs in the late afternoon and early evening

Neuropathology

Hippocampal Sclerosis (6 Patterns)

1. Classic HS with neuronal loss in CA1, hilus and CA3; sparing of CA2 and the sulculum; some patients demonstrate granule cell dispersion (coincident with new fiber sprouting from dentate granule cells)
2. Total HS with neuronal loss in all hippocampal subfields that includes CA2/subiculum
3. <5% demonstrate endfolium sclerosis (EFS); neuronal loss in the hilus and portions of CA3; sparing of CA1 and CA2
4. A small percentage of patients have primary CA1 atrophy (CA1p)
5. Approximately 20% have indeterminate hippocampal sclerosis (HS) with neuronal loss in CA3 and CA2 with preserved CA4
6. Approximately 10% have clinic and EEG findings consistent with MTLE but no HS

Other Hippocampal Sclerosis Pathology

1. Sclerosis that extends more caudally in the hippocampus
2. Neocortical lesions in the amygdala and parahippocampal gyrus
3. Neuronal loss within the hippocampal formation (HF)
4. Extra hippocampal lesions include:
 - a. Migrational defects
 - b. Scars
 - c. Tumor
 - d. Vascular malformations
 - e. Porencephaly
 - f. Hamartoma
 - g. Occur in approximately 30% of patients with hippocampal sclerosis
 - h. 16% of hippocampal sclerosis patients have bilateral abnormalities on MRI in the HF
 - i. Hippocampal sclerosis occurs without hippocampal formation atrophy in 5–10% of patients; they have normal volume of the HF
 - j. Younger children less than 12 years with HF atrophy have:
 - i. Dysplastic lesions and hamartomas more commonly than astrocytic tumors

Neuroimaging Evaluation

1. Unilateral hippocampal atrophy
2. Decreased signal intensity on T1 in the HF
3. Increased signal intensity on T2 in the HF
4. Abnormal anatomic surface modeling of the hippocampal formation
5. Abnormal T2 signal occurs in the contralateral hippocampus in 30–40% of patients
6. Magnetic resonance spectroscopic imaging (MRSI) demonstrates a decrease of N-acetylaspartate to choline plus creatine ratio in 75% of medial TLE patients
 - a. Bilateral changes occur in 45% of patients
7. Functional imaging with PET and SPECT often demonstrate extra HF abnormal areas

Amygdala Sclerosis*Clinical Manifestations*

1. Seizure onset is later than that which occurs with hippocampal sclerosis
2. Amygdala and HF formation involvement account for 50% of ictal events in MTLE
3. In general, there are the same ictal manifestations and auras as those with hippocampal sclerosis

Neuropathology

1. Bilateral histopathologic changes in greater than 50% of patients; in association with hippocampal sclerosis
2. 10% of TLE patients have isolated amygdala involvement
3. Neuronal loss and gliosis occurs in the lateral and basal nuclear groups
4. May have concomitant involvement of the entorhinal cortex and parahippocampal gyrus (in approximately 20% of HS patients)
5. Pathology of amygdala sclerosis includes:
 - a. Microdysgenesis
 - b. Vascular lesions
 - c. Cortical dysplasia
 - d. Abnormal glial cells (large, hyperchromatic)
 - e. Hamartomas (abnormal clusters of neurons and neuroblast cells)
 - f. Low grade tumors

Neuroimaging Evaluation

1. Voxel based morphometry (VBM)
 - a. Significant increase of gray matter volumes of the temporal pole with amygdala enlargement (due to cortical dysplasia)
 - b. Increased gray matter involvement in the affected amygdala
 - c. FDG-PET demonstrates significant glucose hypometabolism the affected amygdala
 - d. MRI studies show greater involvement of the R amygdala with depression and anxiety
2. Endfolium sclerosis:
 - a. Neuronal loss and gliosis confined to the endfolium (hilus and portions of CA3)
 - b. Hypertrophy of endfolium neurons in some patients with MTLE

Neuroimaging of Hippocampal Sclerosis

1. Ultra-High Field Strength Magnetic Resonance – 7 Tesla
 - a. All patients (8 with TLE) had:
 - i. Abnormalities on the epileptogenic side
 - ii. Selective lateral Ammons' horn atrophy in 6/8 patients
 - b. Diffuse Ammon horn and dentate gyrus atrophy in 1/8 patients
 - c. All patients had fewer hippocampal digitations on the epileptogenic side; 3 had similar findings contralaterally
 - d. Hippocampal malrotation in 3/8 patients (also seen in 4 controls)

Ictal Spread of Medial Temporal Lobe Seizures

1. Change from hyperkinetic movements to mild oral and manual automatisms
 - a. Frontal to temporal lobe spread
 - b. Rarely hyperkinetic movements may be initiated from the temporal lobe
2. No difference in seizure onset patterns in those that remain focal vs those patients that had generalized to GTCS
 - a. More prominent activation of posterior-lateral regions in those patients that had generalized convulsions
3. Patterns of medial temporal lobe propagation are primarily to the prefrontal cortex

Clinical Features of Medial Temporal Sclerosis Base on Voxel-Based Morphometry (VBM)

1. Mesial auras:
 - a. Ipsilateral gray matter volume reductions in the hippocampus and amygdala (R > L); right-sided involved patients demonstrated > reduction in the entorhinal cortex
 - b. Anterior mesio-lateral aura:
 - i. Auras particularly of epigastric rising sensation were associated with reduction in hippocampus, amygdala and insula
 - c. Left temporal lobe patients demonstrate:
 - i. More dispersed gray matter volume (GMV) loss than the right-sided temporal lobe patients
 - ii. Ipsilateral hippocampus, temporal neocortex, uncus, insula, precentral gyrus, thalamus, parietal lobe, cuneus and bilateral cingulum demonstrated atrophy
 - d. GMV reduction corresponds to auras elicited by direct cortical stimulation
 - e. Thalamic abnormalities were restricted to areas of the thalamus that were preferentially connected to the epileptogenic zone

Neocortical Temporal Lobe Epilepsy (NCTLE)*General Characteristics*

1. Older at onset than MTLE
2. In general, seizures are shorter than MTLE
3. There is no seizure free interval once seizures are initiated

Clinical Manifestations

1. Psychical:
 - a. Déjà vu, Jamais vu
 - b. Depersonalization
 - c. Forced thinking
 - d. Autoscapy
 - e. Heightened sensitivity
2. Auditory hallucinations
3. Vertigo/dizziness
4. Visual hallucinations
5. Somatosensory auras

Seizure Onset in Neocortical TLE

1. Motionless stare
2. Upper extremity automatism (Ipsilateral to seizure focus)
3. Dystonic posture of the contralateral arm
4. Bilateral upper extremity automatisms
5. Contralateral tonic or clonic activity of the face or extremities; rarely and early manifestation of the seizure

General Differential Feature Between MTLE and MCTLE

1. Mesial temporal lobe epilepsy (MTLE)
 - a. Fear
 - b. Visceral sensations (epigastric rising; antero-mesial)
 - c. High frequency of bitemporal interictal epileptiform abnormalities
 - d. Oral-buccal automatisms
 - e. Olfactory aura
2. Neocortical temporal lobe epilepsy (NCTLE)
 - a. Psychical auras
 - b. Experiential auras
 - c. Somatic, visual, auditory vertiginous aura
 - d. Dystonic upper extremity (contralateral to the focus)
 - e. Less prominent MRI features
 - f. More lateralized EEG
 - g. Interictal EEG demonstrates epileptiform temporal discharges in approximately 60% of patients
 - h. Associated with mutations in LGI1 in a third of patients

Unusual Neocortical TLE Presentations

1. General characteristics autosomal dominant lateral TLE
 - a. Mutations in the leucine rich, glioma inactivated 1 (LGI1) gene is responsible for approximately 50% of affected families
 - i. Micro deletion with a probable loss of function affected
2. Clinical Manifestations

- a. Variable age of onset (childhood to the fifth decade)
- b. Approximately 3/4 have elementary, complex or secondary generalized seizure
- c. Auditory auras in more than 60% of patients
- d. Other auras include:
 - i. Visual hallucinations
 - ii. Vertigo
 - iii. Déjà vu
- e. Sudden noises precipitate seizures in approximately 20%

Neuroimaging

1. MRI – normal

Epileptic Forced Thinking*Definition*

1. Recurrent intrusive thoughts; crowding of thoughts
2. Obsessive thoughts, auditory hallucinations, auditory perseverations, limbic illusions (new thoughts not previously experienced)

Clinical Features of Temporal Lobe Forced Thinking

1. Out of context to the environment prior to the seizure (e.g. a need to think of letters that begin with “L”, need to think of numbers)
2. Obscene thoughts:
 - a. Patient feels a need to resist or negate the irrational thought

Clinical Features of Frontal Lobe Forced Thinking

1. Speech Arrest:
 - a. Seizure of motor language areas (primarily Broca’s area (BA44))
 - b. Speech arrest or disturbances with intrusive thoughts (urge to shout)
 - c. Forced thoughts less stereotypic than from a temporal lobe focus (whatever words or thoughts used by the patient at the time of the seizure)
 - d. Variability of thought
 - e. Context dependency
 - f. Experiential imagery

Special Clinical Aspects of TLE

1. Reproductive dysfunction:
 - a. 50% of women with TLE have:
 - i. Sexual dysfunction
 - ii. Hormonal abnormalities
 - iii. 14–20% have amenorrhea
 - iv. Fertility reduced by 30%
 - b. Men with TLE:
 - i. Approximately 50–70% have sexual dysfunction (lack of libido)
 - ii. Rarely satyriasis occurs
 - c. Associated reproductive dysfunction in women:

- i. Hypogonadotropic and hypergonadotropic hypogonadism
 - ii. Functional hyperprolactinemia
 - iii. Polycystic ovary disease
 - iv. Anovulatory cycles
2. Prolactin surge after medial temporal lobe seizure:
- a. Levels peak approximately 20 minutes after the seizure
 - b. Prolactin is often elevated, but frequently there are no baseline measurements which makes determination of non-epileptic seizure less reliable
 - c. Direct amygdala connections to the VM hypothalamus

Interictal Personality Traits in TLE

1. Diagnostic specificity and validity of specific personality traits in TLE are controversial:
 - a. Existence of these traits in patients with other seizure disorders
 - b. Prevalence is variable
 - c. Common in the general population
2. Noted interictal traits are:
 - a. Catastrophic overemphasis (left temporal lobe)
 - b. Ideational musings (left temporal lobe)
 - c. Overly emotional (right temporal lobe)
 - d. Denial (right temporal lobe)
 - e. Inclusiveness
 - f. Hypersexuality (rare: usually hyposexuality is seen)
 - g. Dependence
 - h. Obsessive/compulsive behavior
 - i. Hypergraphic
 - j. Hyper-religious
 - k. Hypermoral
3. TLE personality traits and psychopathology:
 - a. Most adult TLE patients are well adjusted and functional
 - b. Personality traits that are noted are primarily with bilateral temporal lobe involvement
 - c. Patients with TLE have a higher incidence of psychiatric disorders than a control population. It is primarily:
 - i. Depression
 - ii. Anxiety
 - d. Psychosis ictally or post-ictally resembles paranoid schizophrenia in some patients:
 - i. Better preservation of affect in TLE vs schizophrenic patients
 - ii. Less personal isolation than schizophrenic patients
 - iii. More prevalent in patients with frequent seizures of long duration
4. There may be evidence of semicontinuous epileptic discharge in limbic areas during psychotic and hallucinatory behavior
5. Characteristics of aggressive violent behavior in TLE:
 - a. It is almost always non-directed
 - b. Short lived

- c. Fragmentary
 - d. May be a stereotyped manifestation
6. Temporal lobectomy may cause:
- a. New onset of psychosis
 - b. Improvement of instability and aggressiveness
7. Predictive variables for the development of interictal psychosis in seizure disorders:
- a. Earlier age of onset of the epilepsy
 - b. Complex partial seizure of the temporal lobe and GTCS are the usual seizure types
 - c. A family history of psychosis
 - d. Borderline cognitive function

Clinical Manifestations of Bilateral Temporal Lobe Lesions

1. Klüver-Bucy syndrome:
 - a. General characteristics:
 - i. The syndrome may occur from temporal lobe epilepsy, temporal lobectomy and partial status epilepticus
 - ii. May occur at any age
 - iii. Children are similarly affected as adults
 - b. Clinical manifestations:
 - i. Oral exploration of objects
 - ii. Hypermetamorphopsia (all objects are examined with the same degree of interest and intensity)
 - iii. Short term memory deficit
 - iv. Marked and indiscriminate hypersexuality
 - v. Shame rage
 1. Trivial provoking events cause anger that reaches maximum intensity instantly and returns to the baseline affective state quickly
 - c. Neuropathology
 - i. Medial temporal sclerosis with migrational disorders
 - ii. Trauma (bilateral temporal lobe involvement)
 - iii. Surgery on one temporal lobe (usually lobectomy)
 1. The remaining temporal lobe being dysfunctional
 - iv. X-RT through the temporal lobes
 1. Pituitary tumors
 - v. Viral encephalitis
 1. Herpes simplex
 - vi. Autoimmune
 1. Limbic encephalitis
 - vii. Mucopolysaccharidoses type IIIA
 - viii. Pick's disease
 - ix. Alzheimer disease
 - x. Heat stroke
 - d. Neuroimaging
 - i. MRI:
 1. Bitemporal involvement with extratemporal involvement (frontal lobe, generalized atrophy, extratemporal deficits) depending on specific pathology

Differential Diagnosis of TLE

1. Facial blankness and staring may resemble absence seizures
2. Complex partial seizures (CPS) from the temporal lobe versus affective psychosis

TLE Associated with

1. Geshwind's syndrome (TLE personality traits):
 - a. Schizoid behavior (often bitemporal involvement)
 - b. Hyper-religiousness (3 religious conversions)
 - c. Hypergraphia (lists of every seizure event)
 - d. Viscous (unable to terminate appropriate questions or a personal interaction)
2. Signs and symptoms supporting seizure rather than psychosis:
 - a. Simple visual or auditory hallucination and illusions
 - b. Usually these are of short duration, stereotyped and intermittent
 - c. Associated speech arrest (primarily receptive)
 - d. Autonomic phenomena
 - e. Patients have insight
3. TLE versus episodic dyscontrol syndrome:
 - a. Episodic dyscontrol syndrome:
 - i. Uncontrolled rage
 - ii. May be alcohol triggered
 - iii. Occurs with provocation
 - iv. Out of patients usual character
 - v. May have CNS deficits
 - vi. May have documented seizures
 - vii. Followed by fatigue and confusion
 - viii. May be amnesic
 - ix. Violence against individuals is common
 - b. TLE:
 - i. Personally directed violence is rare
 - ii. Stereotyped
 - iii. Associated signs and symptoms of seizure activity
4. Migraine with abdominal pain or nausea vs. TLE (or insular cortex seizure focus):
 - a. In children with migraine; the abdominal symptoms may be associated with headaches
 - b. TLE the abdominal auras are followed or associated with rising heat sensations, impairment of consciousness or other epileptic phenomena
 - c. Total duration of episodes is longer in migraine episodes than seizures
 - d. Migraine auras last approximately 5 minutes prior to headache onset, epileptic auras are usually only a few seconds to less than 5 minutes
 - e. Consciousness usually intact with migraine (may be lost with Bickerstaff's migraine or some confusional states)
 - f. Automations support the diagnosis of seizure
 - g. Following migraine, there is less alteration of consciousness than after seizures

5. TLE vs. cardiac arrhythmia:

- a. Major cardiac mechanisms that cause altered consciousness are:
 - i. Cardiac arrhythmia
 - ii. Pump failure (ejection fraction <30)
 - iii. Outflow tract dysfunction
 - iv. Long QT syndrome
 - v. Conduction blocks
- b. Insular seizures may be associated both with chest discomfort and autonomic control of blood pressure
- c. TLE and Cardiac Phenomena:
 - i. Attacks are not associated with the usual cardiac risk factors
 - ii. Associated with other epileptic phenomena
- d. Altered consciousness:
 - i. Tachyarrhythmias are usually noted by the patient prior to decreased cerebral perfusion; bradyarrhythmias may cause loss of consciousness without warning (long QT and heart block)
 - ii. Chest pain in TLE not in the usual cardiac distributions (may involve the throat)
 - iii. Post-ictal phenomena (fatigue, dull headache and thirst) greater with TLE. Cardiac syncope rarely causes post-event confusion

6. TLE vs. Vasovagal syncope:

- a. Clinical characteristics of vasovagal syncope:
 - i. Characteristic pallor prior to the episode
 - ii. A precipitating event (specific site or stress)
 - iii. Slow pulse (adults < 40 beats per minute (bpm))
 - iv. Less than 30 seconds in duration; usually less than 10 seconds
 - v. No confusion or other post event phenomena
 - vi. Patients may have a few myoclonic jerks

7. TLE vs. Vasodepressor syncope:

- a. Vasodepressor syncope clinical characteristics:
 - i. Precipitating event (prolonged bed rest; hypertensive medications; sudden upright posture)
 - ii. Rapid pulse (> 120 beats per minute (bpm))
 - iii. Loss of awareness is brief
 - iv. Recovery of consciousness is often very brief (less than 5 seconds, but may take up to 30 seconds)
 - v. Some transient disorientation but no behavioral confusion
 - vi. Patients insight of the event is maintained

8. Syncope by definition is a brief loss of consciousness and postural tone due to insufficient cerebral perfusion. Its prodromes (more often with vasodepressor than vasovagal) are light headedness, dimming of vision (tend to close in from the side) nausea, muffled hearing (sounds distant), diaphoresis and generalized weakness**9. TLE vs. movement disorders**

- a. Repetitive or sustained movements are against TLE and include:
 - i. Tremors
 - ii. Chorea

- iii. Athetosis
- iv. Dystonia
- b. Episodic:
 - i. Tics
 - ii. Myoclonus
 - iii. Hyperekplexia
 - iv. Paroxysmal dyskinesia

Paroxysmal Dyskinesia vs. Frontal or Temporal Lobe Seizures

1. A frontal lobe focus is much more common than a temporal lobe focus with paroxysmal dyskinesia
2. Kinesigenic or non-kinesigenic paroxysmal dyskinesia may mimic hyperkinetic frontal or temporal lobe seizure:
 - a. Features favoring frontal lobe seizures include:
 - i. Explosive onset
 - ii. Duration of <30 seconds
 - iii. Automatisms, extreme restlessness, pedaling of legs, loud vocalizations
 - iv. Progression into tonic or clonic activity
 - v. Post-ictal weakness
 - vi. Impairment of consciousness
 - vii. EEG discharges and post-ictal slowing clinch the seizure diagnosis, but may be absent in up to 40% of patients
 - b. Features favoring paroxysmal dyskinesia
 - i. Onset of abnormal movements is slower
 - ii. Attacks can last for minutes to hours (only a few seconds, with kinesigenic paroxysmal dyskinesia)
 - iii. No impairment of consciousness
 - iv. Paroxysmal choreoathetosis is associated with provoking factors (sudden movement (kinesigenic), physical exertion, alcohol, caffeine, and hyperventilation)

Stereotypies vs. Complex Partial Temporal Lobe Seizure

General Features of Stereotypies

1. Involuntary, patterned, repetitive, purposeless movements or behavior
2. Occur most often in patients with cognitive impairment, autistic spectrum disorders and Reth syndrome
3. Repertoire of stereotypic behavior may be present
4. Duration and frequency of stereotypic movements are of longer duration and occur several times/day; TLE shorter and less frequent
5. No alteration of consciousness with stereotypies
6. Associated with precipitating events
7. Stereotypies occur during wakefulness

Factors Favoring Seizures

1. Duration and frequency are shorter
2. Associated automatisms
3. Alteration of consciousness
4. No repertoire of movements

5. Often arise out of sleep
6. Impairment of consciousness
7. Cardiac arrhythmias that may occur during TLE complex partial seizures that may be associated with altered consciousness:
 - a. Supraventricular tachycardia
 - b. Sinus tachycardia
 - c. Sinus bradycardia
 - d. Sinus arrest
 - e. AV block
 - f. Asystole
 - g. Reduced heart rate variability
8. General features of cardiac arrhythmias during seizures:
 - a. Sudden induced arrhythmias is a cause of death in seizure patients (SUDEP)
 - b. Ictal tachycardias are more common than bradyarrhythmias
 - c. Bradyarrhythmias occur with both right and left temporal lobe seizures
 - d. Intraoperative stimulation of the insular cortex produces
 - i. Tachyarrhythmias and a pressor response (right anterior insular cortex)
 - ii. Bradycardia and depressor response with L anterior insular cortex stimulation
 - e. Sinus arrest with asystole with left temporal cortex stimulation
 - f. Ictal bradycardia; increased parasympathetic outflow through the vagus nerve
 - g. Stimulation of the amygdala causes bradycardia
 - h. Stimulation of the orbital frontal cortex and cingulate gyrus cause brady- and tachyarrhythmias

Insular Cortex Seizure

1. General Characteristics
 - a. The only cortex that is not visible on the brain surface
 - b. Triangular in shape
 - c. Separated from the frontoparietal and temporal opercular cortex by the anterior, superior and peri-insular sulci
 - d. It is morphologically divided by the central insular sulcus:
 - i. The anterior insula is composed of three short gyri
 - ii. The posterior insula contains two long gyri
 - e. The insula is functionally involved in:
 - i. Cardiac rhythm and arterial blood pressure control
 - ii. Visceromotor function
 - iii. Viscero sensation
 - iv. Processing of nociceptive input
 - v. Interoception
 - f. Insular discharges (recorded by stereoelectroencephalography (SEEG)
 - i. Similar to symptomatology to that of the medial temporal lobe
 - ii. Respiratory viscerosensitive (chest or abdominal constriction)

- iii. Oroalimentary (chewing and swallowing) manifestations
- iv. Unpleasant contralateral somatosensory paresthesias opposite the ictal focus (may be painful)
- v. Ictal signs occur with full consciousness (simple partial seizures)
- vi. Temporal lobe seizures frequently propagate to the insula; possibly 10% of TLE originate in the insula
- vii. Hemisensory sensations and dysgusia an insular pattern
- g. Progression in some patients:
 - i. Sensation of laryngeal constriction
 - ii. Unpleasant contralateral somatosensory paresthesias
 - iii. Dysarthric speech and/or elementary auditory hallucinations
 - iv. Seizures terminated with focal dystonic postures
- 2. Clinical Manifestations
 - a. Respiratory
 - i. Modulation of the amplitude and frequency of respiratory movement
 - ii. Patients feel chest fullness and constriction
 - b. Viscerosomatic:
 - i. Chest constriction ascending to the anterior cervical region associated with nausea
 - ii. Abdominal constriction and heaviness
 - iii. Intense distressing abdominal pain
 - iv. A feeling of throat and laryngeal constriction
 - c. Contralateral somatosensory paresthesias
 - i. Ascending retrosternal feeling of heat
 - ii. Unpleasant and at times painful hemisensory paresthesias
 - d. Painful somatosensory seizures
 - i. Analysis of ictal recordings and stimulation with intracerebral electrodes (5 patients)
 - 1. Pain intensity is greater than from stimulation of SI
 - 2. Elicited pain was not somatotopically organized
 - 3. Large receptive fields
 - 4. The insula and SII (at the foot of SI) were involved at the onset of seizures
 - e. Oroalimentary manifestations:
 - i. Sensation of laryngeal constriction
 - ii. Chewing and swallowing
 - f. In six out of 50 patients with insula seizures a specific ictal sequence occurred:
 - i. The patients were fully conscious; the ictal event was initiated by a feeling of laryngeal constriction and paresthesia followed by unpleasant hemibody sensations and terminally by dysarthria and focal motor signs that included focal dystonic postures
 - g. Dysarthric speech and elementary hallucinations are seen as a pattern
 - h. Temporal lobe seizures frequently propagate to the insula; possibly 10% of TLE originates in the insula

- i. Sleep-related hypermotor seizures may originate in the insula
 - i. Complex motor manifestations occur when the ictal discharges spread to frontomesial areas (the cingulum, superior frontal gyrus and the supplementary motor area) or to neocortical temporal lobe

Parietal Lobe Seizures

- 1. General Characteristics
 - a. Greater than 90% of patients exhibit auras
 - b. The electrophysiological organization and clinical manifestations are complex due to propagation pathways and the wide connectivity of the parietal lobe
 - c. Ictal spread to frontal, supplementary motor or temporolimbic areas
 - d. Recognized parietal and occipital epilepsy syndromes include:
 - i. Benign epilepsy of childhood with centrotemporal spikes
 - ii. Benign epilepsy of childhood with parietal evoked spikes
 - iii. Migraine/epilepsy associations
 - e. Frequent poor correlation between clinical and EEG characteristics
- 2. Clinical Manifestations
 - a. Somatosensory auras:
 - i. Paresthesias
 - ii. Rarely painful (SI involved)
 - iii. Thermal (heat; SII)
 - iv. Sexual sensations
 - v. Disturbances of body image
 - b. Visual auras:
 - i. The environment may be tilted
 - 1. Alteration in the subjective visual vertical
 - ii. Complex hallucinations and illusions of body parts
 - 1. Most often in severe pain states the affected body part may be distorted
 - iii. Oculogyric and eyelid flutter
 - c. Vertiginous sensations (originate from the intraparietal sulcus)
 - d. Tonic posturing (epileptic zones that include the superior parietal lobule)
 - e. Automatisms (epileptic zone that extends to the inferior parietal lobe)
 - f. Disturbance of body image (inferior parietal lobule)
 - g. Anosognosia, apraxia (ideational), alexia and aphasia
 - i. Involvement of BA39, BA40, BA41, BA42
 - h. Aphemia
 - i. Severe dysarthria
 - ii. Difficulty with initiation of speech with retained receptive speech
 - i. Confusional states

- j. Gustatory symptoms
 - k. Ipsilateral version
 - l. Oral gestural automatisms; a small proportion with complex automatisms
 - m. Adversive movements
 - n. Unilateral clonic activity
 - o. Hyperkinetic motor behavior (inferior parietal lobule)
3. EEG Evaluation
- a. Frequently there is poor correlation between scalp EEG and Clinical Semiology
 - b. Interictal discharges demonstrate scatter outside of the parietal lobe
 - c. The majority of patients have more than one spike population

Occipital Lobe Seizures

Overview

Seizures emanating from the occipital lobe present a variety of signs and symptoms both from initial areas of activation and from spread. Visual symptoms are the most common feature of occipital lobe seizures. Elementary visual hallucinations that occur with visual seizures usually from seconds to 1–5 minutes. They consist of colored and small circular patterns that may flash and appear in a temporal hemifield. Blurred vision may occur prior to visual hallucinations. Ictal blindness may occur. Eye movement sensations, eyelid fluttering or forced blinking in association with eye or head deviation is common (contralateral to the seizure focus). Ipsilateral head and eye deviation can be seen. Spread to the temporal lobe with concomitant automatism and loss of awareness is common. Percentage of patients demonstrate myoclonic tonic or focal clonic motor activity characteristic of frontal lobe involvement. Visual reflex seizures may be triggered by patterned flashing lights (video games, strobe lights). Seizure triggering properties of video ensembles include brightness, pattern flicker frequency and color.

Simple Partial Seizure of the Occipital Lobe

1. General Characteristics
 - a. Approximately 2/3 manifest temporal lobe auras
 - b. 1/3 have both temporal and frontal auras
 - c. Spread from an occipital lobe focus is by:
 - i. The inferior longitudinal fasciculus
 - ii. Inferior occipital-frontal fasciculus
 - iii. Occipital-parietal junction to the frontal lobe through the superior longitudinal fasciculus
2. Clinical Manifestations
 - a. Initial signs and symptoms
 - i. Forced eye blinking with head version
 - ii. Blurred vision
 - iii. Flashing lights
 - iv. Ictal blindness
 - v. Elementary visual hallucinations

- b. Occipital pole ictal focus (BA17)
 - i. Simple non-colored flashes of light (dots and circles)
 - ii. Do not move across the visual field
- c. Area 18 and 19 ictal focus (visual association cortex):
 - i. Colored (red, green, yellow, blue) dots, circles and geometric figures are experienced
 - ii. Figures and patterns move across the contralateral visual field (migraine and vascular etiologies > seizure)
 - iii. Putatively secondary to cortical spreading depression from stroke or migraine
- d. Posterior temporal/parieto/occipital cortex junction ictal focus:
 - i. Distortion of objects
 - ii. Images are colored
 - iii. Often associated with other temporal lobe semiologic phenomena
 - iv. Unilateral eye blinking (rare)
 - v. Cortical blindness (rare)
 - vi. Epileptic akinetopsia:
 1. Illusory motion perception
 2. The contralateral visual field is affected
 - vii. Epileptic monocular nystagmus
- e. Signs of occipital seizure spread to the temporal lobe
 - i. Specific visual field deficits (superior quadrantanopsia)
 - ii. Psychical aura
 - iii. Olfactory aura
 - iv. Dizziness
 - v. Somatosensory aura

Idiopathic Childhood Occipital Epilepsy of Gastaut (ICOE-G)

1. General Characteristics
 - a. Relatively rare; approximately 2.7% of benign childhood focal seizures
2. Clinical Manifestations
 - a. Elementary visual hallucinations with multi-colored circular patterns and ictal blindness
 - b. Eye deviation with concomitant head version
 - c. Non-visual ictal symptoms follow the visual ones
 - d. Eyelid fluttering may portend secondary generalization
 - e. Headache and post-ictal transient blindness may occur after prolonged seizures
 - f. Consciousness is preserved at onset but becomes clouded with seizure progression
 - g. There is 50–80% remission within 2–4 years at onset
 - h. Often misdiagnosed as migraine with visual aura
3. Neuropathology
 - a. Functional derangement of systemic brain maturation
4. Neuroimaging
 - a. MRI:
 - i. No structural lesions
5. Laboratory Evaluation

- a. EEG:
 - i. Occipital spike-and-wave pattern
 - ii. "Fixation off" sensitive epileptic activity is induced with eye closure and terminated when the eyes are open (fixation)
 - iii. Elementary visual hallucinations occur with fast spike activity
 - iv. Complex visual hallucinations occur with slower ictal discharges
 - v. Ictal fast spike rhythm may occur prior to eye deviation
- 1. Absence
- 2. Myoclonic
- 3. GTCS
- vii. Epilepsy provoked by television and video games
 - 1. The EEG is activated by:
 - a. Video screens
 - b. Flickering screen light
 - c. Patterns that produce parallel lines that form the image
 - d. Frequency of 25 Hz activate approximately 75% of susceptible patients
 - 2. Seizure types provoked are similar to other photosensitive epilepsies; also provoke partial occipital lobe seizures

Photosensitive Epilepsy

1. General Characteristics

- a. Definition:
 - i. Photosensitivity is defined by the elicitation of occipital or diffuse electroencephalographic spikes and waves by intermittent light stimulation
- b. Photosensitive epilepsies are most common in childhood and adolescence or a feature of idiopathic generalized epilepsies
- c. NEDD4-2 (Neuronally Expressed Developmentally Downregulated 4) gene
 - i. Encodes a ubiquitin protein ligase
 - ii. Regulates cell surface levels of ion channels, receptors and transporters that influence neuronal excitability
 - iii. Possible susceptibility gene for epileptic photosensitivity

2. Clinical Manifestations

- a. Affects 1:4000 seizure patients
- b. High incidence of a family history
- c. General features:
 - i. Stimuli are flashing lights or high contrast patterned stimuli
 - ii. Chromatic sensitivity
 - iii. Stimulus frequency: 10–30 Hz
 - iv. Pattern sensitivity: 5–6 cycles/degree
 - 1. There are chromatic sensitive seizure variants
 - 2. Photo paroxysmal response to rapid color frame changes (blue to red: monochromatic light changes)
 - v. Sensitivity to seizures is increased by:
 - 1. Screen brightness
 - 2. Highly contrasted patterns
 - 3. Fatigue
 - 4. Fever
 - 5. Closeness to the stimulus
 - 6. Sleep deprivation
 - 7. "Fixation off" sensitivity
 - a. Elimination of central vision and fixation induces spikes on the EEG (unilateral or bilateral; of high amplitude)
 - vi. Seizure types that are provoked:

3. Neuropathology

- a. In some patients with occipital lobe epilepsy:
 - i. Periventricular subcortical nodular heterotopias
 - ii. Focal cortical dysplasia which includes polymicrogyria, heterotopias and abnormal cortical lamination
 - iii. Migrational disorders tend to occur posteriorly
 - iv. Vascular disease, tumor, head trauma and inflammatory conditions (Balo's concentric demyelination and tumefactive MS) all occur in the occipital cortex

4. Neuroimaging

- a. MRI:
 - i. Pathology specific disorders (stroke, tumor, inflammation)
 - ii. Migrational defects

5. Laboratory Evaluation

- a. Occipital and diffuse electroencephalographic spikes and waves induced by intermittent light stimulation
- b. Only the diffuse spikes and waves induced by intermittent light stimulation are correlated with epilepsy. Spikes are accentuated by sleep in the childhood form
- c. Magnetoencephalography:
 - i. Cortical responses to a static grating stimulus with altered power but not frequency and increased visual gamma responses are characteristic of photosensitive epilepsy

6. Differential Diagnosis Between Occipital Seizures and Migraine Visual Auras

- a. Visual hallucinations of colored and small circular patterns that flash and are noted in any hemifield are most common in occipital lobe seizures
- b. Elementary and visual hallucinations and visual loss may also occur with anteromedial temporal and occipitotemporal foci
- c. Lesions of the lateral occipital lobe (BA18 and BA19) may elicit twinkling or pulsating lights contralaterally
- d. Linear zig zag lines (fortification scotoma) and achromatic black and white patterns are much more common in migraine
- e. Visual seizures are often frequent and occur in clusters:

- i. A segway into temporal lobe or frontal lobe symptomatology
- ii. Ictal blindness may occur from a seizure due to a focus in one occipital lobe
- f. Vomiting may be ictal (focus in the insular cortex) or a component of seizure provoked migraine
- g. A hemicranial headache that occurs during a seizure:
 - i. Seizure focus may be the ipsilateral amygdala or the hippocampal formation
- h. Rapid onset and resolution of symptoms are most often an epileptic discharge
- i. Ictal epileptic headaches occur and are characterized by:
 - i. An onset and termination coincident with scalp or deep EEG pattern of an epileptic discharge
 - ii. May be followed by motor, sensory or autonomic manifestations
 - iii. Migraine may be the sole epileptic manifestation of the seizure
- j. Points favoring migraine:
 - i. Triggering events
 - ii. Prolonged attack
 - iii. Cortical spreading depression (visual signs/symptoms followed by parietal and frontal neurologic deficits)
 - iv. Slight impairment of cognitive processing rather than complete unresponsiveness

Convulsive Status Epilepticus

1. General Characteristics
 - a. Definition:
 - i. Failure to regain consciousness between seizures (convulsive status)
 - ii. Mortality has dramatically fallen with intensive care and newer medications
2. Clinical Characteristics
 - a. Prolonged status of greater than 30 minutes may be associated with neurologic deficits
 - b. Medical associations include:
 - i. Acidosis
 - ii. Hypotension in general but occasionally severe hypertension
 - c. Hyperthermia
 - d. Renal failure secondary to myoglobinuria
 - e. Injury:
 - i. Posterior shoulder dislocation
 - ii. Subdural hematoma (falls)
 - iii. Fractured vertebrae
 - f. Rare neurogenic pulmonary edema
 - g. Deficits in memory (amnesic state)
3. Neuropathology
 - a. Drug withdrawal
 - b. Alcohol withdrawal
 - i. Approximately 2% develop status epilepticus

- c. Vascular disease, head trauma, encephalitis, autoimmune diseases and brain tumors are major causes. All primary causes may cause status epilepticus
- d. Hypoxic changes and borderzone ischemia; putatively hippocampal formation sclerosis
- 4. Neuroimaging
 - a. MRI:
 - i. FLAIR and DWIC (diffusion weighted images) define areas of the focal seizure or in the hippocampal formation
 - ii. The signal changes may last for days

Clinical Variants of Status Epilepticus

Absence Status

1. General Characteristics
 - a. The most common childhood epilepsy
 - b. Absence status is diagnosed when there is no interval of normal mental activity between attacks which may be bunched per day
2. Clinical Manifestations
 - a. Seizures are short
 - b. Rapid onset and termination
 - c. Sudden loss of consciousness
 - d. A brief stare and cessation of activity
 - i. 10% of patients are motionless
 - ii. Most have bursts of myoclonic movements of the eyelids or facial muscles, fingers or synchronous movements of the arms at 3 per second
 - iii. May have minor automatisms
 - iv. Vasomotor alterations occur
 - e. Absence status occurs in adults
 - i. Associated with generalized tonic-clonic seizures
 - f. Carbamazepine or phenytoin may induce absence status in idiopathic generalized epilepsy, atypical absence epilepsy and both typical and atypical myoclonic epilepsy

Myoclonic Status Epilepticus in Juvenile Myoclonic Epilepsy (MSE)

1. General Characteristics
 - a. Rarely occurs in juvenile myoclonic epilepsy
2. Clinical Manifestations (7 patients/247)
 - a. Age range from 17–73 years
 - b. Incidence of 3.2/1000 patient years
3. Three subtypes:
 - a. MSE with only myoclonus (2/7)
 - b. MSE with GTCS (3/7)
 - c. GTCS with myoclonus absence status (2/7)
4. One patient had repeated episodes of MSE
5. Precipitating events:
 - a. Drug withdrawal (4/7)
 - b. Sleep deprivation and alcohol (1/7)

Refractory Status Epilepticus

1. General Characteristics

- a. Definition:
 - i. Status epilepticus that fails to respond to the acute administration of two antiepileptic medications
 - ii. Occurs in approximately 1/3 patients with status epilepticus
 - iii. Is associated with increased mortality and functional disability
- b. If status epilepticus is continuous or recurs 24 hours or more after administration of anesthetics it is termed super refractory status epilepticus (RSE)
2. Clinical Manifestations
 - a. Generalized convulsive status epilepticus or complex partial status epilepticus that fails initial therapies
 - b. Stupor or coma following a GCTS or complex partial seizure
 - c. Stupor or coma following brain surgery or acute brain injury
 - d. Patients with cardiopulmonary complications and prolonged drug-induced have worse functional outcomes
 - i. 75% of RSEs have a poor outcome
 - e. A condition of ongoing or intermittent clinical epileptic activity without convulsions for at least 30 minutes
 - f. It is seen in a heterogeneous group of illnesses and accounts for approximately 20–30% of status epilepticus patients
 - g. The most frequent form is complex-partial status epilepticus
2. Clinical Manifestations
 - a. Partial status epilepticus
 - b. Absence status
 - c. Aura status
 - d. Subtle status
 - e. A possible diagnosis in all patients with unexplained change or altered level of consciousness or behavior
 - f. In the pediatric population
 - i. Can occur in acute neurological injuries
 - ii. Specific childhood epilepsy syndromes
 - iii. Patients with learning difficulties
3. Laboratory Evaluation
 - a. EEG
 - i. Low cut-off frequency limit of 2.5–3 Hz for non-evolving patterns
 - ii. Discharge evolution of frequency, location or morphology
 - iii. A secondary criterion:
 1. A significant clinical or EEG improvement after the administration of a rapidly acting anti-epileptic drug

Electrical Status Epilepticus in Sleep

1. General characteristics
 - a. Electrical status epilepticus in sleep (ESES)
 - i. An EEG pattern of activation of epileptiform discharges in sleep
 - ii. The two clinical epileptic syndromes seen with ESEs are
 1. Continuous spike-and-wave in slow-wave sleep (CSWS)
 2. Landau-Kleffner syndrome (LKS)
2. Clinical Manifestations
 - a. There is an overlap between the two syndromes
 - b. CSWS:
 - i. A global regression of function
 - ii. Difficult to treat seizures
 - iii. EEG foci are primarily in the frontotemporal or frontocentral regions
 - c. Landau-Kleffner syndrome
 - i. Have an acquired auditory agnosia
 - ii. Fewer seizures
 - iii. EEG ictal focus in posterotemporal areas
 - d. Electrical status epilepticus in slow wave sleep
 - i. Is self-limited
 - ii. EEG abnormalities of continuous epileptic activity persists through 85% of non-rapid eye movement sleep
 1. EEG activity is spike-and-wave epileptic discharges
 - iii. The developmental and neuropsychological prognosis is correlated with the length of the ESEs

Non-Convulsive Status Epilepticus

1. General Characteristics
 - a. Definition:
 - i. A wide variety of etiologies have been described as causative and include:
 - i. Rasmussen's syndrome
 - ii. Russian spring-summer tick-borne encephalitis

Epilepsia Partialis Continua

1. General Characteristics
 - a. The eponym for the disease is Kozhevnikov epilepsy
 - b. Typically associated with lesions of the cerebral cortex
2. Clinical Manifestations
 - a. Persistent rhythmic clonic movements of one muscle group most often of the face, arm or leg
 - b. Occur at regular intervals and may last for months without spread to other muscle groups
 - c. It is a focal motor status epilepticus
 - d. The distal muscles of the hand and fingers are more often affected than proximal muscles
 - e. The corner of the mouth and eyelids are most often affected in the face
 - f. Rarely isolated muscles of the neck and trunk may be affected unilaterally
 - g. Different proprioceptive input from the involved muscles may decrease the movements
 - h. The movements may be diminished not abolished in sleep
3. Neuropathology
 - a. A wide variety of etiologies have been described as causative and include:
 - i. Rasmussen's syndrome
 - ii. Russian spring-summer tick-borne encephalitis

- iii. Vascular disease
 - iv. Multiple sclerosis
 - v. Steroid responsive encephalopathy with autoimmune thyroiditis
 - vi. Mitochondrial diseases
 - vii. Alcohol-responsive (one patient reported)
 - viii. Developmental anomalies
 - ix. Hyperosmotic syndromes
 - x. Degenerative disease
 - xi. Unknown cause
 - xii. Autopsy has revealed involvement of the contralateral motor cortex
4. Neuroimaging
- a. MRI
 - i. Characteristics of the underlying neuropathologic cause
5. Laboratory Evaluation
- a. EEG:
 - i. Focal EEG abnormalities that include
 - 1. Repetitive slow wave discharges
 - 2. Sharp waves or spikes either over the central areas of the contralateral hemisphere or the area of discharge
 - b. Some patients have demonstrated concomitant cortical myoclonus with epilepsia partialis continua

Focal Seizures Characterized by Altered Awareness

- 1. General Characteristics
 - a. Focal status epilepticus most commonly occurs from an ictal focus in the temporal lobe. The second most common focus is the frontal lobe
- 2. Clinical Manifestations
 - a. Patients with temporal lobe focal status epilepticus demonstrate:
 - i. Altered awareness and behavior
 - ii. Often manifest by automatism that are perseverative or de-novo
 - iii. Lip-smacking and chewing
 - iv. The patient is amnesic for the event
 - v. The episode may last for hours and rarely for days
 - b. Frontal lobe focal status
 - i. May be associated with complex motor functions
 - 1. Bicycling or pedaling movements, running and complex automatisms
 - 2. Dystonias of the extremities contralateral to the focus
 - 3. Version (forced) of the head and eyes
 - 4. Gyrotory movements
- 3. Neuropathology
 - a. Temporal Lobe status
 - i. Medial hippocampal sclerosis
 - ii. Developmental anomalies of the temporal lobe
 - iii. Low grade astrocytomas
 - iv. Arteriovenous malformations
 - v. Migrational defects

- vi. Head trauma
 - vii. Vascular disease
 - viii. Rare autoimmune or inflammatory disease
 - ix. Paraneoplastic syndromes
- b. Frontal Lobe status
- i. Head trauma
 - ii. Primary or metastatic tumor
 - iii. Migrational defects
 - iv. Vascular disease (stroke or hemorrhage)
 - v. Arteriovenous malformation
 - vi. Autoimmune or inflammatory conditions
 - vii. Rasmussen's encephalitis
 - viii. Paraneoplastic syndromes (Anti-Hu antibody and those associated antibodies to potassium channel complexes)
4. Neuroimaging
- a. MRI:
 - i. Lesions of the underlying pathology
5. Laboratory Evaluation
- a. EEG
 - i. Ictal discharges are demonstrated during the seizure activity

Psychogenic Non-Epileptiform Seizures (PNES)

- 1. General Characteristics
 - a. Definition:
 - i. Episodes which simulate convulsive or non-convulsive seizures that are not the result of an epileptic discharge
 - ii. Comprise a proportion of treatment resistant epilepsies; possibly >50% of patients with PNES have been treated with anti-epileptic medication (AEDs)
 - iii. Approximately 4% of patients with transient loss of consciousness and many with apparent status epilepticus
 - iv. A significant portion of patients with PNES have true epileptic seizures
- 2. Clinical Manifestations
 - a. Synchronous thrashing
 - b. Side-to-side head movements
 - c. Tip of the tongue biting
 - d. Pelvic thrusting; rapid tremor
 - e. Opisthotonic posturing
 - f. Screaming or speaking during the episode
 - g. Forced eye closure against resistance
 - i. Lids are open or demonstrate clonic movements during seizures
 - h. Prolonged episodes
 - i. Rapid breathing
 - i. Apnea occurs during or after an ictal event
 - j. Occur in the presence of observers
 - k. Are precipitated by emotional events
 - l. Continence is maintained
 - m. Avoidance of dangerous falls
 - n. Prolonged vague states may be PNES

- o. Sexual abuse and previous psychiatric difficulties prior to PNES onset
- 3. Neuropathology
 - a. Abnormal functional connectivity density
 - i. Functional connectivity density mapping (voxel-wise data driven technique) has demonstrated:
 - 1. Abnormal functional connectivity density in the frontal cortex, sensorimotor cortex, cingulate gyrus and insula
 - 2. PNES patients demonstrated abnormalities in several resting state networks
- 4. Neuroimaging
 - a. MRI:
 - i. May be abnormal in approximately 1/3 of patients due to varying pathologies
- 5. Laboratory Evaluation
 - a. Video-EEG
 - i. Is able to distinguish symptoms compatible for PNES from Epileptic seizures
 - ii. Interictal EEG may be abnormal in a significant mesiofrontal region and anterior nuclei of the thalamus
 - b. GCTC patients showed no differences from controls

IGE Evaluated by Diffusion-Tensor Imaging

- 1. Analysis of fractional anisotropy (FA), mean diffusivity (MD), axial and radial diffusivity
- 2. There are widespread FA reductions and increases of mean and radial diffusivity as compared to controls in the JME in the:
 - a. Corpus callosum
 - b. Corticospinal tracts
 - c. Superior and inferior longitudinal fasciculi
 - d. The anterior limb of the internal capsule
- 3. There were no fractional anisotropy differences in idiopathic generalized epilepsy with tonic-clonic seizures (IGE-GTC) number of patients
- 4. Epileptiform activity is seen in <10% of patients
- 5. The serum creatinine kinase is normal after PNES episodes

Reflex Epilepsies

- 1. General Characteristics
 - a. Seizures can be evoked in predisposed patients by specific external or internal stimuli
 - b. The classification of these types of seizures is based on the stimulus characteristics
- 2. Clinical Manifestations
 - a. Visual stimuli
 - i. Patterns, colors, frequency of flicker
 - b. Auditory stimuli
 - i. Startle
 - ii. Specific sounds
 - iii. Music (particular tones)
 - iv. Voice
 - c. Somatosensory

- i. Rubbing or touching a specific
- ii. Thermal stimuli (hot bath)
- d. Reading, writing, mental arithmetic, chess playing and various praxis

Characterization by Generalized Versus Focal Reflex Seizures

- 1. Generalized reflex seizures
 - a. Precipitated by specific aspects of light stimuli
 - b. Various aspects of thinking and decision making
 - c. Respond to valproic acid
- 2. Focal reflex seizures
 - a. Reading, writing, other language functions
 - b. Startle
 - c. Somatosensory stimulation (brief or sustained)
 - d. Proprioception
 - e. Auditory stimuli
 - f. Thermal (hot water immersion)
 - g. Vestibular stimuli
 - h. Eating
 - i. Orgasm
- 3. Types of seizures elicited by specific stimuli
 - a. Partial complex seizures
 - i. Reading
 - ii. Voices
 - iii. Eating
 - b. Visual stimuli:
 - i. Myoclonic
 - ii. Generalized tonic-clonic
 - c. Music induced:
 - i. Myoclonic
 - ii. Simple or complex partial seizures
 - d. Visual and higher cortical functions
 - i. Generalized tonic-clonic seizures
 - e. Focal seizures (beginning in a specific body part) may evolve from myoclonic jerks to an absence or GTCS
- 4. Neuropathology
 - a. Focal lesions of the occipital lobe in some instances
 - b. Regions of cortical hyperexcitability or distributed neural circuits that are physiologically activated by sensory, motor or cognitive input
 - c. Migrational defects
- 5. Neuroimaging
 - a. MRI:
 - i. Often normal
 - ii. Rarely a migrational defect or structural lesion most often in the occipital lobe

Sudden Unexplained Death in Epilepsy (SUDEP)

- 1. General Characteristics
 - a. SUDEP is the leading cause of death in patients with refractory epilepsy
 - b. Risk may be as high as 35% in this population
 - c. Occurs most often in adulthood
- 2. Clinical Manifestations
 - a. Most patients have history of GTCS and die in bed

- b. In children a higher risk is seen with:
 - i. Refractory epilepsy
 - ii. Developmental delay
 - iii. Tuberous sclerosis
 - iv. Some epileptic syndromes
- c. Risk factors in adults
 - i. Refractory seizures
 - ii. Non-therapeutic anti-epileptic drugs
 - iii. Post-ictal period following a tonic-clonic seizure
 - iv. Early adulthood
 - v. Cognitive impairment
 - vi. v3 GCTS in the prior year
- 3. Neuropathology
 - a. Putative seizure-induced cardiac and respiratory arrest
 - b. Defects in the serotonergic system
 - c. Ictal adenosine release
 - d. Autonomic dysregulation
- 4. Neuroimaging
 - a. MRI:
 - i. Normal other than the pathologies that may be associated with the underlying seizure disorder
- 5. Laboratory Evaluation
 - a. EEG
 - i. Post-ictal generalized EEG suppression

Laboratory Abnormalities Associated with Seizures

- 1. Disruption of the blood-brain barrier (BBB)
 - a. Following a focal seizure there may be focal cerebral edema at the ictal zone demonstrated by:
 - b. Increased T2-weighted, FLAIR (fluid-attenuated inversion recovery) and DWI (diffusion-weighted) sequence signal in the ictal zone. There may be slight gadolinium enhancement in the same area
 - c. There is a correlation between the length of the seizure and these neuroimaging signal abnormalities
 - d. Angiography and perfusion imaging techniques may also demonstrate increased blood flow and volume in the ictal zone
 - e. Neuroimaging deficits rarely last for more than 24 hours
 - f. Increased T2 signal intensity and DWI signal may be seen in other structures following a prolonged seizure. These include:
 - i. Hippocampus
 - ii. Thalamus
 - iii. Cerebellum
 - iv. Splenium of the corpus callosum
- 2. Systemic abnormalities following prolonged convulsive seizures
 - a. Increased lactic acid with a drop of serum pH to 6.8–7.0
 - b. Rise in serum creatine kinase that lasts for hours (following a convulsive seizure)
 - c. Increased serum prolactin are elevated for 10–20 minutes following all types of seizures with the exception of absence or myoclonic seizures. There may be a slight rise after a syncopal episode

- d. There is a slight rise of ACTH and serum cortisol that have longer latency and brief duration
- 3. The cerebrospinal fluid (CSF)
 - a. In approximately 15 percent of patients there may be 10–50 cells/mm³ in the CSF
 - b. A slight elevation of protein may occur
 - c. The glucose is normal

Neuroimaging Features of Specific Epilepsies

- 1. Dravet's syndrome (SME1; severe myoclonic epilepsy of infancy)
 - a. 2 Tesla MRI (13/58 patients)
 - i. Cortical brain atrophy (8/13)
 - ii. White matter hyperintensities (1/13)
 - iii. Cerebellar atrophy (1/13)
 - iv. Hippocampal sclerosis (1/13)
 - v. Forced cortical dysplasia (1/13)
 - vi. Ventricular enlargement (3/13)
 - b. Visible MRI demonstrated more gross abnormalities in those patients without SCN1A mutations (39% to 11%)
 - c. Approximately 20% of Dravet's patients had gross MRI alterations.
 - d. Brain morphometry (voxel brain morphometry) as well as cortical thickness and gyrification measurements
 - i. There were global reductions of gray and white matter
 - ii. Volume reductions in white matter were noted in:
 - 1. Brainstem, cerebellum, corpus callosum, corticospinal tracts and the left inferior fronto-occipital fasciculus and left uncinate fasciculus
 - iii. Reduced cortical folding in the right precentral gyrus
 - iv. These abnormalities are putatively linked to the SCN1A mutation

Idiopathic Generalized Epilepsies

- 1. Comprise:
 - a. Generalized tonic-clonic seizures
 - b. Childhood and juvenile absence epilepsy
 - c. Juvenile myoclonic epilepsy (JME)
 - d. GTCS on awakening
- 2. Visual assessment of routine MRI in patients with IGE is usually normal
- 3. Voxel based morphometry
 - a. JMC demonstrated increased gray matter concentration in frontobasal regions
 - b. Absence seizures showed increased gray matter in the superior mesiofrontal region

Analysis of Generalized Clonic-Tonic Seizures by Resting State fMRI

- 1. General Characteristics
 - a. fMRI networks are:
 - i. Reproducible across subjects
 - ii. Have appropriate test-retest reliability

- iii. Correspond to brain circuits that are engaged in specific activities
 - iv. Have a close correspondence between intrinsic functional connections and anatomical pathways (demonstrated experimentally)
 - v. Resting-state connectivity is altered in pathologic conditions
2. Generalized tonic-clonic seizures
 - a. As compared to controls GCTS demonstrate:
 - i. Increased interhemispheric functional connectivity between the bilateral cuneus and anterior cingulate cortex
 - b. Decreased functional connectivity between the bilateral olfactory cortex, inferior frontal gyrus, supramarginal gyrus and temporal pole

Functional Neuroimaging Abnormalities in Idiopathic Generalized Epilepsy

1. General Characteristics
 - a. Abnormalities of the amplitude of low frequency fluctuations (ALFF) is neuronally based and is decreased in pathologies of localized areas
 - b. Abnormalities of amplitude of low frequency oscillations have been in widespread disorders such as attention deficit hyperactivity disorder (ADHD)
2. fMRI (amplitude of low frequency fluctuations)
 - a. The studied patients had a normal MRI on visual inspection as well as no deficits in cortical thickness, gray-white contrast measures or thalamic volumes
 - b. There was no structural difference in the anterior medial PFC; abnormal signaling with the thalamus from this area is thought to be pivotal in IGE
 - c. Decreases in fALFF (amplitude of low frequency fluctuations $< .1$ Hz) in the PFC thalamus subregion
 - d. Resting state functional connectivity (RSFC)
 - i. Anterior medial prefrontal cortex (mPFC) is abnormally integrated into the default mode network in IGE patients

Neuroimaging of Focal Epilepsy for the Temporal Lobe

1. General Characteristics
 - a. Temporal lobe epilepsy patients are divided into lesional TLE or non-lesional that is based on MRI visualized structural abnormalities
 - b. High resolution 3T MRI with automated segmentation was used for evaluation
2. MRI segmentation analysis:
 - a. Both groups of patients (lesional and non-lesional) demonstrated:
 - i. Lower normal brain volume (NBV) compared to controls
 - ii. Lower normal white matter volume compared to controls
 - b. Lesional TLE patients had:
 - i. Lower hippocampal volume than healthy control or IGE patients
 - ii. Atrophy in both ipsilateral and contralateral structures

- c. Both lesional and non-lesional TLE patients had:
 - i. Lower amygdala volume than healthy controls
- d. A trend for lower caudate volumes in patients with lesional TLE

Resting State fMRI Network Analysis in Temporal Lobe Epilepsy

1. Impaired connectivity has been demonstrated between:
 - a. The rostral and caudal hippocampus and the entorhinal cortex ipsilaterally to the seizure focus
 - b. Reduced functional connectivity between the ipsilateral and contralateral hippocampi
 - c. Reduced functional connectivity between the epileptogenic mesial temporal structures and bilateral temporal neocortices
2. Abnormal connectivity has been demonstrated between the epileptogenic mesio-temporal regions and the default mode network (prefrontal cortex, posterior cingulate cortex, precuneus, inferior parietal lobules)

Diffusion Tensor Imaging in Temporal Lobe Epilepsy

1. Decreased fractional anisotropy has been demonstrated in the:
 - a. Inferior and superior longitudinal fasciculi
 - b. The internal and external capsule
 - c. The corpus callosum
2. Less extensive disruption in mean diffusivity

Hippocampal Sclerosis

1. MRI features of hippocampal sclerosis include:
 - a. Reduced hippocampal volume
 - b. Increased signal intensity on T2-weighted imaging
 - c. Disturbed internal architecture
 - d. Major pathologic correlates of these MRI features include:
 - i. Neuronal loss
 - ii. Chronic fibrillary gliosis of the pyramidal cell layer
 - iii. Granule cell dispersion
 - iv. Mossy fiber sprouting
 - v. Alterations in interneurons
 - e. Hippocampal sclerosis may occur with a second lesion most often ipsilateral to the HS. It may be in the temporal lobe or extratemporally
 - f. There may be more extensive sclerosis that extends to the amygdala and para hippocampus
 - g. Focal cortical dysplasias type IIIa are increasingly demonstrated in addition to the HS by higher field strength magnets

Pathology of Epilepsy

1. Primary generalized epilepsy

- a. Genetic varieties:
 - i. CNS is grossly and microscopically normal in mutations of ion channels
- b. No lesions are noted in transient episodes of:
 - i. Drug intoxication and withdrawal

Abnormal Neuronal and Alial Proliferation or Differentiation *Tuberus Sclerosis*

A. General characteristics

- a. Autosomal dominant monogenetic disease that causes benign tumors in skin, heart, kidney, lungs as well as brain malformations and neuronal defects
- b. Genetics: The illness is caused by inactivating mutations in one of two genes, TSC1 and TSC2. The inactivation causes increased activity of the mammalian target of rapamycin (mTOR)
- c. TSC1 on chromosome 9q34 and TSC2 on chromosome 16p13 encodes the protein hamartin and tuberlin respectively
- d. The majority of patients is born with at least one identifiable mutation and is heterozygous for either TSC1 or TSC2. There may be subsequent inactivating mutations of the functioning allele which causes loss of heterozygosity. This process occurs somatically in a subset of cells and may be detectable in the brain or other affected tissues
- e. The inactivating mutations cause hyperactivation of mTORC1, hyperphosphorylation of HE-BP1 and activation of ribosomal protein S6 through S6K1 phosphorylation. This pathway activation causes sustained translation of growth promoting transcripts
- f. 1/3 of patients have inherited mutations that are identified in parents; 2–3% of patients have de novo mutations that occurs as a result of germline mosaicism
- g. A small proportion of patients may have sporadic mutations that arise in very early somatic cells and may be unequally expressed in organ systems
- h. Patients are considered to have a mutant allele although some organs exhibit somatic mosaicism
- i. The acquired allelic mutations from the parents as well as the timing of the somatic mutations cause the phenotypic spectrum seen in TSC patients
- j. TSC2 gene mutations have a worse prognosis than those in TSC1 patients
- k. Typically, patients are born with a functional allele of TSC1 or TSC2. A second hit occurs in which the functional allele is mutated in a founder somatic cell that results in loss of heterozygosity or haploinsufficiency with consequent hamartoma formation
- l. The incidence of TSC is approximately 1:6,000 to 1:10,000 individuals

B. Clinical manifestations

- a. The major neurological signs and symptoms of tuberous sclerosis are:
 - i. Seizures

- ii. Cognitive impairment
- iii. Autistic features
- iv. Hydrocephalus
- b. A few patients may have minimal or no neurological deficits in the face of alevor malitis in other organ symptoms
- c. Rarely a patient may have cerebral lesions and be asymptomatic
- d. Seizures
 - i. Epileptic seizures occur in approximately 75% of patients with 30–40% being unresponsive to drug therapies
 - ii. The majority of patients present with infantile spasms
 - iii. The seizures are usually partial with the severity correlated with the number of tubers

C. Neuropathology

- a. Cortical tuber form in utero during corticogenesis
- b. Histologic evaluation of tuber demonstrates:
 - i. Gliosis (subpial fibrillary)
 - ii. Loss of lamination
 - iii. Cytomegalic neurons that are ectopic and dysmorphic
 - iv. At the base of the tubers there may be clusters of cytomegalic neurons that form nodules in white matter (heterotopias) that are associated with hypomyelination
 - v. Tubers may become cystic and may calcify
 - vi. The enlarged neurons of cortical tubers are high in mTOR activity and have increased ribosomal protein S6 phosphorylation
 - vii. Subependymal nodules:
 - 1. Are the most common brain lesions associated with TSC (affect approximately 95% of patients)
 - 2. Histologically subependymal nodules are composed of:
 - a. Enlarged neurons and glia
 - b. Giant or multinucleated cells similar to tubers
 - c. Lesions < 10 mm in diameter are nodules; lesions > than 10 mm in diameter with greater than 5 mm of growth are classified as SEGA (subependymal giant astrocytomas)
 - 3. SEGA are:
 - a. Benign
 - b. Slow-growing grade 1 astrocytomas
 - c. Express both neuronal and astrocytic markers
 - d. Have a low proliferative index
 - 4. TSC is associated with circuit alterations from its effects on dendrites, spine and axons
- c. Neuroimaging
 - i. MRI:

1. Cortical tubers subependymal nodules and giant cells astrocytomas and linear white matter abnormalities
2. In addition MRI may demonstrate:
 - a. Cerebellar tubers
 - b. Cortical dysplasia
 - c. Transmantle dysplasia
 - d. Hemimegalencephaly
 - e. Focal megalencephaly
 - f. Cortical infolding

Focal Cortical Dysplasia (FCDs)

- A. General characteristics
 - a. Method of classification divide FCD both to architectural or cytoarchitectural degree and the presence or absence of balloon cells or large dysmorphic neurons
 - b. Genetics
 - i. There are pathogenic germline and mosaic mutations in P13K/AKT genes
 - ii. DEPDC5 (DEP domain containing protein 5) gene mutations
 1. Encodes a repressor of the mTORC1 signaling pathway
 2. Has been identified in FCDII and FCDI patients
- B. Clinical manifestations
 - a. Seizures
 - i. May be initiated from in utero to adulthood; most present in childhood.
 - ii. Extratemporal FCD has an earlier age of onset than temporal FCD
 - iii. The age and location of the lesions determine if the seizures will be:
 1. Simple partial
 2. Complex partial
 3. Secondarily generalized
 4. The seizure disorder is often medicine refractory
 5. Developmental delay
 6. Cognitive impairment
- C. Neuropathology
 - a. FCD has a spectrum in regard to morphology, topography and histologic features
 - i. Microdysgenesis is the least severe form of the process and is characterized by:
 1. Neuronal heterotopias
 2. Cortical laminations disruption
 3. Neuronal clusters in minimally cellular areas
 4. Abnormal cells within the cortex
 - ii. Focal cortical dysplasia may involve:
 1. A focal area in a gyrus or involvement of several gyri
 2. Transmantle dysplasia (that comprise an area from the lateral ventricle to the cortex)
 3. Lobar dysplasia

4. Hemispheric dysplasia
5. Multifocal bilateral dysplasia
- iii. TSC and SCNA1 mutations may be seen concomitantly with FCDs
- iv. FCD type IA and IIA have been identified in surgical material
- b. Neuroimaging
 - i. MRI
 1. FCD may not be visible by 3T MRI
 2. Subtle abnormalities of:
 - a. Gyration pattern
 - b. Cortical thickness
 - c. Blurring of the gray-white function
 - d. Increased signal intensity on FLAIR and T2-weighted sequences (possibly due to balloon cells)
 - e. White matter alterations (increased signal) may occur in surrounding areas of an FCD that produces intractable seizures (may be due to myelin changes from the seizures or dysplastic white matter)
 3. Focal transmantle dysplasia (FTD)
 - a. Is seen in a wedge of dysplastic and disorganized tissue from the lateral ventricle to the cortical surface with increased T2 signal
 - i. Composed of balloon cells and astrogliosis
 4. Sublobar dysplasia demonstrates:
 - a. Deep infolding of the cortex which is thickened
 - b. Poor gray-white differentiation in the affected area
 - c. Associated brain abnormalities include:
 - i. Ventricular dysmorphism
 - ii. Calloral and cerebellar dysgenesis
 5. Posterior quadrant dysplasia is a form of FCD
 - a. Affects one of both posterior quadrants

Hemimegalencephaly (HME)

- A. General characteristics
 - a. A brain malformation that causes an enlarged and dysplastic hemisphere
 - b. Localized megalencephaly is approximately 25% of HME; it appears to be more prevalent in the left sides
 - c. There are three forms of disease
 - i. Isolated form (66%)
 - ii. Syndromic form (associated with neurocutaneous illnesses)
 - iii. Total HME (least common form)
 - iv. Genetics
 1. De novo somatic mutations in components of the P13K-AKT3-mTOR pathway
 - a. Somatic activation of AKT3 may be causative

B. Clinical manifestations

- a. Intractable partial seizures that start in infancy or the neonatal period
- b. Children may present with tonic seizures, infantile spasms similar to Ohtahara or West syndromes
- c. Contralateral hemiparesis
- d. Severe cognitive impairment
- e. Rarely can present in an adult

C. Neuropathology

- a. HMEG is associated with neurocutaneous syndrome that include:
 - i. Linear nerves sebaceous syndrome
 - 1. Approximately 50% have HME
 - 2. Hypomelanosis of Ito
 - 3. Tuberous sclerosis
 - 4. Neurofibromatosis
 - 5. Macroscopically there is enlargement of one hemisphere; there is no predilection for one side
 - 6. The contralateral hemisphere may be compressed but may also be small
 - ii. Cortical dysgenesis
 - iii. White matter hypertrophy
 - iv. Affiliated and dysmorphic lateral ventricle
 - v. The majority of the hemisphere is affected
 - vi. Histological features:
 - 1. Polymicrogyria (in some patients)
 - 2. Heterotopic gray matter
 - 3. Cortical dyslamination
 - 4. Bizarre enlarged neurons
 - 5. Balloon cells
 - 6. Blurring of the gray-white functions
 - 7. Increased number of neurons and astrocytes

D. Neuroimaging

- a. MRI:
 - i. The cortical gray matter shows areas of thickened and gyral simplification similar to pachygyria or overfolding that is similar to what occurs with polymicrogyria (PMG)
 - ii. An indistinct gray-white junction
 - iii. Markedly increased volume of white matter that contains gray matter heterotopias
 - iv. White matter signal change consistent with demyelination
 - v. The ipsilateral ventricle is enlarged and the posterior horn may extend across the midline
 - vi. Some patients have enlargement of the ipsilateral cerebellar hemisphere and brain stem

Abnormal Neuronal Migration

Classical Lissencephaly

A. General characteristics

- a. The lissencephalies are usually monogenetic disorders that affect neuronal migration during development of the cortex

b. The mature brain is not gyrated

c. Genetics:

- i. Mutations in neuron-specific L- and B-tubulin genes have been found in both lissencephaly and polymicrogyria
- ii. These mutations are often associated with:
 - 1. Callosal hypoplasia or agenesis
 - 2. Cerebellar hypoplasia
 - 3. Abnormal basal ganglia
- iii. Tubulin proteins that are transcribed:
 - 1. Form heterodimers that incorporate into microtubules that are pivotal for cell motility and function
- iv. Mutations in TUBA1A and TUBB2B have been identified in patients with lissencephaly
- v. There appears to be a tubulinopathy-associated spectrum that causes lissencephaly to polymicrogyric cortical dysplasias
- vi. Lissencephaly associated with cerebellar hypoplasia has been associated with mutations in the RELN gene
- vii. Lissencephaly associated with agenesis of the corpus callosum has been described with mutations of the ARX gene
- viii. The major genes associated with lissencephaly are:
 - 1. LIS1 (normal migrations)
 - 2. DCX (normal migration)
 - 3. ARX
 - a. Required for tangential migration
 - 4. RELN (normal migrations)
 - 5. YWHAD (normal migration)
 - 6. TUBA1A (normal migration)
- ix. The LIS gene mutations are the most common cause of lissencephaly
 - 1. LIS protein is required for normal migration, cellular proliferation and intracellular transport

B. Neuropathology

- a. Reduced or absent gyration that is combined with cerebral cortex thickening (seen in classical LIS)
- b. Most patients have a combination of agyria and pachygyria (broad simplified gyration)
- c. Poorly developed Sylvian and Rolandic fissures
- d. Failure of opercularization of the insular areas
- e. Associated with malformations include:
 - i. Enlarged lateral ventricles
 - ii. Absence of the claustrum and external capsules
 - iii. Dysgenesis of the corpus callosum
 - iv. Persistence of the cavum septum pellucidum
 - v. Hypoplasia of the CSTs
 - vi. Heterotopia of the inferior olives
 - vii. Cerebellar abnormalities
- f. Histological features:
 - i. Poorly defined marginal zone

C. Clinical manifestations

- a. Are dependent upon associated congenital malformations, the topography of the malformation and abnormal function of other organ systems
- b. Intractable seizures (often presenting as infantile spasms)
- c. Developmental delay
- d. Cognitive impairment
- e. Early hypotonia that may persist or evolve to mixed axial hypotonia and limb spasticity
- f. The Miller-Dieker syndrome (MDS) has a severe form of lissencephaly with increased cellularity
- g. A cortical gray zone with diffusely scattered neurons
- h. A neuron sparse zone
- i. A deep cortical gray zone with a columnar organization that is thicker than the superficial gray zone and more cellular. Putatively neurons that failed complete migration to the cortex

D. Neuroimaging

- a. MRI:
 - i. Agyria and pachygyria
 - ii. Cerebral surface is smooth with absent opercularization and “figure eight” appearance
 - iii. Grading system for MRI evaluation
 1. Based on the severity of the gyral pattern simplification and a gradient along the anterior to posterior axis
 2. The posterior > anterior gradient is most common with LIS gene mutation but also occurs with TUBA1 mutations

Subcortical Band Heterotopia (SBA)

A. General characteristics

- a. X-linked isolated lissencephaly and subcortical band heterotopias are allelic disorders
- b. The majority of both sporadic and familial cases of the most common form of SBH, that are bilateral symmetric and with frontal predominance are due to mutations in the gene DCX
- c. Males with DCX mutations usually have the lissencephaly phenotype while females have SBH
- d. Females that have SBH from DCX mutations have two populations of neurons:
 - i. Mutant gene inactive group that migrated and formed normal cortex
 - ii. A population in which the normal gene is inactivated which migrate abnormally and form the heterotopic band
 - iii. Carriers of mild DCX mutations may be MRI negative but still may suffer seizures and be cognitively impaired
 - iv. Patients with posterior SBH may have somatic mutations in the LIS1 gene.
 - v. SBH has been reported in patients with trisomy 9P
 - vi. DSX encodes:

1. A microtubules associated protein that is involved in neuronal migration

B. Clinical manifestations

- a. Mild-to-moderate cognitive impairment
- b. Seizures disorder:
 - i. Onset at any age but may be delayed until the second or third decade
 - ii. Mixed seizures type
 - iii. Clinical features are roughly correlated with the thickness of the heterotopic band
 - iv. Females are affected markedly more than males
 - v. Mild partial forms of SBH may be asymptomatic
 - vi. There are usually no dysmorphic features or other congenital malformations

C. Neuropathology

- a. Bilateral bands of heterotopic gray matter imbedded in the white matter between the lateral ventricles and the cortex
- b. There are shallow sulci in the overlying cortex
- c. The bands are symmetric bilaterally with a slight anterior predominance; rarely the bands are restricted to the frontal lobes in the occipital parietal area (partial posterior)
- d. Rarely SBH merges anteriorly with pachygyria cortex
- e. The bands are composed of;
 - i. Superficial zone of disorganized neurons; an intermediate zone of small neurons with a partial columnar organization
 - ii. Deeper zone where heterotopias become nodules
 - iii. The heterotopic band is formed by abnormal neuroblast migrations

D. Neuroimaging

- a. MRI:
 - i. Demonstrates a four layered cerebral parenchyma that comprises:
 1. Normal periventricular white matter
 2. Layer of heterotopic gray matter
 3. A thin layer of subcortical white matter
 4. Normal cortical gray matter

Periventricular Nodular Heterotopia (PNH)

A. General characteristics

- a. Definition:
 - i. Heterotopias are groups of cells that are found in an inappropriate location of the correct tissue of origin
 - ii. Heterotopias occur:
 1. In isolation
 2. In association with other developmental anomalies
 3. As a component of congenital anomaly syndrome
- b. Genetics:
 - i. Classic bilateral PNH is the longest subgyria (approximately 56%) which is an X-linked disorder; there > than 15 PNH subgroups

- ii. Approximately 20% of sporadic patients demonstrate mutations of the filamin A gene (FLNA gene)
 - iii. PNH has also been described in:
 1. 6q terminal deletion syndrome
 2. ARFGEF2 (ADP-ribosylation factor guanine nucleotide exchange factor)
 3. Frontonasal encephalocele, corpus callosal dysgenesis and arachnoid cyst
 4. Peritrigonal and temporo-occipital heterotopias with corpus callosum and cerebellar dysgenesis
 - B. Clinical manifestations
 - a. Epilepsy
 - i. Is present in 80–90% of patients
 - ii. Primarily partial seizures that are intractable
 - iii. The nodules are intrinsically epileptogenic
 - iv. Females > males with bilateral PNH
 - v. Most patients have normal intelligence
 - vi. Autism has been described in association with PNH with peritrigonal and temporo-occipital heterotopias with corpus callosum and cerebellar dysgenesis
 - vii. Described in association with Ehlers-Danlos syndrome
 - C. Neuropathology
 - a. Most nodules are located in the walls of the lateral ventricles; they may be contiguous
 - b. They may be unilateral, bilateral or in the trigone of the occipital horn
 - c. They vary in size and are usually longer than the subependymal nodules of TSC
 - d. PNH is associated with the brain's malformations
 - e. Microscopically:
 - i. Heterotopic gray matter:
 1. Forms clusters of rounded, irregular nodules separated by layers of myelinated fibers
 2. Neurons and glia in the nodules may be disorganized or have rudimentary lamination
 - D. Neuroimaging
 - a. MRI:
 - i. T1-weighted sequences demonstrate the nodules to have identical signal intensity to cortical gray matter
 - ii. Associated malformations include:
 1. Hippocampal sclerosis
 2. Polymicrogyria
 3. Hypoplasia of the cerebellar vermis
 - iii. Classic bilateral PNH is associated with:
 1. Hypoplasia of the corpus callosum and cerebellar vermis
 2. Rarely the heterotopias may be large enough to deform the lateral ventricles
 3. Heterotopic nodules:
 - a. Usually located along the ventricles; may be peritrigonal and in temporo-occipital areas
 - b. They can be single, multiple symmetric or asymmetric as well as unilateral or bilateral
- Abnormal Cortical Organization Polymicrogyria*
- A. General characteristics
 - a. A complex cortical malformation whose most consistent feature is disruption of the brain surface with pial defects, over migration of cells, thickening and duplication of pial collagen layers, increased leptomeningeal vascularity due to processes in the early stage of corticogenesis
 - b. May be an isolated cortical malformation or in conjunction with other cerebral malformations or multiple congenital anomaly syndromes
 - c. Associated with both genetic and non-genetic mechanisms
 - d. Major genes involved include:
 - i. Those involved in peroxisomal disorders
 - ii. 22q11.2 and 1p36 contiguous gene deletion syndromes
 - iii. Mutations in the DISK-AKT pathway (PMG and megalencephaly)
 - iv. Tubulin gene family mutations
 - v. SPPX2; PAX6; TBR2; KIAA1279; COL18A; RAB
 - B. Clinical manifestations
 - a. The clinical manifestations of PMG have a wide spectrum which is due to the extent and location of the malformations and concomitant brain abnormalities that include:
 - i. Metabolic disorders
 - ii. Chromosome deletion syndromes
 - iii. Other congenital malformations
 - b. Oromotor dysfunction with seizures (congenital bilateral perisylvian syndrome)
 - i. Decreased tongue protrusion and lateral movement
 - ii. Problem with facial and pharyngeal movement
 - iii. Facial diplegia
 - iv. Decreased swallowing
 - v. Dysarthria and expressive dysphasia
 - vi. Increased jaw jerk and an absent gag reflex
 - c. Cognitive impairment is seen in approximately 75% of patients
 - d. Approximately 60–85% of patients with PMG have epilepsy
 - i. Seizure onset may be delayed until the second decade but usually starts between 4–12 years of age
 - ii. Seizure types include:
 1. A typical absence (62%)
 2. Atonic and tonic drop attacks (73%)
 3. GTCs (35%)
 4. Partial (26%) that rarely generalize
 5. Rare bilateral facial motor seizures with awareness

6. A few patients present with infantile spasms in contrast with patients with LIS, TSC or FCID
 7. Intractable seizures occur in approximately 50% of patients
- C. Neuropathology
- a. PMG has an irregular cortical surface and may be located:
 - i. Bilateral frontally
 - ii. Unilateral perisylvian
 - iii. Bilateral frontoparietal
 - iv. Parasagittal parieto-occipital (bilateral)
 - v. Bilateral parieto-occipital
 - vi. Multi-lobar
 - vii. Bilateral generalized
 - viii. Bilateral perisylvian (the most common location)
 - b. The perisylvian cortex involvement:
 - i. Sylvian fissures are extended and superiorly oriented posteriorly
 - c. PMG occurs in the periphery of porencephalic or hydrocephalic malformations
 - d. Associated anomalies occur in:
 - i. The corpus callosum
 - ii. Brain stem and cerebellum
 - iii. And may be associated with enlarged ventricles
 - e. Histologic evaluation reveals:
 - i. Abnormal cortical lamination
 - ii. Excessive folding and fusion of adjacent gyri
 - iii. Unlayered and layered forms of PMG are described
 - f. Other mechanisms that have been suggested to cause PMG are:
 - i. Premature folding of the neuronal band
 - ii. Abnormal fusion of adjacent gyri
 - iii. Laminar necrosis of the developing cortex
 - iv. Cytomegalic virus infection
 - v. Metabolic and peroxisomal disorders
 - vi. In utero ischemia
- D. Neuroimaging
- a. MRI:
 - i. Apparent mildly thickened cortex due to probable overfolding
 - ii. Microgyri and microsulci
 - iii. Cortical T2 signal is usually normal; diffuse white matter hyperintensity signals suggest:
 1. Peroxisomal disease (Zellweger's syndrome)
 2. Congenital CMV infection
 - iv. Enlarged subarachnoid space over PMG with anomalous venous drainage (most common in the Sylvian fissure)
 - v. Overfolding of the cortex
 - vi. Structural connectivity between contiguous primary gyri (short U-fibers)
 - vii. Reduced connectivity between distant gyri (long association fibers)
 - viii. Altered cortical network topology

Schizencephaly (SCZ)

1. General Characteristics
 - a. Definition:
 - i. A malformation of the brain characterized by a gray matter-lined defect that extends from the pial surface to the lateral ventricles
 - b. Clefts are frontal or parietal in approximately 65% or temporal or occipital in approximately 35%
 - c. Clefts may be associated with other brain malformations
 - d. Genetics: Familial cases have been identified:
 - i. with mutations in the EMX2 homeobox gene
 - ii. and in patients with chromosomal aneuploidy
2. Clinical Manifestations
 - a. The clinical features depend on
 - i. If the defect is unilateral or bilateral
 - ii. Open-lipped or closed-lipped types
 - b. Patients with a closed-lipped pattern have:
 - i. Hemiparesis or motor delay
 - c. Open-lipped form present with:
 - i. Seizures
 - ii. Hydrocephalus
 - d. Epilepsy occurs in approximately 50% of patients
 - e. Developmental delay in approximately 83%
 - f. Seizures:
 - i. Median age for seizure onset is 13 months
 - ii. Open-lipped form has an earlier seizure onset
 - iii. Seizure types include:
 1. Complex partial (most common)
 2. Infantile spasms
 3. Tonic and atonic
 4. GTCS
 5. The severity and type of seizure does not correlate with the topography of the SCZ
 6. Bilateral open-lipped SCZ has the worst seizure prognosis
 - g. Associated malformations include:
 - i. Agenesis of the septum pellucidum
 - ii. Focal cortical dysplasia
 - iii. Dysgenesis of the corpus callosum
 - iv. The associated malformations may influence the severity of the seizures
3. Neuropathology
 - a. The clefts may be unilateral or bilateral as well as "open-lipped" or "closed-lipped"
 - b. Open-lipped SCZ:
 - i. The walls of the clefts do not oppose each other
 - c. Closed-lipped SCZ:
 - i. The walls of the cleft are opposed and often fused; a line of continuity between the lateral ventricle and subarachnoid space may be visible in fused SCZ
 - d. The gray matter lining the clefts is similar to that of PMG
4. Neuroimaging
 - a. MRI:

- i. The clefts are usually visible on routine MRI sequences and demonstrate if they are “open or closed-lipped”
- ii. SCZ may also demonstrate:
 - 1. “Puckering” or a “dimple” at the margin of the lateral ventricle
 - 2. The cleft is lined by gray matter with imaging characteristics of polymicrogyria that include:
 - a. Apparent cortical thickening
 - b. Irregularity of the surface
 - c. Stippling of the gray-white interface
 - d. SCZ may be asymmetric; the contralateral hemisphere may demonstrate subtle SCZ or PMG
 - e. Agenesis of the septum pellucidum occurs in approximately 30% of patients
- iii. Subtle SCZ may demonstrate:
 - 1. “Puckering” or a “dimple” at the margin of the lateral ventricle
 - 2. Clefts are lined by gray matter
 - 3. White matter or T2 increase

Differential Diagnosis in Epilepsy

- 1. The Generalized Epilepsies
 - a. Arising in and rapidly spreading to bilaterally distributed networks
 - b. Generalized seizures
 - i. Tonic-clonic
 - ii. Absence (typical and atypical)
 - 1. Myoclonic absence
 - 2. Eyelid myoclonia
 - iii. Clonic
 - iv. Atonic
 - v. Myoclonic:
 - 1. Myoclonic-atonic
 - 2. Myoclonic-tonic
- 2. Focal Epilepsies
 - a. Originating within networks limited to one hemisphere
 - b. Simple (without alteration of consciousness)
 - i. Aura
 - 1. Psychic
 - 2. Somatosensory
 - 3. Visual
 - 4. Auditory
 - 5. Olfactory
 - 6. Visceral
 - 7. Vertiginous
 - ii. Motor
 - iii. Autonomic
 - iv. Awareness is unaltered
- 3. Unclassifiable
 - a. Cannot be classified as focal or generalized
 - b. Epileptic spasms

Differential Diagnosis by Age of Onset

- A. Neonatal Syndromes
 - 1. Benign familial neonatal epilepsy (BFNE)
 - 2. Ohtahara syndrome
 - 3. Epileptic encephalopathies
 - 4. Early myoclonic encephalopathy (EME)
- B. Seizure Syndromes in Infancy
 - 1. Febrile seizures
 - 2. Febrile seizures plus (FS)
 - 3. Benign familial infantile epilepsy (BFIE)
 - 4. West syndrome (hypsarrhythmia)
 - 5. Dravet syndrome (severe myoclonic seizures of epilepsy)
 - 6. Myoclonic epilepsy in infancy (MEI)
 - 7. Myoclonic epilepsy in non-progressive disorder (components of other epileptic syndromes)
 - 8. Epilepsy with migrating focal seizures
- C. Childhood Epilepsy
 - 1. Febrile convulsions
 - a. Usual temperature above 38°C
 - b. Precipitants:
 - i. Viral or bacterial illness
 - ii. Immunization (MMR)
 - iii. Herpesvirus
 - c. Genetic mutations
 - i. SCN1A; SCN2A
 - ii. PRRT2
 - iii. ANO3
 - 2. Febrile seizures plus (GEFS plus)
 - a. Genes that encode several Na⁺ channel subunits
 - b. Gamma 2 subunit of GABA A
 - 3. Early onset childhood occipital epilepsy (Panayiotopoulos syndrome); autonomic seizures
 - 4. Epilepsy with myoclonic atonic seizures
 - 5. Childhood absence epilepsy (CAE)
 - 6. Benign epilepsy with centro-temporal spikes (BECTS)
 - 7. Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)
 - 8. Late onset childhood occipital epilepsy (Gastaut)
 - 9. Epilepsy with myoclonic absences
 - 10. Lennox-Gastaut syndrome (LGS)
 - 11. Epileptic encephalopathy with continuous spike-and-wave during sleep
 - 12. Landau-Kleffner syndrome
- D. Seizures in Adolescence to Adulthood
 - 1. Juvenile absence epilepsy (JAE)
 - 2. Juvenile myoclonic epilepsy
 - 3. Epilepsy with GTCS
 - 4. Autosomal dominant temporal lobe epilepsy (ADTLE)
 - 5. Familial temporal lobe epilepsy:
 - a. ADFLE (autosomal dominant frontal lobe epilepsy)
 - i. CHRNA4, CHRNA2, CHRN2 and KCNT1
 - ii. Autosomal dominant epilepsy with auditory features

1. LGI1 (encodes epitempin)
 - iii. DEPDC5 (DEP domain-containing protein 5) gene mutations occur in:
 1. ADNFLE
 2. FTLE
 3. FFEVF
 - E. Seizures with Variable Age at Onset
 1. Familial focal epilepsy with variable foci (FFEVF)
 - a. Childhood to adulthood
 2. Progressive myoclonic epilepsy
 - a. Lafora body disease
 - b. Unverricht-Lundborg
 - c. Sialidosis type I
 - d. Ceroid lipofuscinosis type 6
 - e. MERRF (myoclonic epilepsy with ragged red fibers)
 - f. Gaucher's disease
 - g. Dentatorubro-pallidoluysian atrophy
 3. Reflex epilepsies
 - a. Generalized reflex seizure
 - i. Precipitated by specific characteristics of light
 - ii. Various aspects of cognition and decision making
 - b. Focal reflex seizures
 - i. Reading, writing, other language functions
 - ii. Startle response
 - iii. Somatosensory stimulation (brief or sustained; rubbing a specific area of the body surface)
 - iv. Proprioceptive changes of an extremity
 - v. Auditory stimuli
 - vi. Thermal stimuli (hot water immersion)
 - vii. Vestibular stimuli
 - viii. Eating
 - ix. Orgasm
 - iv. HCN channel mutations
 1. HCN2
 2. Metabolic causes
 - a. Hypoglycemia
 - b. Hypocalcemia
 - c. Hypomagnesemia
 - d. Uremia
 - e. Hepatic failure
 - f. Hypo/hyponatremia
 - g. Inappropriate ADH
 - h. Hyperosmotic states
 - i. Pulmonary failure
 3. Drugs/Toxins (partial list)
 - a. Methanol
 - b. INH
 - c. Phenothiazine
 - d. Insulin
 - e. Theophylline
 - f. Amphetamines
 - g. Lithium
 - h. Cocaine
 - i. Inhalational anesthetics
 - j. PCP
 - k. Penicillin
 - l. Anticonvulsants
 - m. Alcohol withdrawal
 4. Infections Associated with GTCS
 - a. Associated with cortical strokes
 - i. Tuberculosis
 - ii. Cryptococcus
 - iii. Mucormycoses
 - iv. Aspergillus
 - v. Listeria monocytogenes
 - vi. HIV
 - vii. SBE
 - viii. Cysticercosis
 - ix. Malaria
 - x. Chagas
 - xi. Herpes simplex
 - xii. Herpes zoster
 - xiii. Enteroviruses
 - xiv. Bacterial associated with meningitis
 - xv. Syphilis
- Differential Diagnosis of Generalized Tonic-Clonic Seizures (GTCS)**
1. Channelopathies
 - a. Mutations in Na^+ channels or their subunits
 - i. SCN1A, SCN2A, SCN8, SCN1B
 - ii. Potassium channel mutations
 1. KCNQ ($K_v7.2$)
 2. KCNQ3 ($K_v7.3$)
 3. KCNA1 ($K_v1.1$)
 4. KCNJ1 ($K_{nn4.1}$)
 5. KCNF10 (glial $K_v4.1$ channel)
 6. KCTD7 – (unknown function)
 7. KCNJ11 – ($K_v6.2$)
 - iii. Calcium channelopathies
 1. $Ca_v2.1$ (P/Q); loss of function
 2. $Ca_v3(T)$ channels; gain of function
 3. CACNA1A gene
 4. CACNB4 gene
 5. CACNA1H
- GTCS by Age (Adults < 40 Years)**
1. Lack of compliance or inadequate medication levels
 2. Localization related with secondary generalization
 3. Vascular: embolus > infarction > hemorrhage; venous (cancer)
 4. Metabolic causes
 5. Tumor (metastatic > primary)
 6. Drugs (illicit, hypnotic sedatives, withdrawal)
 7. HIV (associated opportunistic infections)

8. Herpes simplex
9. Herpes zoster (v1 distribution with delayed carotid artery stroke)
10. Migrational disorders
11. Post-partum/cancer (venous strokes)
12. Head injury

GTCS by Age (Adults > 60 Years of Age)

1. Vascular: ischemic > embolic > hemorrhage
2. Cardiac arrhythmia (AF > tachy – brady)
3. Metabolic dysfunction
4. Prior CNS structural lesion with consequent glial scar
5. Tumor (metastatic > meningioma > glioma or lymphoma)
6. Herpes simplex encephalitis
7. Head injury
8. Prior stroke
9. Anticonvulsant withdrawal or inadequate dosage

Differential Diagnosis of Absence Seizures

1. Childhood absence epilepsy
 - a. Typical/atypical
2. Juvenile absence
3. Absence epilepsy with specific features
 - a. Myoclonic absence
 - b. Eyelid myoclonia
4. Absence epilepsy in adults
5. Genetic mutations
 - a. GABRB3
 - b. SLC2A1 (glucose transporter 1)
 - c. CACNA1A

Differential Diagnosis of Absence Syndromes

1. Epileptic encephalopathy
2. Early myoclonic epilepsy (neonatal)
3. Ohtahara syndrome (neonatal)
4. West syndrome (infancy)
5. Dravet syndrome (infancy)
6. Myoclonic status in non-progressive encephalopathy of childhood
7. Lennox-Gastaut syndrome (childhood)
8. Landau-Kleffner syndrome (childhood)
9. Epilepsy with continuous spike-and-wave during slow wave sleep in childhood and adolescence
10. Migrating partial seizures in infancy
11. Severe epilepsy with multiple independent spike foci

Differential Diagnosis of Progressive Myoclonic Epilepsy

1. Epileptic encephalopathies with a component of myoclonic epilepsy
 - a. Dravet syndrome
 - b. Channelopathies
 - i. SCN1A and SCN1B

- ii. CACNA1, CACNB4, CACN1H
- iii. GABA, GABRD, GABRG2
- c. Severe myoclonic epilepsy in infancy (SMEI)
- d. GEFS
2. Lafora body disease
3. Unverricht-Lundborg disease
4. Neuronal ceroid lipofuscinosis (CLN6)
5. Gaucher's disease
6. Sialidosis (cherry red spot myoclonus)
7. MERRF/MELAS/POLG
8. Action myoclonus renal failure syndrome
9. Dentatorubral-pallidoluysian atrophy

Differential Diagnosis of Myoclonic Epilepsy

1. Progressive myoclonic epilepsies
2. Rare causes of autosomal recessive myoclonic epilepsy
3. Epilepsy with myoclonic absences
4. Generalized electrographic seizures presenting as perioral myoclonus
5. Familial cortical myoclonic tremor with epilepsy

Differential Diagnosis of Motor Seizures

1. Infantile spasms
2. Localization related generalized tonic-clonic seizures
3. Major motor seizure
4. Tonic seizures
5. Motor patterns of secondarily generalized seizures
6. Epileptic spasms
7. Clonic seizures
8. Versive seizures
9. Complex motor seizures
10. Automotor seizures
11. Gelastic seizures
12. Atonic seizures
13. Dystonic posturing

Differential Diagnosis of Localization Related Epilepsy

1. Frontal lobe
 - a. Dorsolateral frontal lobe
 - b. Prefrontal cortex
 - c. Premotor cortex
 - d. Supplementary motor area (SMA)
 - e. Cingulate cortex
 - f. Frontal opercular cortex
 - g. Frontopolar cortex
 - h. Orbitofrontal cortex

Differential Diagnosis of Hyperkinetic Frontal Lobe Seizures

1. Orbitofrontal cortex
2. Dorsolateral prefrontal cortex
3. Frontomesial cortex
4. Frontopolar cortex

Differential Diagnosis of Temporal Lobe Epilepsy

1. Hippocampal sclerosis
2. Amygdala sclerosis
3. Dual pathology with hippocampal sclerosis (extratemporal heterotopias)
4. Head trauma
5. Vascular malformations (cavernous hemangiomas, telangiectasia, arteriovenous malformations)
6. Low grade astrocytomas
7. Metastatic tumors
8. Migration disorders (dyslamination, heterotopias)
9. Congenital malformations (hippocampal malrotation)
10. Ischemic vascular disease
11. Autoimmune disorders (antibody paraneoplastic limbic encephalitis)
12. Infections (Herpes simplex and zoster)
13. Urbach-Wiethe disease

Differential Diagnosis of Medial Temporal Lobe Syndrome

1. Hippocampal sclerosis
2. Amygdala sclerosis
3. Dual pathology (hippocampal sclerosis plus extratemporal migration defects)
4. Trauma
5. Status epilepticus (hippocampal damage)
6. Prolonged febrile convulsion
7. Low grade astrocytoma
8. Vascular malformations

Differential Diagnosis of Neocortical Temporal Lobe Epilepsy

1. Autosomal dominant temporal lobe epilepsy with auditory features
2. Low grade astrocytoma
3. Vascular disease (ischemic)
4. Malformations
5. Head trauma
6. Migrational defects
7. Viral infections (HS, HZ)
8. Psychiatric disease (usually depression; schizophrenia)
9. Episodic dyscontrol
10. Migraine (abdominal aura)
11. Cardiac arrhythmia (R temporal lobe sympathetic; L parasympathetic)
12. Transient global amnesia
13. Vasovagal and vasodepressor syncope
14. Movement disorders (paroxysmal dyskinesia; stereotypies)
15. Cardiac arrhythmia (often from propagation into the insular cortex)

Differential Diagnosis of Insular Cortex Seizures

1. Foix-Chavany-Marie stroke

2. Low grade glial tumors
3. Temporal lobe epilepsy
4. Regional neuropathic pain
5. Cardiac arrhythmia
6. Sleep related hypermotor seizures

Differential Diagnosis of Parietal Lobe Seizures

1. Post-stroke
2. Metastatic and primary glial tumor
3. Benign epilepsy of childhood with centrotemporal spikes
4. Benign epilepsy of childhood with parietal evoked spikes
5. Migraine headaches
6. Frontal lobe (movement) or temporal lobe (aura) epilepsy

Differential Diagnosis of Occipital Lobe Epilepsy

1. Idiopathic childhood occipital epilepsy of Gastaut (IOEE-G)
2. Photosensitive epilepsy
3. Seizures provoked by television and video games
4. Migraine headaches

Differential Diagnosis of Status Epilepticus

1. Convulsive status
2. Absence status
3. Myoclonic status in JME
4. Myoclonic status
5. Electrical status epilepticus in sleep
 - a. Continuous spike-and-wave in slow-wave sleep (CSWS)
 - b. Landau-Kleffner syndrome
6. Non-convulsive status

Differential Diagnosis of Epilepsia Partialis Continua

1. Rasmussen's syndrome
2. Russian spring-summer tick-borne encephalitis
3. Vascular disease (stroke)
4. Multiple sclerosis
5. Steroid responsive encephalopathy with autoimmune thyroiditis
6. Mitochondrial disease
7. Alcohol-responsive
8. Developmental anomalies
9. Hyperosmotic syndromes
10. Degenerative disease
11. Idiopathic

Differential Diagnosis of the Reflex Epilepsies

1. Generalized reflex seizures
 - a. Precipitated by specific aspects of light
 - b. Cognitive precipitant (decision making)
2. Focal reflex seizures (precipitants)
 - a. Language functions
 - b. Startle

- c. Somatosensory
- d. Proprioceptive positions (limbs)
- e. Auditory
- f. Thermal (hot water immersion)
- g. Vestibular
- h. Eating
- i. Orgasm

Differential Diagnosis of Lesional Epilepsy

1. Neuronal loss and gliosis from head trauma (cortical scar)
2. All forms of vascular disease
3. Heterotopias
4. Focal cortical dysgenesis (dyslamination)
5. Cortical migrational alterations
6. Hamartoma
7. Vascular malformations (syndromic)
8. Tumors:
 - a. Primary glial and metastatic
 - b. Benign (meningioma, ganglioneuroma)
 - c. Dysembryoplastic neuroectodermal tumors (DNET)
 - d. Low-grade astrocytomas
9. Autoimmune
 - a. Multiple sclerosis
 - b. Acute disseminated encephalomyelitis
 - c. Acute hemorrhagic leukoencephalitis
 - d. Rasmussen's encephalitis
 - e. Paraneoplastic syndromes (limbic encephalitis)
 - f. Systemic autoimmune disease (with vasculitis); SLE
10. Infections (viral and bacterial)
 - a. Meningitis (bacterial/viral)
 - b. Varicella zoster
 - c. Herpes simplex
 - d. Coxsackie, adeno, enteroviral infections; HIV
 - e. Fungal infection (cryptococcosis)
 - f. Malaria
 - g. Chagas (emboli from the heart)
 - h. Cysticercosis
 - i. HIV (<200 cells mm³) with opportunistic infections (cryptococcosis, tuberculosis, toxoplasmosis and syphilis)

Differential Diagnosis of Major Malformations of Cortical Development

1. Tuberous sclerosis
2. Focal cortical dysplasia
3. Hemimegalencephaly
4. Lissencephaly
5. Subcortical band heterotopia
6. Periventricular nodular heterotopia
7. Polymicrogyria
8. Holoprosencephaly
9. Double cortex syndrome

Differential Diagnosis of Monogenetic Causes of Malformations with Seizures

1. Angelman syndrome
2. Walker-Warburg syndrome
3. Muscle-eye-brain disease
4. Holoprosencephaly
5. Schizencephaly
6. Tuberous sclerosis
7. Lissencephaly
8. Double cortex syndrome
9. Heterotopia
10. Fukuyama muscular dystrophy

Differential Diagnosis of Monogenetic Epilepsy with Mixed Seizure Phenotypes

1. Urbach-Wiethe disease
2. Autosomal dominant lateral temporal lobe epilepsy
3. Neuronal ceroid lipofuscinosis type 8
4. Pyridoxine deficiency

Further Reading

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Chapter 3

Anterior Horn Cell Disease

Introduction

The hereditary anterior horn cell diseases most often affect children. The major anterior horn cell spectrum that confronts the adult neurologist is that of late onset spinal muscular atrophy, adolescent Kugelberg-Welander disease, and amyotrophic lateral sclerosis and its variant. Storage and degenerative diseases also affect anterior horn cells. The molecular revolution has discovered multiple genes (SMN1, SMN2, NAIP, P44, H4F5, occludin) that affect all components of the motor unit and contribute to the phenotype of anterior horn cell disease. Due to its treatment potential, other exciting aspects of anterior horn cell diseases are the autoimmune causes of motor neuron pathology and axonopathy such as GM1, GALNac-GD1a in autoimmune axonal neuropathy (AMAN) and the range of immune globulin G (IgG) antiganglioside antibodies that may be part of the differential diagnosis of anterior horn cell disease. There are many variants of both ALS and anterior horn cell disease that are associated with hereditary degenerative disease such as Frontotemporal lobe dementia with gene mutation chromosome 9 open reading frame 72 (C9ORF72). It is now important to characterize anterior horn cell entities because of gene therapies and conformity for upcoming clinical trials with small molecules.

Adult Spinal Muscular Atrophies Linked to Chromosome 5q11.12-13.3

Spinal muscular atrophy (SMA) is a heterogeneous genotypic and phenotypic group of lower motor neuron diseases. They show dominant, recessive, or x-linked inheritance patterns. The most common form of SMA is that linked to 5q, a proximal recessive form that is caused by loss or mutation of the survival motor neuron 1 gene (SMN1) with retention of the SMN2 gene. Other types of SMA are caused by mutations in genes that are expressed in both the CNS and other tissues.

Proximal 5q SMA

1. Clinical Subtypes:
 - a. Type O
 - i. Most severe
 - ii. Weakness at birth
 - b. Type 1
 - i. Onset < 6 months
 - ii. Inability to sit
 - iii. Most common
 - c. Type 2

- i. Onset between 6–18 months
 - ii. Achieves sitting, but unable to walk
- d. Type 3
 - i. Onset > 18 months
 - ii. Temporally achieves ambulation
- e. Type 4
 - i. Adult onset
 - ii. Mild proximal weakness

Genetics

1. The loss of mutation of the SMN1 gene with retention of the SMN2 gene causes SMA
2. There is a one nucleotide difference between SMN1 and SMN2 in exon 7 that alters a splice modulator. SMN2 transcripts lack exon 7 which alters oligomerization and results in degradation of the SMN protein
3. Phenotypic severity of SMAs is related to the copy number of SMN2. The greater the copy number of SMN2 the less severe the illness
 - a. Variations in the SMN2 gene itself may increase full-length SMN protein and is seen in milder SMA
 - b. There are modifiers of SMA that are outside of the SMN locus
 - c. Mutations of regulators of SMN2 splicing may underlie differences in phenotypic expression in haploidentical patients

SMN Protein Function

1. Pivotal in the assembly of Sm protein into small nuclear RNA (snRNAs) which is essential to splicing
2. Putative mechanisms of SMN function:
 - a. Splicing
 - b. Axonal function
 - c. Combination of above functions
3. SnRNA most affected by SMN reduction
 - a. Involved in splicing minor introns

Other Functions of SMN

1. Decreased SMN in axons cause decreased B-actin, mRNA transport, and axon defects
2. Interaction with the Golgi adaptor protein COP and Hu D which are present in some RNA granules in axons
3. Possible defects in transport of SM1

The Spinal Muscular Atrophies

SMA (Infantile) Werdnig-Hoffman Disease

General Characteristics

1. Autosomal recessive
2. Homozygous SMN1 deletion
3. Onset less than six months
4. Incidence is between 4–10 per 100,000 live births
5. The most severe form of SMA

Clinical Manifestations

1. Short life expectancy
2. Tongue fasciculations
3. Arthrogryposis
4. Mothers may recognize a decrease of fetal movements in utero
5. Severe proximal predominant or generalized weakness with hypotonia
6. Minimal or spared facial musculature and no oculomotor involvement
7. Fasciculations of the tongue are present
8. Abdominal breathing > poor cry and suck are evident
9. Intercostal > diaphragmatic weakness
10. Pectus excavatum and decreased anterior-posterior chest diameter are present
11. Cognition is normal

Laboratory Evaluation

1. CK is less 5x normal values
2. EMG:
 - a. Low amplitude compound muscle action potentials
 - b. Fibrillation potentials and positive sharp waves
 - c. Reduced number of motor unit potentials of increased amplitude and duration
 - d. Normal sensory nerve action potentials (SNAP) amplitude

Neuropathology

1. Muscle biopsy
 - a. Rounded atrophic fibers of both fiber types
 - b. Some hypertrophic type 1 fibers; rare type grouping
2. SMN1 deletion with L3SMN2 copies

SMA Type II*General Characteristics*

1. Autosomal recessive homozygous

Clinical Manifestations

1. Onset between 6–18 months
2. Can sit independently but are never able to stand
3. Generalized proximally predominant weakness
4. Tongue fasciculations
5. Postural hand tremor
6. Areflexia
7. Kyphoscoliosis
8. Approximately 2/3 of patients survive until age 25

Neuropathology

1. Muscle biopsy similar to SMA I or may demonstrate hypertrophic type 2 fibers and type grouping
2. Denervation and reinnervation

SMA III (Juvenile Form, Kugelberg-Welander Disease)*General Characteristics*

1. Genetics:
 - a. AR homozygous

Clinical Manifestations

1. Onset after 18 months
2. Patients stand and walk
3. Proximal weakness, areflexia, tongue fasciculations and hand tremor
4. A large percentage of patients are walking at age 60 (if the onset > 3 years) and may have a normal life expectancy
5. Limb fasciculations

Neuropathology

1. Muscle biopsy demonstrates type grouping and group atrophy of type 1 and 2 fibers
2. Some fiber splitting, endomysial connective tissue and increased internal nuclei (pseudomyopathic features)

Laboratory Evaluation

1. Mutational analysis
2. Mildly elevated CK
3. SMN1 Deletion with four SMN2 copies
4. Partial denervation and denervation

SMA IV (Adult Onset)*General Characteristics*

1. Genetics:
 - a. 30% AD
 - b. AR may be SMN related
 - c. X-linked form

Clinical Manifestations

1. Onset in the third or fourth decade in the AR form
2. Proximal weakness of the hip flexors and extensors and knee extensors; shoulder abductor and elbow extensor weakness occurs after weakness of the lower extremities
3. Tongue fasciculations, hand tremor, and rarely calf hypertrophy occur
4. Normal life expectancy

Laboratory Evaluation

1. EMG
 - a. Chronic partial denervation and reinnervation
2. Molecular genetics analysis

Neuropathology

1. Muscle biopsy reveals features of chronic denervation

Genetic Correlations in SMA I–III

1. Severity of the phenotype correlates with the number of SMN2 copies:
 - a. SMN2 gene lacks exon 7. Its protein product is unstable and degraded, but its SMN protein is partially effective
 - b. Two copies of SMN2 gene are associated with SMA I
 - c. Three copies SMA II
 - d. Four copies with SMA III
 - e. Homozygous patients for SMN I mutations that have 5 copies of the SMN2 gene may be asymptomatic

X-Linked Bulbospinal Muscular Atrophy (Kennedy's Disease)

General Characteristics

1. Genetics:
 - a. X-linked androgen receptor gene mutation
 - b. Instability of CAG triplet repeats that encode polyglutamine (pol Q) stretches in the gene

Clinical Manifestations

1. Onset in the fourth to the fifth decade
2. Early symptoms include muscle cramping associated with CK (creatinine kinase) elevation; weakness occurs in mid to late adulthood
3. Proximal predominant symmetrical muscle weakness; some patients have an asymmetric onset
4. Approximately 10% of patients have initial swallowing alterations, and a dropped jaw (weakness of muscles innervated by cranial nerve V)
5. Perioral and tongue fasciculations
6. Associated sensory neuropathy
7. Rarely occurs in women who are heterozygous (similar features to young men)
8. Androgen insensitivity that causes:
 - a. Gynecomastia
 - b. Impotence
 - c. Testicular atrophy
 - d. Decreased fertility
 - e. Increased incidence of DM
9. Tremor

Laboratory Evaluation

1. EMG
 - a. Partial denervation and reinnervation
 - b. CMAP are decreased or normal
 - c. Absent or low SNAPs and H reflexes
2. Increased CK

Neuropathology

1. Muscle biopsy
 - a. Neurogenic atrophy of both fiber types, pyknic nuclear clumps (tombstones of neurogenic atrophy); fiber type grouping
2. Some pseudomyopathic features (inflammation around necrotic fibers)
3. Sural nerve biopsy demonstrates loss of myelinated fibers
4. Consequences of androgen receptor poly Q chain elongation
 - a. AR (androgen receptor) nuclear and cytoplasmic aggregates
 - b. AR coactivators are sequestered into the nuclear inclusions that putatively cause translational dysregulation

Juvenile Segmental SMA (Hirayama Disease)

General Characteristics

1. Genetics:
 - a. Sporadic inheritance

Clinical Manifestations

1. Insidious onset in the teens of unilateral or asymmetric atrophy of the hand and forearm of C7, C8, T1 innervated roots
2. Sparing of the brachioradialis
3. Primarily a disease of young males between 15 and 25 years of age
4. Irregular course tremors
5. May be bilateral
6. Progression for 1–3 years and then either an arrest of the disease or a benign course
7. Worsening of symptoms with cold ("cold paresis")
8. Over years, there may be spread to more proximal arm muscles
9. Absent sensory loss, preservation of reflexes with no cranial nerve, pyramidal tract, lower limb, sphincter or cerebellar deficit
10. Hyperhidrosis of the involved limb
11. An Indian variant affecting the lower extremity with primary involvement of the quadriceps has been described

Laboratory Evaluation

1. EMG evaluation
 - a. Segmental motor neuron disease
 - b. Variably reduced median and ulnar CMAP with normal motor and sensory conduction velocities
 - c. Distal latencies and F-wave latencies are normal or variably affected. Sparing of C5, C6 dermatomes

Neuroimaging

1. MRI protocol in neutral position followed by imaging in hyperflexion
 - a. Asymmetrical or symmetrical atrophy of the lower cervical cord, anterior shifting of the posterior dural sac on flexion, and prominences and enhancement of the posterior epidural venous plexus on dynamic flexion
 - b. Loss of the attachment between the posterior dural sac and subjacent lamina in the neutral position

Neuropathology

1. Abnormal cervical dura with few elastic fibers
2. Loss of motor neurons in involve segments from ischemia

Scapuloperoneal Form of SMA (Davydenko Syndrome)

General Characteristics

1. Genetics:
 - a. Autosomal dominant; 1 patient with 17P11.2 deletion
 - b. Scapuloperoneal spinal muscular atrophy and CMT2C are allelic disorders:
 - i. Mutations in the gene encoding the transient receptor potential cation channel, subfamily V, member 4 (TRPV4)

- ii. Both diseases display increased calcium channel activity
- iii. Maps to Chromosome 12q24.1-q24.31

Clinical Manifestations

1. Onset in late childhood
2. Initial manifestations are weakness of shoulder girdle and foot dorsiflexion muscles
3. Weakness may generalized over time
4. High-arched foot deformity
5. Distal large fiber sensory loss

Laboratory Evaluation

1. EMG
 - a. Chronic partial denervation and re-innervation

Neuropathology

1. Muscle biopsy
 - a. Fiber type grouping and atrophy, endomysial fibrosis, variability of fiber size, nuclear bags, and fiber splitting; type 1 and 2 fibers are affected
 - b. No loss of neurons in the brain or spinal cord (one autopsied patient)
 - c. Pathologic features support a diagnosis of spinal neurogenic amyotrophy secondary to a peripheral motor neuropathy

Autosomal Dominant SMA (B1CD2)

General Characteristics

1. Genetics:
 - a. Mutations in B1CD2 (bicaudal D homologue-2 (*Drosophila*)) that map to chromosome 9q22.3
 - b. The gene encodes:
 - i. A Golgi and motor adaptor protein involved in antegrade and retrograde transport, synaptic vesicle and membrane traffic and Golgi structure; dynein-dynactin microtubular transport (links dynein molecular motor with its cargo)

Clinical Manifestations

1. Proximal and distal muscle weakness with atrophy of the lower limbs; muscle cramps
2. Waddling gait
3. Congenital contractures of the ankle and feet (some patients)
4. Benign slowly progressive course
5. Early childhood onset

Laboratory Evaluation

1. EMG
 - a. Motor nerve conduction velocities and amplitude and CMAP are normal; sensory NCVs are also normal

Neuropathology

1. Muscle biopsy demonstrates neurogenic features
2. Golgi fragmentations (electron microscopy)

Autosomal Dominant SMA (DYNC1H1) Mutations

General Characteristics

1. Genetics:
 - a. Chromosome 14q32.31
 - b. Mutations in the tail domain of the heavy chain of cytoplasm dynein (DYNC1H1)
 - i. Disrupts dynein complex assembly and function

Clinical Manifestations

1. Early childhood onset
2. Proximal leg weakness and muscle atrophy
3. Waddling gait
4. Minimal progression of weakness
5. Late in disease hand interosseous muscle atrophy without fasciculations or contracture
6. Hip extension and flexion and muscles of the upper extremity are minimally involved
7. Quadriceps more affected than the hamstrings
8. Excessive lumbar lordosis
9. No sensory loss
10. A different missense mutation causes a CMT phenotype (CMT20)
 - a. Length-dependent weakness
11. Tail domain mutations may also demonstrate learning disabilities
12. A phenotypic spectrum exists for DYNC1H1-related diseases

Laboratory Evaluation

1. EMG (clinically weak muscles)
 - a. Chronic denervation with giant motor unit action potentials (> 10 mV)
 - b. Nerve conduction studies demonstrated small motor response amplitudes in the feet and normal sensory amplitudes

Neuropathology

1. Decreased binding to microtubules in the presence of ATP

Brown-Vialetto-Van Laere Syndrome (Childhood Bulbar SMA)

General Characteristics

1. Genetics:
 - a. Brown-Vialetto-Van Laere (BVVL) syndrome is caused by a homozygous mutation in the C200rf54 gene that maps to chromosome 20p13
 - b. BVVL syndrome and Fazio-Londe disease are now considered the same entity
 - c. BVVLS2 is caused by a mutation Mutations occur in the SLC52A2 gene and maps to chromosome 8q
 - i. Encodes the intestinal (hRFT2) riboflavin transporter is causative in some patients

Clinical Manifestations

1. The onset of the disorder is usually in the second decade, but earlier and later patients have been described

2. The first symptom is usually sensorineural deafness which is progressive and severe
3. The onset of other signs and symptoms in males is five years and females up to 11 years of age
4. Other initial features include:
 - a. Weakness
 - b. Respiratory compromise
 - c. Dysarthria
 - d. Facial, neck and shoulder weakness
 - e. Infections have been associated with disease onset in some patients
 - f. Manifestation may be vocal cord paralysis (Stridor) with early onset patients
5. Lower cranial nerves VII–XII are most commonly affected; less frequent involvement of CN II–VI occurs
6. Lower motor signs are seen in the lower extremities; rare upper motor signs are seen
7. Sensation is rarely affected
8. Rare reported fundoscopic signs that have been reported include:
 - a. Optic atrophy
 - b. Retinitis pigmentosa
 - c. Macular hyperpigmentation
9. Rare signs and symptoms include:
 - a. Autonomic dysfunction
 - b. Seizure
 - c. Cognitive impairment
 - d. Decreased horizontal eye movements
 - e. Tremor
10. Non-neurologic manifestations include:
 - a. Auditory hallucinations
 - b. Abnormal behavior
 - c. Diabetes insipidus
 - d. Delayed puberty and hypogonadism
 - e. Dismorphisms
 - f. Gynecomastia
 - g. Hypertension

Neuropathology

1. Neuronal loss in cranial nerve nuclei III, V, VI as well as VII–XI
2. Loss of anterior horn cells
3. Degeneration of corticospinal and spinocerebellar tracts
4. Loss of neurons in brainstem nuclei

Laboratory Evaluation

1. EMG evaluation
 - a. Chronic or active muscle degeneration
 - b. Visual evoked potential
 - i. Prolonged latencies in approximately 50% of patients
 - c. Auditory sensorineural deafness
2. MRI
 - a. Atrophy of the brainstem and cerebellum in some patients
3. CSF protein may be mildly elevated

Madras Motor Neuron Disease Variant (MMNDV) and Familial MMND

General Characteristics

1. Genetics:
 - a. Reported from Southern India
 - b. No genetic defects have been identified
 - c. Families with autosomal dominant and X-linked inheritance have been described

Clinical Manifestations

1. Onset prior to age 15
2. Slight male predominance
3. Thin habitus
4. Distal limb muscle wasting and weakness
5. Bilateral optic atrophy (some patients)
6. Impaired hearing
7. Dysarthria, hypophonia and tongue atrophy
8. Pyramidal tract dysfunction in some patients

Neuropathology

1. Severe loss of anterior horn cells
2. Sclerosis of the ventrolateral columns
3. Neuronal loss in cranial nerves VII, IX, and XII

Laboratory Evaluation

1. Audiological assessment
2. Screening to rule out SLC52A1, SLC52A2 and SLC52A3 as well as C9orf72 expression
3. EMG
 - a. Neurogenic findings in affected muscles

Differential Diagnosis

1. Amyotrophic lateral sclerosis
2. SCA syndromes
3. Brown-Vialetto-Van Laere (BVVL) syndrome
4. Progressive spinal muscular atrophy
5. Post-polio syndrome

Distal Spinal Muscular Atrophy

Overview

These are a heterogeneous group of progressive hereditary disorders that cause distal symmetric weakness without sensory loss. They are autosomal dominant, recessive and rarely X-linked.

As noted earlier, SMN protein is localized to both the nucleus and cytoplasm and is pivotal in the assembly of small nuclear ribonucleoproteins (snRNPs). These are key components of spliceosomes. There is mounting evidence derived primarily from animal models that snRNP assembly and pre-mRNA splicing are defective in autosomal recessive SMA. Experimented evidence now supports a role for SMN in the maintenance of motor neurons by regulation of cytoplasmic and axonal mRNAs. Defects in these functions may be important in the dying back axonopathies represented by the distal SMAs.

The distal hereditary motor neuropathies are genetically heterogeneous and show a wide spectrum of phenotypic features. Some of the dHMNs genes underlie Charcot-Marie-Tooth (CMT) disease and spinal muscular atrophy SMA. There is overlap between phenotypically distinct forms of dHMN. In general, they show a length-dependent predominant motor neuropathy, but some forms also have minor sensory abnormalities and upper motor neuron features. They may overlap within 1. axonal forms of CMT; 2. juvenile forms of ALS; and 3. hereditary spastic paraplegias. They demonstrate autosomal dominant, recessive and X-linked pattern of inheritance. It is apparent that approximately 80% of patients have undiscovered gene mutations.

Functional patterns caused by these gene mutations can be characterized by:

1. Mutations that cause protein misfolding:
 - a. HSPB1
 - b. BSPB8
 - c. BSCL2
2. Mutations involved in RNA metabolism:
 - a. IGHMBP2
 - b. SETX
 - c. GARS
3. Mutations involved in axonal transport:
 - a. HSPB1
 - b. DYNC1H1
 - c. DCTN1
4. Mutations causing cation-channel dysfunction:
 - a. ATP7A
 - b. TRPV4

Mutations in Genes That Cause AD Distal HMN

1. Glycyl-t RNA synthetase (GARS)
2. Dynactin 1 (DCTN1)
3. Small heat shock 27 kDa protein (HSPB1)
4. Small heat shock 22 kDa protein 8 (HSPB8)
5. Berardinelli-SEIP congenital lipodystrophy (BSCL2)
6. Senataxin (SETX)
7. Mutation in the (VAMP) associated protein B and C genes
 - a. Brazilian families
 - b. AD inherited MND
 - c. Clinically atypical
8. A C-terminal HSPB1-mutation is associated with upper motor neuron signs

Dominant Mutation in FBX038 with Distal Spinal Muscular Atrophy

General Characteristics

1. Genetics:
 - a. Mutation in F-box protein 38
 - b. Encodes a protein coactivator of the transcription factor Kruppel-like factor (KLF7); regulates genes for neuronal axon outgrowth and repair and possibly motor neuron maintenance. Also, may impair the activation of KLF7 target genes

Clinical Manifestations

1. Onset from 13–48 years
2. Weakness beginning in the calves with slowly progressive weakness of both distal and proximal leg and arm muscles
3. Particular upper extremity weakness
 - a. Intrinsic hand muscles (abductor pollicis brevis and first dorsal interosseous muscles)
 - b. Triceps
4. Loss of ankle tendon reflexes
5. Possible sensory loss in some patients (confounding illnesses)

Laboratory Evaluation

1. EMG
 - a. Chronic neurogenic pattern that includes fibrillation and positive sharp waves that support active denervation
 - b. Nerve conduction studies
 - i. Reduced motor-evoked amplitudes in the lower limbs with normal sensory conduction

Neuropathology

1. Muscle biopsy neurogenic changes

DYNC1H1 Mutations in Distal SMA

General Characteristics

1. Genetics:
 - a. Neck and motor domain mutations
 - i. Encodes the heavy chain of cytoplasmic dynein 1
 1. A motor complex important for retrograde axonal transport

Clinical Manifestations

1. Mutations in DYNC1H1 associated with:
 - a. Autosomal dominant CMT type 2
 - b. Distal SMA affecting the legs
 - c. A form of cognitive dysfunction and migrational disorder

Neuropathology

1. These two novel mutations in DYNC1H1 (c.3581A>G and c.9142G>A)
2. Affect Golgi function
3. Associated with cortical malformations
4. A motor for the intracellular retrograde motility of vesicles and organelles along microtubules

Laboratory Evaluation

1. Molecular genetic evaluation
2. EMG
 - a. Neurogenic findings in the lower extremities

Receptor Expression-Enhancing Protein 1 (REEP1) Mutations Associated with Distal Hereditary Motor Neuropathy Type V

General Characteristics

1. Genetics:

- a. Missense mutations in GARS are found in classic dHMN and dHMNV as well as overlapping CMT2D
- b. BSCL2 mutations also seen in dHMNV
 - i. Missense mutations (c.263A>G) and (c.264C>T) that affect glycosylation
 - ii. Associated with:
 - 1. Silver syndrome
 - 2. Spastic paraplegia
- 2. Clinical manifestations of classic dsHMN:
 - a. The motor features include:
 - i. Muscle weakness and wasting primarily of thenar and first dorsal interosseous muscles

Neuropathology

- 1. REEP (receptor expression enhancing protein 1) mutations:
 - a. Underlie SPG 31 (AD form of HSP)
 - b. The mutation identified with distal hereditary motor neuropathy c.304-2A>G lacks exon 5
 - c. Function of REEP protein:
 - i. Stabilize of the membrane curvature in the tubular endoplasmic reticulum (ER)
 - d. REEP1 clinical spectrum correlates closely with BSCL2 missense mutations
 - e. Clinically REEP mutations have a phenotypic spectrum for both upper and lower motor neuron disease

Laboratory Evaluation

- 1. Molecular genetic evaluation
- 2. EMG
 - a. Neurogenic findings in affected muscles

Outline of dSMA (Hereditary Distal Motor Neuropathies)

- 1. dSMA I
 - a. Genetics
 - i. AD
 - b. Clinical features
 - i. Juvenile onset
 - ii. CMT phenotype
- 2. dSMA II
 - a. Genetics
 - i. Chromosome 12q24.3
 - 1. AD
 - 2. Encodes heat shock protein 22
 - 3. Allelic to CMT2F
 - ii. Chromosome 7q11-q21
 - 1. AD
 - 2. Encodes heat shock protein 27
 - b. Clinical features
 - i. Onset 15–25 years of age
 - ii. Rapid progression
 - iii. CMT phenotype
 - 1. CMT phenotype
- 3. dSMA III
 - a. Genetics
 - i. AR
 - b. Clinical features
 - i. Early adult onset
 - ii. Slow progression
- 4. dSMA IV
 - a. Genetics
 - i. AR
 - b. Clinical Manifestations
 - i. Juvenile onset
 - ii. Severe
 - iii. Diaphragmatic paralysis
- 5. dSMA V (see above)
 - a. Genetics
 - i. AD
 - ii. Maps to Chromosome 7p15
 - iii. Encodes glycyl t-RNA synthetase
 - iv. Allelic to CMT2D
 - b. Clinical features
 - i. Onset in hands (APB and first dorsal interosseous muscles)
 - ii. Some patients with spastic paraparesis
 - c. Genetics (alternate form)
 - i. AD; Chromosome 11q12-q14
 - 1. Gene mutated is BSCL2
 - 2. Allelic to Silver syndrome (SPG17) whose clinical features are:
 - a. AD inheritance
 - b. Lower limb spasticity
 - c. Amyotrophy of hand muscles
 - ii. BSCL2 (Seipin)
 - 1. Allelic to Berardinelli-Seip congenital lipodystrophy
 - 2. Clinical features are:
 - a. AR
 - b. Severe generalized lipodystrophy
 - c. Insulin resistance
 - d. Development of diabetes mellitus and dyslipidemia
 - e. Dysmorphic facial features
- 6. dSMA VI
 - a. Genetics
 - 1. AR 11q13-q21
 - a. Encodes immunoglobulin-binding protein 2
 - 2. Clinical features
 - a. Infantile-onset severe diaphragmatic paralysis
- 7. dSMA VII
 - a. Chromosome 2p14 Genetics
 - i. AD
 - ii. Clinical features
 - 1. Adult onset vocal cord paralysis
 - a. No upper motor neuron signs and no sensory loss
 - b. Chromosome 2p13 Genetics
 - i. AD

- ii. DCTN1 (dynactin)
- iii. Clinical features
 - 1. Adult onset associated vocal cord paralysis and facial weakness
- c. X-linked (Xq13.1-q21)
 - i. Brazilian families
- 8. Congenital non-progressive dSMA with arthrogryposis
 - a. Chromosome 12q23 Genetics
 - i. AD
 - b. Clinical manifestations
 - i. Congenital, non-progressive with arthrogryposis
- 9. Jerash Type – Jordanian children
 - a. Chromosome 9p21.1-p12 Genetics
 - i. AR
 - b. Clinical manifestations
 - i. Onset 6–12 years of age
 - ii. Pyramidal tract and sural nerve involvement
- 10. Juvenile onset CMT phenotype
 - a. Chromosome 9q34 Genetics
 - i. AD
 - ii. Allelic to ALSH
 - iii. Encodes senataxin
 - b. Clinical manifestation
 - i. Some upper motor signs and symptoms
 - ii. CMT phenotype
- 11. Austrian Kinship
 - a. Clinical manifestations
 - i. Onset in arms with pyramidal tract involvement
- iii. Facial diplegia
- iv. Contracture
- v. Mental retardation
- d. Congenital myasthenia syndromes
 - i. Fatigable muscle weakness
 - ii. Pattern of weakness is determined by which genes are mutated
 - iii. Ocular, bulbar and limb muscle involvement
- e. Pompe's disease:
 - i. Large fasciculating tongue
 - ii. Cardiomegaly
- f. Congenital myopathy:
 - i. Nemaline
 - 1. Hypotonia
 - 2. Proximal weakness
 - 3. Lax ligaments
 - 4. Areflexia
 - 5. Skeletal deformities
 - ii. Centronuclear (myotubular myopathy):
 - 1. X-linked form
 - 2. Marked weakness
 - 3. External ophthalmoplegia
 - 4. Respiratory failure
- g. Infantile Botulism:
 - i. Symmetric cranial nerve palsies
 - ii. Flaccid paralysis of voluntary muscles
 - iii. Respiratory compromise
- h. Congenital Hypomyelination Neuropathy
 - i. Hypotonia
 - ii. Distal muscle weakness
 - iii. Areflexia
- i. Infantile Mitochondrial Myopathy:
 - i. Multiorgan involvement
 - ii. Encephalopathy
 - iii. Peripheral Neuropathy
 - iv. Lactic acidosis
- j. Neonatal tetanus:
 - i. Severe spasms
 - ii. Lower cranial nerve involvement
 - iii. Spasms in facial muscles

Summary of Manifestations of Distal SMA

1. Weakness of ankle dorsiflexors, evertors and toe extensors
2. Pes cavus
3. Four genotypes of dSMA have concomitant pyramidal features:
 - a. Glycyl-t-RNA synthetase (chromosome 7p15; dSMA5)
 - b. BSCL2 gene (chromosome 11q12-q14); dSMA5
 - c. Senataxin gene
 - d. Jerash kindred
4. There is clinical overlap with phenotypes of hereditary spastic paralysis (HSP), CMT and ALS

Differential Diagnosis of the Spinal Muscular Atrophies

Congenital Presentation

1. The floppy infant
 - a. CNS alterations
 - b. Neuromuscular diseases
 - i. The infants are alert, cognitively intact, but areflexic
 - c. Congenital myotonic dystrophy:
 - i. Hypotonia
 - ii. Respiratory failure

Diagnostic Point

1. Fasciculations of the tongue favor the diagnosis of Werdnig-Hoffman disease
2. Pompe's disease has fasciculations of the tongue with cardiomegaly

Differential Diagnosis of Proximal Symmetric Weakness of Childhood to Early Adulthood Versus SMA (II, III, IV)

1. Limb-girdle muscular dystrophy
2. Congenital myopathy
3. Glycogen or lipid storage myopathy

4. CIDP
5. Emery-Dreifuss muscular dystrophy
6. Mitochondrial disease
7. Myotonic dystrophies

Diagnostic Features for SMA

1. Tongue and limb fasciculation
2. Tremor
3. Other disorders have specific features:
 - a. Mitochondrial disease (short stature, hearing loss, fatigue, short stature)
 - b. Congenital myopathies:
 - i. Thin muscles
 - ii. Dysmorphisms
 - c. Emery-Dreifuss:
 - i. Cardiac abnormalities
 - ii. Contractures
 - d. Specific features of LGMD
 - e. Dystrophinopathy
 - i. Calf hypertrophy
4. Laboratory evaluations:
 - a. DNA mutational analysis for SMA or dystrophinopathy
 - b. EMG and nerve conduction studies for MG and neuropathy (CIDP)
 - c. Assays for botulinum toxin and EMG

Diagnostic Features of Kennedy's Disease

1. Seminal clinical features of Kennedy's disease
 - a. Presents in men in the 3rd–5th decade
 - b. Proximal > distal weakness
 - c. Distal weakness in the upper extremities > lower (wasting of intrinsic hand muscles)
 - d. Neurogenic cramps
 - e. Hand tremor may occur prior to weakness
 - f. Facial fasciculations
 - i. Most prominent around the mouth and chin
 - g. Weakness and atrophy of facial muscles and those of mastication may precede that of other muscles
 - h. Dysarthria and dysphagia after ten years
 - i. Normal sensory exam
 - j. Gynecomastia
 - k. Absent/hypoactive deep tendon reflexes
 - l. Some patients with joint contractures
2. Laboratory evaluation
 - a. Elevated CK
 - b. Denervation on muscle biopsy
 - c. DNA mutational analysis
3. EMG evaluation
 - a. Weak and wasted muscle:
 - i. Normal NCV
 - ii. CMAP is low
 - b. Low amplitude or absent SNAPs

c. Needle EMG

- i. Denervation of extremity muscles; facial and mentalis muscles; grouped repetitive discharges with activation

ALS

1. Progressive bulbar palsy form
 - a. Symptomatic dysphagia early in the disease process
2. Myasthenia gravis:
 - a. Degrees of ophthalmoplegia
 - b. Weakness with exercise
 - c. Retained reflexes
 - d. Minimal, if any wasting
 - e. Laboratory evaluation
 - i. EMG
 - ii. Anti-acetylcholine receptor and muscle-specific kinase antibodies
3. Inclusion body myositis:
 - a. Seminal clinical features
 - i. Older age male
 - ii. Difficulty swallowing and limb weakness
 - iii. Wrist and finger flexion weakness
 - b. Laboratory evaluation:
 - i. Muscle biopsy (inflammatory)
 - ii. EMG
4. Lambert-Eaton syndrome:
 - a. Increased strength with exercise
 - b. Limited cranial nerve involvement (ptosis)
 - c. Loss of reflexes
 - d. Laboratory evaluation
 - i. EMG
 - ii. Antivoltage calcium channel antibodies
5. Oculopharyngeal dystrophy
 - a. Limb weakness
 - b. Mild dysphagia
 - c. Ptosis often presenting signs
 - d. Laboratory diagnosis
 - i. EMG
 - ii. DNA mutational analysis for polyadenylate-binding protein type 1
6. Multifocal motor neuropathy
 - a. Seminal clinical features
 - i. Weakness without atrophy
 - ii. Distribution is in a nerve rather than a segmental distribution; not limited to C7, C8, T1 as in Hirayama
 - b. EMG evaluations
 - i. Demyelinating characteristic in nerve conduction studies
 - c. Laboratory evaluation
 - i. GM1 ganglioside antibodies and GM1/GalNAc-GD1a antibodies
7. ALS (brachial variant)
8. Syringomyelia

- a. Pain and suspended sensory loss (primarily spinothalamic modalities)
 - b. Segmental atrophy
 - c. May have increased reflexes below the syrinx (absent at the segmental level)
 - d. Neuropathic shoulder joint
 - e. MRI:
 - i. Demonstrates the syrinx
 - ii. Some tumors have associated syrinx
9. Cervical cord pathology
- a. Cervical spondylosis and stenosis
 - b. Calcified posterior longitudinal ligament
 - c. Dislocation of C2–C3
 - d. Schwannoma (dumbbell tumor)
 - e. Neuroimaging
 - i. Cervical cord MRI with enhancement
 - f. Laboratory features
 - i. Anti-CM1 and GM1/GaNC1-GD1a antibodies

Differential Diagnosis of the Spinal Muscular Atrophy

1. The fluffy hypotonic infant:
 - a. The majority of hypotonic infants (approximately two-thirds) have a CNS disorder
2. Infant child neuromuscular disorders are characterized by:
 - a. Cognitively intact child
 - b. Diminished or absent deep tendon reflexes
3. The differential diagnosis includes:
 - a. Congenital myasthenic syndrome
 - b. Neonatal myotonic dystrophy
 - c. Pompe's disease
 - d. Nemaline myopathy
 - e. Myotubular myopathy
 - f. Centro nuclear myopathy
 - g. Rod body myopathy
 - h. Central core disease
 - i. Infantile botulism
 - j. Hypomyelinating neuropathy

Differential Point

1. A large fasciculating tongue with concomitant heart disease such as Pompe's disease; a small fasciculating tongue is more for Weinig-Hoffman disease
2. Ptosis, constipation, and loss of head control favor infantile botulism
3. Proximal muscle weakness of childhood in early adulthood
4. Dystrophinopathy
 - a. Large calves (pseudohypertrophy)
 - b. Loss of reflexes
 - c. Cardiac involvement
5. Limb-girdle muscular dystrophies
 - a. Equal occurrence in males and females
 - b. Specific features are defined by the specific mutations

- c. Congenital myopathies
 - i. Thin muscles surprisingly strong for their appearance
 - ii. Dysmorphic features
- d. Glycogen and lipid storage myopathies
- e. CIPD
 - i. Sensory loss (large > small fibers)
 - ii. Loss of reflexes

Differential Diagnosis of Kennedy's Disease

1. Bulbar ALS
2. Inclusion body myositis
 - a. Atrophy and contracture of forearm musculature
 - b. Atrophy of distal 1/3 of the quadriceps muscle
3. Myasthenia gravis
 - a. Ptosis and ophthalmoplegia
 - b. Reflexes are generally retained
 - c. Fatigue with exercise
 - d. Fazio-Londe disease
 - e. Brown-Vialetto-Van-Laere disease
 - i. VIIIth cranial nerve involvement
 - f. Lambert-Eaton syndrome
 - i. Autoimmune symptomatology
 - ii. Increased strength with exercise
 - iii. Loss of reflexes
 - g. Oculopharyngeal dystrophy
 - i. Symmetrical severe ptosis and ophthalmoplegia

Differential Diagnosis of Hirayama Disease

1. Multifocal motor neuropathy
2. ALS (monomelic variant)
3. Syringomyelia
4. Cervical disc disease
5. Congenital cervical malformations
6. Diseases with lax ligaments (affecting the cruciate ligament of the odontoid process)

Differential Diagnosis of Scapulothoracic Syndrome

1. FSH dystrophy
2. Congenital myopathy
3. Charcot-Marie-Tooth

Differential Diagnosis of Distal SMAs

1. Charcot-Marie-Tooth (axonal form)
 - a. The presence of sensory abnormalities is a major differential point
2. Mutations of the kinesin motor protein-1-b (KIF1B) gene, heat shock protein gene 27 (7q11-7q21), and a specific

- mutation of chromosome 7B may be associated with CMT2A, 2F, and 2D or with a distal SMA phenotype
3. Distal myopathies
 - a. Distal SMAs and distal myopathies both are:
 - i. Slowly progressive
 - ii. Symmetric weakness of dorsiflexion
 - iii. Both may be associated with vocal cord paralysis and fast deformities

Differential Diagnosis of Fazio-Londe and Brown-Vialetto-Van Laere Syndrome

1. Infiltrative brainstem astrocytoma or glioma
2. Bulbar ALS

Amyotrophic Lateral Sclerosis

Introduction

Amyotrophic lateral sclerosis is a lethal motor neuron disease with multiple variants that progresses to paralysis of almost all skeletal muscles. Lumbosacral motor neurons appear more susceptible than cervical ones and extra-ocular, and sphincter muscles are resistant. The cellular pathology appears focal at onset and spread by the involvement of contiguous motor neuron populations. Pathology reveals aggregated proteins in motor neurons and oligodendrocytes (approximately 10% of cases are inherited: approximately 24 familial genes and six for sporadic disease). There are approximately five patients per 100,000 individuals/year.

Molecular research in ALS began with discovery of mutations in the superoxide dismutase (SOD1) gene.

SOD1 General Characteristics

1. Ubiquitously expressed protein that catalyzes the detoxification of superoxide
2. >150 mutations of the SOD1 gene associated with ALS most of which are dominant and missense
3. Mutant SOD1 toxicity is mediated by:
 - a. Protein misfolding
 - b. Oligomerization
 - c. Gain of function toxicity
4. Effects of toxicity are:
 - a. Altered mitochondrial metabolism
 - b. Axonal transport failure and degeneration
 - c. Excitotoxicity
 - d. Proteasome disruption
 - e. Endoplasmic reticulum stress
5. Wild-type SOD1 toxicity is being investigated in sporadic ALS (SALS); putative conformational change that propagates similarly to prion disease

TDP-43 General Characteristics

1. TDP-43 gene mutations occur in approximate 4% of familial ALS

2. TDP-43 is a ubiquitously expressed DNA/RNA-binding protein whose function include:
 - a. Gene transcription
 - b. RNA splicing
 - c. RNA shuttling and translation
 - d. MicroRNA biogenesis
3. In disease states: TDP-43 is ubiquitinated, hyperphosphorylated and cleared:
 - a. Forms intranuclear and cytoplasmic inclusions
 - b. Transported from the nucleus to the cytoplasm and axons
4. TDP-43 importance:
 - a. In development
 - b. Maintenance of motor neurons

FUS/TLS (*Fused in Sarcoma/Translated in Liposarcoma*) Gene Mutations

1. Cause approximately 4% of familial ALS
2. ALS-related mutations putatively may alter its intranuclear structure that dysregulates its function and cause intracytosolic aggregation. A mechanism of its pathogenesis in ALS may be the propagation of misfolding of its protein and its interaction with TDP-43 aggregates

C9orf72 Gene

The most common genetic cause of ALS is the hexanucleotide expansion in chromosome 9 open reading frame 72 (C9orf72) gene. It accounts for approximately 50% of familial ALS (FALS) in patients of European descent, 25% of familial Frontal Temporal Lobe Dementia (FTLD) and approximately 5% of sporadic ALS.

The putative mechanisms of C9orf72 mediated ALS are:

1. Haploinsufficiency as there is decreased C9orf72 transcripts in autopsied CNS material of ALS patients
2. Formation of nuclear RNA foci that form G-quadruplex structures and hairpin loops in both DNA and RNA. The G-quadruplex are important for transcription, translation, RNA transport, and telomeric stability. The C9orf72 expansion may sequester the proteins which G-quadruple bind. The repeat may also bind and sequester transcription factors. Another mechanism suggested for the neurotoxicity of the C9orf72 expansion is deregulated protein translation termed repeat-associated non-ATG (RAN) translation which has been identified in spinocerebellar ataxia 8 and myotonic dystrophy 1 (DM1)

Accumulating evidence supports a role for the axons, dendrites, and synapses in the neuropathology of ALS. The earliest changes in ALS occur in these peripheral components of the motor unit. TDP-43 aggregates are seen early within motor axons, and mutant-SOD1 mice develop denervation and terminal axonal degeneration prior to anterior horn cell loss.

Multiple other genes and non-neuronal cells can modulate the ALS phenotype.

The modified El Escorial Criteria is an excellent platform to define the clinical diagnosis of ALS. A clinically

definite diagnosis requires the presence of upper motor neuron (UMN), as well as lower motor neuron (LMN) signs in three body regions. Probable ALS has clinical evidence of UMN and LMN signs in at least two body regions with some UMN signs rostral to the LMN signs. Clinically probable and laboratory-supported ALS patients have clinical signs of UMN and LMN in one region or if clinical UMN signs are present in one region associated with LMN signs defined by EMG criteria in at least two limbs. Clinically possible ALS is the association of UMN and LMN signs that are in only one, two, or more regions or if LMN signs are found above UMN signs, but there is no EMG evidence of spread to LMN disease.

Some clinical difficulties remain with the criteria. Some patients with motor neuron disease (MND) have a restricted syndrome with a divergent natural history from ALS, and approximately 25% of patients with rapidly progressive MND succumb prior to meeting clinical criteria. ALS affects the autonomic system as well as cognitive behavioral networks in some patients. MND may occur with both autoimmune and neurodegenerative diseases.

Epidemiology of ALS

1. Incidence of ALS is 1.8/100,000 individuals
2. Women are affected twice as frequently as men
3. There is evidence that the incidence is equal after menopause
4. Women may have a greater incidence of bulbar signs
5. There are specific geographical areas with a high incidence such as Guam and the Western Pacific as well as the Ryukyu Islands of Japan
6. There are many specific clinical variants both in type of ALS and in patients with SNPs within the genetic forms of the disease
7. Genetic mutations are thought to account for 5–10% of patients. Over 24 genes have been identified for familial ALS and 6 for the sporadic disease

Clinical Manifestations

1. Initial signs and symptoms
 - a. The signs are asymmetric and often monomelic (one extremity)
 - b. Approximately 10% of patients present with bulbar symptomatology
 - c. Decreased head control
 - d. Altered breathing
 - e. Fasciculations (in some patients); fasciculation in weak muscles with atrophy
 - f. Cramping (neurogenic) in an exercised muscle

Lower Motor Neuron Signs

1. Weakness
2. Atrophy
3. Loss of deep tendon reflexes

4. Fasciculation
5. Coordinative difficulty in proportion to weakness

Upper Motor Neuron Disease

1. Difficulty in initiating and maintaining fractionated extremity movements
2. Synkinetic muscle contraction to overcome weakness of prime movers
3. Spasticity
4. Pathologic reflexes (spread from a segmental zone with lower threshold to elicit)
5. Sustained clonus
6. Babinski sign
7. Emotional lability (pseudobulbar palsy) that consists of:
 - a. Pathologic laughter or crying; laughter without mirth; crying without tears
 - b. Increased gag or jaw reflex
 - c. Spasticity
 - d. Hyperreflexia
8. Yawning
9. Increased reflexes in a weak and wasted muscle

Classic ALS

General Characteristics

A patient presents with both UMN and LMN signs and symptoms. Initially, the LMN signs predominate in a limited group of muscles. This is considered LMN-dominant disease (LMN-D).

This pattern in the upper extremity often is initiated by atrophy of intrinsic hand muscles in various patterns:

1. Weakness and atrophy of the first dorsal interosseous muscle
2. Lateral hand split
3. Medial hand, benediction sign

The fourth and fifth fingers are involved first as they are with cervical syringomyelia. In chronic regional pain syndrome (CRPS) these fingers are dystonic. A painless foot drop may be the initial presentation in the lower extremity. Patients may also present with proximal muscle weakness. The differential diagnosis of UMN and LMN signs in one extremity is restricted and is strong for a diagnosis of ALS. Approximately 2/3 of patients with ALS present with limb-onset disease and 1/3 of these present with pure LMN involvement. Approximately 70% of these patients develop the Escorial criteria (with UMN involvement) over a six year period. At autopsy, many patients who demonstrate only LMN features have degeneration of the corticospinal pathways and the ubiquitinated inclusions of MND characteristic of ALS.

A variant of slowly progressive spinal muscle atrophy and ALS is bi-brachial (flail arm syndrome) or causes paraplegia. Over time in both variants, there is a spread of signs to other regions. Five of the autosomal dominant SOD mutations have an LMN dominant phenotype. The A4V SOD1 mutation is the most common of this genetic variant.

The ALS presentation with bulbar signs has the following features:

1. Occurs in approximately 25% of patients
2. Dysarthria is more common than dysphagia
3. Women are more frequently affected than men
4. Associated more frequently with FTLT than limb onset variants
5. May be predominant UMN, LMN or a combination of signs
6. May occur in familial ALS (FALS)
7. A prominent sign of LMN involvement of the cranial nerves is an atrophic fasciculating tongue

Other measures of cranial nerve involvement in ALS are:

1. Neck extension weakness (flexor weakness favors myopathy)
2. Weak tongue protrusion
3. Masseter and pterygoid weakness (dropped jaw is a late feature)
4. Facial weakness
5. Nasal voice (tensor veli palatini weakness)

Ptosis and ophthalmoparesis are extremely rare. With frontal lobe degeneration, patients may present with apraxia of eyelid opening. Synkinesis of jaw movement with side-to-side tongue movement is similar to difficulty with fractionated movement of the fingers in limb dominated ALS.

Primary lateral sclerosis, the exclusive involvement of predominantly UMN, presents in approximately 2–5% of ALS patient.

The primary clinical features of PLS are:

1. Onset at age 50
2. Asymmetry
3. Legs are initially involved in approximately 75% of patients
4. Spasticity is more dysfunctional than weakness
5. In approximately 15% of patients, bulbar signs are initially affected
6. Upper extremities may be initially affected in 10% of patients
7. Detrusor-sphincter dyssynergia occurs due to UMN involvement (extremely rare in classic ALS)
8. A percentage of PLS patients evolve into ALS (usually within four years)
9. Patients may maintain primarily UMN signs for as long as 20 years prior to evident LMN involvement
10. Life expectancy is usually 7–14 years

Less than 1% of ALS patients present with respiratory failure. The symptoms of increased pCO₂ and decreased pO₂ include:

1. Sleep apnea
2. Early morning headache
3. Asterixis
4. Dilated cerebral veins (rare papilledema)
5. Fatigue
6. Orthopnea
7. Cognitive dysfunction

8. Dyspnea on exertion
9. Difficulty weaning from a respirator (in association with another medical condition and similar to myasthenia gravis)
10. Diaphragmatic weakness demonstrated by paradoxical abdominal movements with respiration

Behavioral and Cognitive Alterations in ALS

1. May occur in both sporadic and familial forms of the disease
2. Approximately 10% of ALS patients meet criteria for FTLT
3. Domains affected:
 - a. Executive dysfunction
 - b. Language
 - c. Behavioral

Genetic Mutations Causing FTLT with Associated MND

1. Mutation at 9p13.2-21.3:
 - a. UMN and LMN degeneration
 - b. Behavioral, personality changes
 - c. Language dysfunction
 - d. Pathology:
 - i. Non-tau inclusions in both anterior horn cells and the granular layer of the dentate gyrus
2. Chromosome 17; mutation of the progranulin gene
 - a. Non-tau genetic locus
 - b. Extrapyramidal, behavioral and amyotrophic component
3. Chromosome 3; mutation of the chromatin modifying protein 2B gene
 - a. Usually linked to FTD but patients with bulbar signs and cognitive impairment have been reported

Genetic Forms of ALS

SOD1 Mutation

1. General Characteristics
 - a. Chromosome 21q22.1
 - b. >160 mutations in the gene that associated with ALS
 - c. Catalyzes the detoxification of superoxide dismutase
 - i. Most are dominant missense mutations
 - d. Toxicity is mediated by protein misfolding and oligomerization that leads to:
 - i. Alteration of mitochondrial metabolism
 - ii. Failure of axonal transport
 - iii. Axonal degeneration
 - iv. Excitotoxicity
 - v. Proteasome Disruption
 - vi. Endoplasmic reticulum stress
2. Clinical manifestations:
 - a. LMN predominant – A4V; LS4V; D101N
 - b. UMN predominant – D90A
 - c. Slow progression – G37R; G41D; G93C; L144S; L144F
 - d. Fast progression – A4T; N86S; L106V; V148G

Clinical Manifestations by Mutation

Late onset – G85R; H46R

Early onset – G37R; H46R

Female-predominant – G41D

Bulbar onset – V148I

Low penetrance – D90A; I113T

Posterior column involvement – E100G

Alsin (ALS2)

1. Juvenile AR; chromosome 2q 1SIN
2. Mutation; small deletion; nonsense mutation; missense mutations
 - a. Premature termination of translation; or substitution of an amino acid
3. ALS2 activates Rab5 small GTPase involved in endosome membrane trafficking
4. Clinical manifestations
 - a. AR; ALS2
 - b. Juvenile primary lateral sclerosis
 - c. Infantile-onset ascending hereditary spastic paralysis
 - d. Ascending degeneration of UMN with or without LMN involvement

Senataxin (ALS4)

1. Chromosome 9q34
 - a. Juvenile onset

Senataxin (L389S)

1. Juvenile onset ALS wasting of somatic musculature
2. Involvement of central and peripheral motor neurons
3. Overlap syndrome of ataxia tremor and MND
4. Distal amyotrophic; UMN signs

Dynactin

1. Chromosome 2p13; DCTN1 gene
2. Dynactin is a large multi-protein complex:
 - a. Subunit DCTN1 binds to dynein and microtubules that allow for axonal transport. Putative mechanism in ALS is failed axonal transport due to dysfunction of the dynactin subunit
 - b. Clinical manifestation
 - i. Adult onset LMN signs
 - ii. Some patients with vocal cord paralysis and facial weakness
 - iii. Late-onset Parkinsonism and frontotemporal atrophy
 - iv. Associated with Perry syndrome
 1. AD Parkinsonism
 2. Depression
 3. Weight loss
 4. Central hypoventilation

Vesicular Associated Membrane Protein (VAPB) ALS

1. Chromosome 20q13.33
2. VAPB gene mutations occur in FALS and SALS

3. VAPB is required for intracellular membrane trafficking and dendritic growth; ER morphology
4. P56S and T46I point mutation of hVAPB are causative
5. Form aggregates associated with motor neuron death
6. A recently described mutation V234I-VAPB has similar ALS phenotype without aggregates
7. Clinical manifestations (ALS8)
 - a. Adult onset
 - b. ALS phenotype

Fused in Sarcoma Gene (ALS6)

1. Chromosome 16q12
2. FUS gene
3. In both FALS and SALS; occurs in 5% of FALS
4. An RNA-binding protein (in the nucleus)
5. Major component of ubiquitinated inclusion bodies (autopsy material)
6. FUS mutations have been identified in FTLN with or without motor neuron involvement
7. Interacts with TDP-43
8. Both or either:
 - a. A loss of function (mislocalization from the nucleus to the cytoplasm)
 - b. The gain of function (abnormal accumulation of aggregate-prone protein by the loss of nuclear imports)
9. Clinical manifestations
 - a. Adult onset
 - b. Classic ALS phenotype

TDP-43

1. Chromosome 1P36.22
2. TARBP (TAR DNA-Binding Protein Gene)
 - a. A DNA/RNA-binding protein
 - b. Role in gene transcription; RNA splicing, RNA shuttling/translation and micro-RNA biogenesis
 - c. Possess prion-like domain; insoluble TDP-43 may seed TDP-43 aggregation; may be a mechanism for the propagation of misfolded protein between mutant and wild type TDP-43 proteins
 - d. TDP-43 protein is ubiquitinated, hyperphosphorylated and cleaved to form intranuclear and cytoplasm aggregates; mutant TDP-43 may increase cleavage and is more resistant to degradation than the wild type protein
 - e. Clinical manifestations:
 - i. Adult onset
 - ii. Classic ALS phenotype

Optineurin Gene

1. Chromosome 10
2. Optineurin gene encodes:
 - a. Cytosolic protein
 - b. A negative regulator of the NF-KB pathway; a role in mitotic progression; membrane trafficking pathways for proteins
 - c. Pathology:

- i. Golgi fragmentation
- ii. Foci formation
- iii. Increased apoptotic activity
- d. Clinical manifestations:
 - i. Open-angle glaucoma
 - ii. ALS; adult onset with classic phenotype in FALS Caucasian patients

ALS 7

- 1. Chromosome 20p tei-p13
- 2. Clinical manifestations:
 - a. Adult onset
 - b. Classic ALS phenotype

ALS-FTD

- 1. Chromosome 9q21
- 2. Clinical manifestations
 - a. Adult onset
 - b. Usually FTD phenotype but ALS occurs

ALS 3

- 1. Chromosome 18q21
- 2. Clinical manifestations
 - a. Adult onset
 - b. Classic ALS phenotype

ALS with PD and Dementia

- 1. Chromosome 17q21 microtubule-associated tau
- 2. High prevalence foci of ALS and Parkinsonism-Dementia complex (PDC)
- 3. Exist in Japanese on the Kii Peninsula, in the Chamorro people of Guam and areas of New Guinea
 - a. Some Kii Peninsula ALS patients have C9orf72 repeat expansions
 - b. Polymorphisms in MAPT which encodes tau increases the risk for ALS-PDC complex
- 4. Clinical manifestations:
 - a. Linear epithelial retinopathy
 - b. Severe dementia
 - c. Akinetic-rigid Parkinsonism

ALS X-Linked

- 1. Chromosome XLD-xpII:
 - a. Adult onset
 - b. Classic ALS phenotype
- 2. Inclusions positive for p62, TDP-43, FUS, and OPTN

ALS 5

- 1. AR; chromosome 15q
- 2. Clinical manifestations:
 - a. Juvenile onset
 - b. UMN
 - c. Pseudobulbar signs
 - d. Minimal spasticity
 - e. Long survival

UBQLN2

- 1. Chromosome-Dominant X-linked
- 2. Encodes ubiquitin-like protein
 - a. Ubiquitin 2
- 3. Regulate the degradation of proteins
- 4. Penetrance is 90% by the age of 70
 - a. earlier onset in males than females
- 5. Clinical manifestations:
 - a. Dementia phenotypically FTD which is progressive
 - b. Classic ALS; dementia preceded motor changes in some patients
 - c. X-linked juvenile and adult-onset ALS and ALS/dementia

Valosin Containing Protein (VCP) Mutations

- 1. Chromosome 9
- 2. Valosin-containing protein (VCP) gene
 - a. A member of the AAA-ATPase superfamily
 - b. Affects:
 - i. Muscle (inclusion body myositis)
 - ii. Bone (Paget's disease of bone)
 - iii. Brain (FTD)
- 3. Clinical manifestations:
 - a. Accounts for small percentage of FALS
 - b. Marked intrafamilial and interfamilial phenotypes that include:
 - i. FTD
 - ii. ALS
 - iii. Parkinsonism
 - iv. Myotonia
 - v. Cataracts
 - vi. Anal incompetence
- 4. Putative mechanisms of mutations:
 - a. Altered protein degradation
 - b. Autophagy pathway dysfunction
 - c. Apoptosis
 - d. Mitochondrial dysfunction

Angiotensin

- 1. Chromosome 14
- 2. Angiotensin is the product of the hypoxia responsive gene
 - a. Mutation causes the loss of RNAase and antigenic function
 - b. An important neurodevelopmental protein, mutation way impair neurite outgrowth
 - c. Functionally similar to vascular endothelial growth factor
- 3. Clinical manifestations:
 - a. ALS
 - b. Possible association with PID

Profilin 1

- 1. Chromosome 17
- 2. Profilin 1 gene
 - a. Involved in actin filament formation

- b. Most PFN1 alleles are in FALS the exception being E117G (but also found in control populations)
- 3. Clinical manifestations:
 - a. Primarily limb onset ALS

FIG4 (phosphatidylinositol 3,5-bisphosphate 5-phosphatase)

- 1. Chromosome 6q21
- 2. FIG4
 - a. A lipid phosphatase that regulates PI (3,5) P2, a signaling lipid on the cytosolic surface of membranes of the late endosome compartment
 - i. PI (3,5) P2 mediate retrograde trafficking of endosome vesicles to the trans-Golgi network
- 3. Clinical manifestations:
 - a. Cause CMT4J (involvement of both sensory and motor neurons)
 - b. ALS and PLS patients have been described; 1–2% of ALS patients

Neuropathy Target Esterase (NTE)

- 1. Chromosome 19p13; AR
- 2. Neuropathy Target Gene Esterase (NTE)
- 3. Neuropathy target esterase:
 - a. A neuronal membrane protein
 - b. Hydrolyzes intrinsic membrane lipids
 - c. Cell signaling pathway that controls interactions between neurons and accessory glial cells in the developing nervous system
- 4. Clinical manifestations:
 - a. Consanguineous kindred
 - b. Occurrence of MND in organophosphate compound-induced delayed neuropathy
 - c. Evaluated kindred:
 - i. Ashkenazi, Jewish ethnicity
 - ii. Progressive spastic paraplegia and distal muscle wasting
 - iii. Phenotypically resemblance to patients with Troyer's syndrome (SPG20/spartin) gene mutation and delayed organophosphate neuropathy
- 5. Mechanism in MND
 - a. Role for NTE in maintaining axonal integrity of the corticospinal tract and peripheral motor axons

D-Amino Acid Oxidase (DAO)

- 1. Chromosome 12
- 2. D-amino acid oxidase gene
 - a. Aberrant excitability of motor neurons has been implicated in pathogenesis of ALS
 - b. D-serine, an endogenous coagonist of N-methyl-D-aspartate receptors, is increased in both FALS and SALS
 - c. Mutation in D-amino acid oxidase (DAO) gene:
 - i. Encodes a D-serine degrading enzyme
 - ii. Associated with putative loss of DAO activity in one family with classic ALS
- 3. Clinical manifestation:
 - a. Classic ALS phenotype (R199W-DAO)

TATA-Binding Protein-Associated Factor 15

- 1. Chromosome 17q12
- 2. TATA-binding protein-associated factor 15
 - a. A FET protein (along with Ewing's sarcoma and FUS)
 - b. Physiologic role in RNA transcription, processing, transport, micro-RNA processing, and DNA repair
 - c. Primarily localized in the nucleus but shuttle back and forth to the cytoplasm
 - d. Putative pathogenic defect in transporting mediated nuclear import
- 3. Clinical Manifestations
 - a. Classic phenotypic ALS

Paraoxonase

- 1. Chromosome 7q21.3
- 2. Paraoxonase 1–3 gene cluster
 - a. Single nucleotide polymorphism (SNPs) of the paraoxonase gene family (PON, PON2, PON3)
 - i. Associated with the risk of developing sporadic ALS in Caucasians
- 3. A component of the antioxidant defense system
- 4. Environmental factors that may increase the risk of ALS include:
 - a. Insecticides
 - b. Pesticides
 - c. Arylesterase
 - d. Oxidants in cigarette smoke
 - e. Increased incidence in Gulf War Veterans
- 5. PON1 enzyme is a major protective mechanism to hydrolyze exogenous toxic compounds in the serum. PON2 and 3 protect against lipid peroxidation
- 6. Clinical manifestations
 - a. Association between PON gene cluster polymorphisms an increased risk of SALS

Multisystem Proteinopathy (HNRNPA2B1 and HNRNPA1)

- 1. Heterogeneous nuclear ribonucleoproteins B1 and A1
- 2. Nomenclature (multisystem proteinopathy)
 - a. MSP1 (VCP)
 - b. MSP2 (HNRNPA2B1)
 - c. MSP3 (HNRNPA1)
- 3. Genetic defects in MSP are associated with:
 - a. RNA processing
 - b. Protein Homeostasis
- 4. HNRNPA1-mutation on chromosome 12q
- 5. HNRNPA2B1 mutation on chromosome 7p
- 6. Clinical characteristics:
 - a. Mutations in HNRNPA2B1 and HNRNPA1 are causal in some families with Inclusion Body Myopathy associated with Paget's disease of bone (PDB) and/or Frontotemporal Dementia (IBMPFD)
 - b. Weakness in IBMPFD is caused by myopathy and a neurogenic process
 - c. Deposition of TDP-43, HNRNPA1B1 and HNRNPA1 protein in affected tissues
 - d. Phenotypic ALS

7. Pathogenic mechanism
 - a. Prion-like domains occur in HNRNPA2B1 and HNRNPA1 and are:
 - i. Enriched in proteins that undergo assembly and disassembly into non-membrane-bound organelles (granules)
 - ii. Prion-like domains of these proteins mediate fibrillation, pivotal to recruitment into cytoplasmic granules which may be detrimental to unaffected RNA

ALS/Sigma 1

1. Chromosome 9p
2. Sigma receptor 1 gene
3. Mutations in the gene are associated with:
 - a. Altered location of the receptor
 - b. Loss of function
 - c. Experimental studies demonstrate:
 - i. Abnormal ER morphology
 - ii. Mitochondrial alterations
 - iii. Impaired autophagic degradation
 - iv. Role in lipid raft and intracellular calcium homeostasis
4. Clinical manifestations:
 - a. Juvenile ALS
 - b. FTLN

Ataxin-2

1. Chromosome 12q
2. ATXN2 gene
 - a. Ataxin-2 is a polyglutamine protein
 - b. Ataxin-2 with intermediate length repeats (27–33) increases the risk of ALS
 - c. Ataxin-2 with intermediate length repeat (Q31)
 - i. Modifier of FUS pathology in cellular disease models
 - d. Ataxin-2 colocalizes with FUS in sporadic and FUS-linked familial ALS
 - e. Pathology
 - i. Ataxin-2 Q31 with mutant FUS (in cell lines) is associated with:
 1. Golgi fragmentation
 2. Induces apoptosis
 - f. Clinical manifestations:
 - i. Increased risk of ALS in patients with mutations of Ataxin-2 with intermediate length poly Q expansions

SQSTM1 (Sequestosome 1)

1. Chromosome 5q35
2. SQSTM1 gene:
 - a. Encodes the p62 protein
 - b. p62 protein regulates:
 - i. NF- κ B signaling
 - ii. Autophagy pathways
 - iii. Adaptor protein

- iv. Loads malformed proteins into autophagosome for liposomal degradation; accumulation of NBK/BIK protein may initiate apoptosis
- c. Clinical manifestations:
 - i. FTLN
 - ii. ALS
 - iii. Paget's disease of bone

Genes Associated with Sporadic ALS

1. Approximately 11% of SALS have genetic contributions
2. Chromosome 20; CREST gene
3. SS18L1 (synovial sarcoma translocation gene on chromosome 18-like)
 - a. Encodes a calcium- γ responsive and/or neuronal chromatin remodeling complex subunit
 - b. Amino-altering de novo mutations
4. Chromatin regulation (neuronal chromatin remodeling complex component)
5. Mutations inhibit activity-dependent neurite outgrowth in primary neurons
6. CREST associates with FUS protein
7. Clinical manifestation
 - a. Both bulbar and limb onset ALS phenotype

EPHA4 (Ephrin Type Receptor A4)

1. Chromosome 2
2. EPHA4 (a tyrosine kinase)
 - a. Encodes a receptor in the Ephrin axonal repellent system
3. Motor neurons that are most vulnerable to degeneration in ALS express higher levels of Eph4
 - a. Inhibits reinnervation of axotomy motor neurons (experimental models)
4. In humans
 - a. Mutations are associated with longer survival in ALS patients
 - b. Suggestion that Eph4 genetically modulates the vulnerability of motor neurons after axonal degeneration
5. Clinical manifestation
 - a. Longer survival in ALS patients (modifies in SALS)

UNC13A

1. Chromosome 19p13.3
2. UNC13A gene:
 - a. Variant (rs12608932) located within an intron of UNC13A
 - i. Associated with risk of developing ALS
 - b. The protein encoded is unc-13 homolog A, a presynaptic brain protein
 - i. Mouse homologue of the human protein is involved in neurotransmission and neurite outgrowth
3. Clinical manifestations:
 - a. Increased risk of ALS
 - b. Alteration of survival time (decreased)
 - c. Minor allele (rs12608932) is associated with both increased risk and shorter survival

Chromogranin B (P413L)

1. Chromosome 20
2. CHGB (chromogranin B)
 - a. P413L variant is increased in ALS patient
 - i. Causes defective sorting of CHGB into secretory granules (cell lines)
 - ii. Putative mechanism is the enhancement of accumulation of misfolded SOD1 protein an ER-Golgi system

Clinical Manifestation of Mutations

1. Risk factor for ALS
2. Induces an earlier onset of disease in FALS and SALS by approximately ten years

Kinesin-Associated Protein 3

1. Chromosome 1
2. KIFAP3 gene:
 - a. SNP rs1541160 of potential modifier of ALS phenotype
 - i. Reduced KIFAP3 expression and longer survival
 - b. KIF3A, KIF3B and KIFAP3 form a trimetric, motor complex KIF3 that:
 - i. Mediates binding between motor proteins and their cargoes
 - ii. Binds mutant SOD1 protein that may slow axonal transport
 - iii. Colocalizes with mutant SOD1 (human autopsy material)

Clinical Manifestations

1. Increased survival in patients with the mutation (approximately one year)
2. Increase risk of sporadic ALS

ELP3 (Elongated Acetyltransferase Complex Subunit 3)

1. Chromosome 1
2. ELP3 gene:
 - a. RNA polymerase II component
 - b. Involved in RNA processing and histone acetylation
 - i. ELP3 regulates heat shock protein (HSP) 70 expression by acetylation of H3 and H4
 - c. Axonal biology

Clinical Manifestations

1. Phenotypic ALS
2. Possible protective effect

Pathology of ALS

1. Degeneration and loss of myelination in the corticospinal and corticobulbar pathways
2. Loss of motor neurons at all levels of the spinal cord and many cranial nerve nuclei
3. Notably, spared are:
 - a. III, IV and VIth cranial nerves (rare exceptions)

- b. Onuf's nucleus and the anterior horn of segments 2–4
- c. Ventilator care with prolonged life is starting to reveal rare involvement of these neurons
- d. Minimal to no involvement of the intermediolateral column neurons

Inclusions

1. An extremely active area of research and their specificity and role in pathogenesis is being explored
 - a. Ubiquitin inclusions
 - b. TDP-43 inclusions
 - c. RAN polypeptides that are sequester in insoluble aggregates

Intraneuronal and Intraglial Tau Inclusions (with and without cognitive deficits)

1. Involvement of ascending sensory tracts (primarily the dorsal columns) and descending spinocerebellar tracts in the E100G mutation of SOD1
2. Pathologic changes in ALS occur in various systems that include:
 - a. Extrapyramidal
 - b. Sensory
 - c. Cerebellar
 - d. Optic Autonomic
3. Swelling of the proximal axon may be an early sign; there may be a disproportionate loss of large myelinated fibers in motor nerves
4. Loss of Betz cells in the motor cortex with slight frontal lobe atrophy
5. Loss of fibers in the ventral and lateral funiculi possibly a loss of collaterals of motor neurons
6. In patients with dementia:
 - a. Neuronal loss gliosis and vacuolation in the superior frontal gyri and inferolateral cortex of the temporal lobe
7. Some neurofibrillary degeneration is present but much less than in patients with Guamanian Parkinson-Dementia ALS complex

Neuroimaging

1. Conventional Magnetic Resonance Imaging (FLAIR) or fast spin echo proton density-weighted imaging) demonstrate:
 - a. Hyperintensity of white matter along the corticospinal tracts from the centrum semiovale to the brainstem
 - b. Frontal predominant cortical atrophy
 - c. Hypointensity of MI (rare)
2. Advanced MRI:
 - a. Diffusion-based neuroimaging evaluation of white matter fiber bundles:
 - i. Decreased fractional anisotropy in the intracranial portion of the CST (subcortical white matter, internal capsule, and brainstem)
 - ii. Decreased fractional anisotropy in the corpus callosum

- b. Tractography (DTI reconstruction of three-dimensional geometry of the pyramidal tract)
 - i. Decreases in FA limited to paracentral areas
 - ii. In the corticobulbar tract lower FA occurs in patients with bulbar rather than limb-onset disease
- c. Voxel-based morphometric (VBM)
 - i. Allows automated segmentation and quantification of gray and white matter volumes in ALS which demonstrates:
 - 1. Changes in the basal ganglia
 - 2. Superior and inferior thalamic nuclear changes
 - 3. Lateral and inferior portions of the L hippocampus
 - 4. Medial and superior components of the left caudate
 - 5. Alterations of the front striatal network
 - 6. Patients with c9orf72 with ALS but without dementia
 - a. Demonstrated cortical and subcortical frontotemporal involvement
 - 7. DTI evaluation revealed:
 - a. Sporadic ALS patients have greater white matter involvement in motor and extra motor pathways than SOD1 gene-linked FALS

Spinal Cord Imaging

- 1. New technologies allow DTI and magnetization transfer (MT) imaging of the spinal cord:
 - a. Regional atrophy can be identified
 - b. 3T MRI scanners with 300 mT/m gradients permit evaluation of spinal cord microstructure

Functional MRI

- 1. Evidence for reorganization of cerebral networks
- 2. Possible correlation of rfMRI changes with rate of disease progression

Nuclear Magnetic Resonance Spectroscopy

- 1. Allows for the measurement of the neurochemical profile of specific regions:
 - a. In the motor cortex, a decrease of N-acetyl aspartate (NAA) and/or ratios of NAA to choline-containing compounds (CHO) and creatine (CR) demonstrate loss of neuronal integrity
 - b. NAA has relationship with disability
 - c. Metabolic changes may occur early in the course of the illness
 - d. A small study has demonstrated decreased GABA levels in the cortex

Positron Emission Tomography (PET)

- 1. SPECT studies
 - a. Demonstrate a decrease in cerebral blood flow in:
 - i. Primary motor cortex

- ii. Frontal lobes (particularly in patients with dementia)

2. PET studies:

- a. Demonstrate variable decrease in cerebral metabolism
 - i. In patients with C9orf72 mutations have a more widespread involvement than those non-genetic ALS patients
- b. Less extensive GABA receptor involvement in SOD1-linked familial ALS patients
- c. Nigrostriatal dysfunction has been demonstrated by both SPECT and PET
- d. Abnormalities of microglial activation in the motor cortex and temporal lobes early in the disease process

Differential Diagnosis of Immune-Mediated Motor Neuropathies That May Simulate ALS

Immune-Mediated Lower Motor Neuron Syndromes (Motor Neuropathies)

- 1. Multifocal Motor Neuropathy (MMN)
 - a. MMN is an immune-mediated demyelinating neuropathy
 - b. Clinical manifestations:
 - i. Chronic asymmetric distal limb weakness, atrophy, and fasciculations
 - ii. Distal arms are more frequently involved than the legs
 - iii. Distribution of individual peripheral nerves
 - iv. Minimal or no sensory loss
 - v. 8:1 male to female ratio
 - vi. Most patients begin in the fifth decade (range from childhood to the eighth decade)
 - vii. Initiated with wrist or foot drop which slowly progresses to other muscles; rare cranial nerve involvement
 - viii. Lack of atrophy in weak muscles is a seminal sign
 - ix. Longstanding disease may develop secondary axon loss with denervation atrophy (peripheral nerve distribution; ALS is a myotome distribution)
 - x. Signs and symptoms of sensory loss may develop over the course of the illness

Electrophysiology Evaluation

- 1. Conduction block is the hallmark of the disease but is not mandatory
- 2. EMG features include:
 - a. Prolonged distal latencies
 - b. Temporal dispersion
 - c. Slow conduction velocity with delayed or absent F waves on motor NCS
 - d. Some patients have superimposed features of axonal degeneration
 - e. In general, there is normal sensory nerve conduction velocity across the same segment with conduction block

- f. MMN typically has clinical and EMG abnormalities in more than one nerve
- g. A variant has been described of multifocal acquired motor axonopathy (MAMA)

Laboratory Evaluation

1. CSF is generally normal; high protein suggests MADSAM or CIDP
2. Polyclonal IgM GMI antibodies occur the serum of 40–80% of patients
3. Very high titers of IgM suggest MMN. Low titers occur with GBS and CIDP
4. IgM binding to a disulphate heparin disaccharide (Ns6S) is being evaluated

Neuropathology

1. Sensory nerve biopsies are unrevealing
 - a. One study demonstrated demyelination without inflammation at the site of the motor conduction block

Multifocal Acquired Demyelinating Sensory and Motor (MADSAM) Neuropathy

Clinical Manifestations

1. MADSAM is a chronic sensorimotor mononeuropathy multiplex
 - a. An insidious onset with slow progression
 - b. Initial involvement is in the upper extremities that spreads to distal legs
 - c. Single nerve presentation may progress to symmetrical involvement
 - d. Approximately 50% evolve to a CIDP pattern
 - e. A significant proportion of patients suffers pain and paresthesia
 - f. May involve cranial nerves
 - g. Depressed to absent reflexes with disease progression

Electrophysiology Evaluation

1. Conduction block temporal dispersion, prolonged distal latencies slow conduction velocities
2. Delayed or absent F waves in one or more nerves

Laboratory Evaluation

1. Protein:
 - a. Elevated in >80% of patients
 - b. No anti-GM1 antibodies

Neuropathology

1. Demyelinating features on cutaneous sensory nerve biopsy similar to CIDP

Distal Acquired Demyelinating Symmetric Neuropathy (DADS)

Clinical Manifestations

- a. Distal symmetric demyelinating neuropathy

- b. Primarily sensory signs and symptoms with ataxia and tremor
- c. DADS-M are patients with an IgM Kappa gammopathy
 - i. 90% of patients are men
 - ii. Motor signs are distal with 60% of patients demonstrating dorsi and plantar flexion weakness
 - iii. Most patients have predominant sensory symptoms and signs

Electrophysiology Evaluation

1. Motor NCS demonstrate widespread symmetric slowing of distal sensory and motor nerves
2. Rare conduction block
3. Prolonged distal latencies with a short terminal latency index

Laboratory Evaluation

1. Serum antibodies against myelin-associated glycoprotein (MAG)
2. IgM Kappa monoclonal gammopathy
3. Elevated CSF protein

Neuropathology

1. Widely spaced myelin outer lamellae on electron microscopy
2. Deposits of IgM and complement on sural nerve myelinated fibers
3. Skin biopsies reveal distal > proximal IgM deposits on dermal myelinated fibers
4. Decrease in epidermal nerve fiber density (axonal loss) on skin biopsy

Chronic Inflammatory Sensory Polyradiculopathy (CISP)

Clinical Manifestations

1. Approximately 50% will have gait difficulty (wheelchair bound or walking with a cane)
2. Primarily large fiber sensory deficits with associated slight ataxia

Electrophysiology Evaluation

1. Normal nerve conduction velocities
2. Abnormal somatosensory evoked potentials (SSEP)

Laboratory Evaluation

1. Increased CSF protein

Neuroimaging

1. Lumbar nerve root thickening

Neuropathology

1. Lumbar sensory nerve root biopsy
 - a. Thickened lumbar nerve roots
 - b. Loss of large myelinated fibers, segmental demyelination
 - c. Onion bulb formation
 - d. Endoneurial inflammation

Chronic Ataxic Neuropathy with Ophthalmoparesis, Monoclonal IgM Protein, Cold Agglutinins and Disialosyl Ganglioside Antibodies (CANOMAD)

Clinical Manifestations

1. Heterogeneous modes of presentations
2. Distal weakness
3. Ophthalmoparesis
4. Gait and limb ataxia; leg weakness
5. Cranial nerve V and VII may be involved
6. Slowly progressive course with relapses in motor, sensory, bulbar and ocular modalities

Electrophysiology Evaluation

1. Demyelinating pattern on NCS in most patients

Laboratory Evaluation

1. Elevated CSF protein in >60% of patients
2. M-protein in >90% of patients and approximately 50% demonstrate cold agglutinin
3. BD1b and GQ1b antibodies
4. Small percentage demonstrate white matter hyperintensities on cerebral MRI

Neuropathology

1. Nerve biopsy:
 - a. Both demyelination and axonal features

Differential Diagnosis of Genetic LMN Syndromes

1. SMA Type V
2. Distal spinal muscular atrophies
3. Hereditary spastic paraparesis (uncomplicated and complicated)
 - a. HSP genotypes with a lower motor neuron component include:
 - i. SPG 9
 - ii. SPG 10
 - iii. SPG 14
 - iv. SPG 15
 - v. SPG 17
 - vi. SPG 20
 - vii. SPG 22
 - viii. SPG 26
 - ix. SPG 30
4. Progressive spinal muscle atrophy (PSMA)
 - a. Clinical features:
 - i. Middle-aged patients
 - ii. Slowly progressive asymmetric weakness of upper and lower extremities
 - iii. Fasciculations with muscle wasting
 - iv. No upper motor neuron signs
5. May mimic facioscapulohumeral muscular dystrophy (FSHD)
6. Kennedy's disease (adult):
 - a. Fazio-Londe (childhood)
 - b. Brown-Vialetto-Van Laere (childhood)

Multiple System Disorders with Anterior Horn Cell Involvement

1. Hereditary spastic paraparesis
 - a. Variants 9, 10, 15, 17, 20, 22, 26, 30 have LMN features
2. Adult Tay-Sachs disease
 - a. Mutations of the hexosaminidase (Hex) A gene
 - i. Encodes the alpha-subunit of beta-D-N-acetyl hexosaminidase
 - ii. Juvenile and adult Hex A may have some residual Hex A activity (G269S mutation)
 - iii. Clinical manifestations:
 1. MND
 2. Cerebellar deficits
 3. Psychotic episodes
3. Adult Polyglucosan Body Disease (APBD)
 - a. An AR leukodystrophy:
 - i. Multiple mutations in the GEB1 gene
 1. Encodes glycogen branching enzyme
 - b. Polyglucosan bodies accumulate in both the central and peripheral nervous system
 - c. Clinical manifestations
 - i. Neurogenic bladder
 - ii. Spastic paraplegia with associated vibration loss
 - iii. An ALS presentation with only corticospinal and anterior horn cell signs
 - iv. Normal pressure hydrocephalus presentation without other upper or lower motor signs
 - v. A relapsing variant
 - vi. Axonal neuropathy
 - vii. Cognitive decline with disease progression
 - d. Neuroimaging
 - i. WMHs in the periventricular areas, posterior limb of the internal capsule and external capsule
 - e. EMG evaluation
 - i. Slowing of motor NCVs
 - ii. Low amplitude or absent SNAPs
 - f. Pathology
 - i. Sural nerve biopsy
 1. Intra-axonal polyglucosan body deposition
4. Spinocerebellar Degenerations
 - a. Machado-Joseph disease:
 - i. General Characteristics
 1. AD; ATX3 gene
 - a. Encodes an unstable CAG repeat; associated protein misfolding
 - ii. Clinical manifestations
 1. Varies greatly between and among families
 2. MJD has been divided into
 - a. Type I
 - i. Onset at about age 25
 - ii. Spasticity, rigidity, bradykinesia, and minimal ataxia
 - b. Type II
 - i. Most common form

- ii. Young to mid adult years
- iii. Progressive ataxia and UMN signs
- c. Type III
 - i. Late onset (age 50)
 - ii. Ataxia
 - iii. Amyotrophy from peripheral nerve involvement with fasciculation
- iii. Pathology
 - 1. Degeneration and gliosis of the SN, dentate, pontine, cranial nerve nuclei and anterior horns

Rare Degenerative Disease with a Component of Anterior Horn Cell Involvement

1. Hallervorden-Spatz disease (PANK-2)
2. Guamanian-Parkinsonism-ALS complex
3. Huntington's disease
4. Creutzfeldt-Jakob disease
5. Alzheimer (variant)
6. Hereditary spastic paraparesis

Paraneoplastic Motor Neuron Disease

1. General considerations:
 - a. Occurs with multiple cancers
 - b. Most often with small cell cancer of the lung and breast cancer
2. Rare syndromes in cancer patients
3. Rarely removal of the tumor stabilizes the MND; more often there is no change
4. There is "molecular mimicry" between the nervous system and epitopes on tumor cells
5. The MND may precede discovery of the cancer by 4–10 months
 - a. Tumor removal and immune treatments fail to reverse the neurologic signs and symptoms
6. MND may be associated with encephalomyelitis, dorsal root ganglionitis, and subacute large fiber sensory neuropathy
7. Suggestive of Paraneoplastic MND:
 - a. In patients >70 years of age
 - b. Presence of paraproteinemia
 - c. Pleocytosis greater than high CSF protein levels

Antibodies Associated with MND

1. Anti-Hu in the setting of small cell lung cancer (anti-nuclear neuronal antibody 1 (ANNA1):
 - a. Rapidly progressive in some patients
 - b. Brachial amyotrophic diparesis associated with anti-Hu positive anterior horn cell disease and autonomic dysfunction
2. Anti-MA2Ta antibodies:
 - a. Most often associated with limbic encephalitis in male patients with testicular cancer
 - b. Reported in a female patient with pure progressive spastic paraparesis

3. Breast cancer:
 - a. No specific antigen reported, but with upper motor neuron disease
 - b. Purkinje cell autoantibody type 1 (infiltrating ductal carcinoma)
4. Ri/Nova gene-associated paraneoplastic subacute motor neuropathy
5. Anti-CV2 antibodies
 - a. Associated paraneoplastic syndrome includes:
 - i. Encephalomyelitis
 - ii. Cerebellar degeneration
 - iii. Peripheral neuropathy
 - b. Possible association with ALS

Hodgkin's and Non-Hodgkin's Lymphoma

1. Non-Hodgkin's lymphoma > Hodgkin's:
 - a. Anti-Tn antibodies
 - b. Cerebellar degeneration is greater in HL than NHL
 - c. Motor neuron involvement is greater in NHL than HL

Rare Causes of Motor Neuron Disease

Electrical Energy

General Characteristics

1. Electrical injuries are classified as high voltage (1000 volts and higher) or low voltage (less than 1000 volts)

Neuropathology

1. Three mechanisms of injury are:
 - a. Current flow
 - b. An arc injury (current passes from source to an object)
 - c. Flame injury
2. The final injury is determined by:
 - a. Voltage
 - b. Current (amperage)
 - c. Alternating or direct current
 - d. Duration of contact
 - e. Individual susceptibility
3. Lightning strikes often cause cardiac arrest
4. Neurologic and psychologic symptoms are the most common sequela of electrical and lightning injuries
5. Household electrical currents are usually low voltage of 110 to 200 volts with 60 cycles of alternating current

Clinical Manifestations

1. Causes acute transient weakness and paraplegia which may clear over hours to 5–10 days
2. May cause a delayed upper and LMN syndrome
3. Electrical current often travels down corticospinal and bladder pathways
4. Weakness and atrophy may begin at the site of injury
5. Bulbar signs and UMN weakness and spasticity may develop
6. A common cause of chronic regional pain syndrome (CRPS) with its consequent motor phenomena

Post-Radiation Motor Neuron Syndrome

1. General Considerations:
 - a. Dosages in the cervical spine that cause the syndrome are approximately 3000 cGy (usually for head and neck malignancy)
 - b. Distal spinal cord and cauda equine irradiation for seminoma and lymphoma (>50 reported patients);
 - i. Average irradiation dose was 5,225 cGy
 - ii. Average age 33 years
2. Pathology
 - a. Irradiation causes:
 - i. Microglial activation
 - ii. Decreases neurogenesis
3. Clinical manifestations:
 - a. LMN syndrome and other neurological signs and may occur months to years often treatment
 - b. Atrophy of affected muscles with fasciculations
 - c. No sphincter involvement
 - d. Lower extremities are preferentially involved
 - e. Weakness usually stabilizes but has been described to progress over years
 - f. A similar process occurs in the lower cranial nerves with head and neck X-rt. A long segment of the carotid artery is involved that may cause a delayed stroke
4. EMG evaluation
 - a. Fibrillation potentials occur in affected muscles
 - b. Myokymia discharges
5. Laboratory evaluation
 - a. CSF is usually normal
 - b. Protein may be slightly elevated

Diagnostic Point

1. In a setting of brachial plexus X-rt following breast cancer
 - a. Myokymia and a negative gadolinium-enhanced MRI differentiate X-rt from tumor invasion or sarcoma of the plexus

Hyperparathyroidism

1. General considerations
 - a. Isolated case reports and one series report associated motor neuron signs and symptoms with hyperparathyroidism. Skepticism persists due to the general lack of widespread EMG correlation and failure to halt progression of the signs by removal of the parathyroid glands
2. Clinical manifestations:
 - a. Proximal muscle weakness
 - b. Cramps
 - c. Hyperactive reflexes and spasticity
 - d. Minimal and inconstant sensory loss
 - e. Bladder urgency
3. EMG evaluation
 - a. Neurogenic features in some patients

Hypoglycemia

1. General characteristics

- a. The prevalence of hypoglycemic episodes follows the prevalence of diabetes
- b. Causes of severe hypoglycemia:
 - i. Iatrogenic
 - ii. Infections with sepsis
 - iii. Tumor (insulinoma)
 - iv. Related to autoimmune disease
- c. Autonomic symptoms occur first at blood glucose levels of 60–65 mg/dl
 - i. Neuroglycopenia symptoms at 47–54 mg/dl
 - ii. Cognitive function deteriorates between 20–30 mg/dl
- d. MRI evaluation
 - i. White matter is more sensitive than gray matter to hypoglycemia
 - ii. Diffuse and extensive DWI lesions predict poor prognosis
2. Clinical manifestations
 - a. Wasting of extremities with fasciculation
 - b. CNS manifestations are often seen that include organic brain syndromes. Muscle wasting from anterior horn cell damage occurs

*Drugs Associated with Motor Neuron Disease**Lead*

1. General Considerations:
 - a. 25 mg/dl is the lower range of lead toxicity in adults
 - b. Occupational exposure occurs in the mining and battery manufacturing industries
2. Clinical manifestations:
 - a. Primarily neuropsychological deficits that include:
 - i. Cognitive impairment
 - ii. Decreased learning and memory
 - iii. Decline in executive function
 - iv. Deficits in processing speed and visuospatial skills
 - v. Anxiety and depression
 - b. Occupational exposure may cause progressive cognitive deficits years after exposure
 - c. Lower motor involvement of wrist and fingers extensors
 - d. One report of both upper and LMN involvement
 - e. Anterior horn cell involvement may be activity dependent

Organophosphates

1. General characteristics
 - a. A major global cause of mortality and morbidity in developing countries
 - b. There are three stages to this insecticide poisoning:
 - i. Cholinergic phase
 - ii. Intermediate syndrome
 - iii. Delayed neurotoxicity
2. Clinical manifestations
 - a. Delayed neurotoxicity
 - i. Distal sensorimotor neuropathy

- ii. Pyramidal and dorsal column degeneration in some patients
- iii. Recurrent laryngeal palsy in some patients
- 3. Pathology
 - a. Mechanism
 - i. Depression of neuronal and cholinesterase
 - ii. Subacute levels of organophosphates may interact with a large range of target proteins; neuropathy target esterase (NTE) may be particularly important in this regard

Dapsone and Nitrofurantoin

1. Anterior horn involvement from a dying back mechanism that affects anterior horn cells

Human Immunodeficiency Virus-1 and Human T-Cell Leukemia Virus-1 (HTLV)

1. General characteristics
 - a. A small percentage of patients infected with HIV-1 or HTLV-1 develop ALS-like syndromes
 - b. Most patients with HIV and classic ALS symptoms:
 - i. Develop syndrome at an earlier age than classic ALS
 - ii. May improve with treatment
 - iii. Possible association with HERV (human endogenous retroviral sequence expression)
 1. Recent observation of HERV-K polymerase gene transcripts in HIV post-mortem brain tissue
2. Clinical manifestations
 - a. 32% of patients with LMN form; mixed UMN and LMN form in 57%
 - b. Onset at younger age (primarily in 3–4th decade)
 - c. Can develop at any stage of HIV infection
 - d. CD4 counts of <350 cells/mm³ in 56% of patients
 - e. Prognosis is not related to age at onset or initial CD4 count
 - f. Stavudine has been associated with:
 - i. HIV-associated neuromuscular weakness syndrome (HANWS)
 1. Presents with rapidly progressive limb weakness
 2. Some patients have bulbar and respiratory involvement

Human T-Cell Leukemia Virus-1

1. General characteristics
 - a. Estimates that HTLV-1 infects 15–20 million individuals worldwide in endemic areas
 - b. Associated diseases:
 - i. Adult T-cell leukemia/lymphoma (ALT)
 - ii. HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP)
2. Clinical manifestations of HAM/TSP:
 - a. Slowly progressive

- b. Most patients wheelchair bound after ten years of infection
- c. UMN and LMN signs and symptoms
- d. Bladder dysfunction
- e. Sensory symptoms
- 3. Pathology
 - a. Most consistent with HAM/TSP rather than ALS

Poliomyelitis and Other Neurotropic Viruses

Poliomyelitis

General Characteristics

1. Resurgence of infection in several war-torn areas with unvaccinated populations (primarily the Middle East and portions of Africa)
2. Several hundred thousands of patients survive with the post-polio syndrome

Clinical Manifestations

1. Initial symptoms for 1–2 days:
 - a. Fever, diarrhea, headache, nausea and vomiting in most patients; the infection stops at this point
 - b. Initial symptoms subside for 3–10 days then recur:
 - i. CNS component is the major illness
 1. Meningoencephalitis with or without paralysis
 - ii. Premonitory symptoms prior to paralysis include:
 1. Myalgias
 2. Coughing
 3. Weakness that peaks within 48 hours
2. Clinical neurologic manifestations:
 - a. Asymmetric weakness (flaccid and areflexic)
 - b. Limbs and trunk are affected in 50% of patients:
 - i. Lumbosacral dermatomes > cervical
 - ii. Proximal > distal musculature
 - c. 10–15% have bulbar involvement; VII, IX and X cranial nerves
 - d. Individual fingers and toes may be affected
 - e. Approximately 30–40% have a combination of bulbar and spinal weakness
 - f. No involvement of III, IV, VI cranial nerves
 - g. Painful affected muscles with no objective sensory loss
 - h. Autonomic involvement in severely affected patients:
 - i. Cardiac arrhythmias
 - ii. Blood pressure variation
 - iii. Hyperhidrosis
 - i. Recovery is proportional to the severity of the initial weakness
 - i. Occurs over weeks to months

Laboratory Evaluation

1. In 10% of patients, the CSF may be initially negative
2. In two weeks following initiation of the illness:
 - a. An initial neutrophil leukocytosis
 - b. Usually at this period between 50–200 lymphocytes/mm³
3. Fourfold increase in serum antibody titers
4. Viral culture from stool or pharynx
5. Mild elevation of serum creatine kinase

Neuropathology

1. The polio virus is a small RNA enterovirus of the Picornavirus family
 - a. Serotype 1 is most often associated with paralysis
 - b. Incubation period is 6–20 days
 - c. Oral route of infection is most common; there is a nasopharyngeal route
 - d. Viral load is amplified in non-neural tissue prior to the paralytic phase
 - e. The majority of patients with the major illness (CNS), a small minority of infected patients, develop aseptic meningitis
 - f. Paralytic polio occurs in approximately 2% of infected patients
 - g. The vaccine caused disease is usually type 2 or 3 serotypes; in the USA only inactivated vaccine have been in use since 2000 and therefore vaccine induced poliomyelitis has been eliminated in the USA
2. Early pathology in the ventral horn:
 - a. Pial inflammation
 - b. Vascular dilation
 - c. Petechial hemorrhages
 - d. Perivascular and parenchymal inflammatory infiltrates
 - e. Some degeneration in dorsal root ganglia and the dorsal columns
 - f. Similar changes occur in the:
 - i. CN motor nuclei (Exception III, IV, VI)
 - ii. Vestibular nuclei
 - iii. Brainstem reticular formation
 - iv. Occasional involvement of the paracentral gyrus; the remainder of the cortex is spared

Laboratory Evaluation

1. Confirms involvement of anterior horn cells, ventral or motor nerve in a polysegmental pattern
2. Normal sensory nerve conduction velocities
3. Reduced amplitudes of compound motor action potentials in involved extremities
4. Conduction velocities are normal unless CMAP is <1 mV at which point they may be slowed proportionately to the degree of axon loss
5. Reduced motor unit recruitment with clinical weakness
6. At approximately three weeks following onset, fibrillation, and positive sharp waves are seen in affected muscles
7. After months, there is an increase in both amplitude and duration of motor unit potentials (reinnervation)

Post-Polio Syndrome**General Characteristics**

1. New late manifestations of polio that occur in patients 15–40 years after the acute paralytic illness; occurs in approximately 25–50% of patients

Clinical Manifestations

1. Fatigue

2. Cold intolerance
3. Sleep disorder
4. Possible depression (situational)
5. Muscular skeletal alterations:
 - a. Muscle pain
 - b. Joint pain
 - c. Spondylosis
 - d. Scoliosis (paraspinal muscle involvement-C type)
6. Neurologic manifestations:
 - a. New weakness
 - b. Muscle atrophy
 - c. Dysplasia and dysphonia
 - d. Rare respiratory insufficiency
 - e. Sleep disordered breathing
 - f. Possible cognitive deficits

Laboratory Evaluation

1. Increased levels of the inflammatory cytokines IL-1 and TNF- α

Electrophysiology Evaluation

1. EMG
 - a. Evidence of chronic denervation and reinnervation. Large motor unit potentials

Neuropathology

1. The recovery of an acutely denervated muscle depends on the reinnervation of the denervated muscle by surviving AHCs (collateral sprouting)
 - a. Death of surviving AHCs due to increased metabolic demand
 - b. Acceleration of the aging process

Non-Polio Neurotrophic Viruses Causing Acute Flaccid Paralysis from Anterior Horn Cell Involvement

1. Coxsackie virus group A type 7
2. Rabies
3. Enterovirus 6, 70, 71
4. West Nile Virus
5. Japanese encephalitis virus
6. ECHO virus 6

Enterovirus**General Characteristics**

1. Genus enterovirus; family Picornavirus
2. Traditional taxonomy
 - a. Echovirus
 - b. Coxsackie virus group A and B
 - c. Polioviruses
 - d. Since 1960 newly identified viruses receive a numeric designation (e.g.: enterovirus 71)
 - e. New taxonomy, based on molecular and biologic characteristics, divides human enterovirus into four categories:
 - f. HEV
 - i. A, B, C, D

3. Many acute flaccid paralysis in America are associated with non-polio enterovirus infection (NPEV)
4. Paralysis has been reported with:
 - a. Coxsackie virus B2–B6
 - b. Enterovirus 71
 - c. Echovirus type 3, 4, 6, 9, 11, 19 and 22

Laboratory Evaluation

1. Enterovirus isolates can be obtained from:
 - a. Feces
 - b. Pharyngeal washings
 - c. CSF
 - d. Spinal cord
 - e. Brain
 - f. Heart
 - g. Blood
 - h. Conjunctivae skin
 - i. Mucous membranes

Clinical Manifestations

1. Approximately 60% have fever at the onset of paralysis
2. Asymmetric weakness in >60% of patients
 - a. Approximately 10% have IIIrd cranial nerve involvement
3. Legs are affected > arms
4. Approximately four days from onset to peak of paralysis; residual paralysis in 25%
5. Most patients are young children

Neuropathology

1. Neurophagia
2. Astrocytosis
3. Mononuclear cell infiltration

Enterovirus 71 (EV71)

General Characteristics

1. Major Cause of Hand, Foot, Mouth Disease (HFMD)
2. Large outbreaks recorded from Southeast Asia
3. Primarily a disease of children, but adults may be infected
4. HFMD primarily caused by:
 - a. Enter viruses of the enterovirus A species:
 - i. Coxsackie virus A2–8, 10, 12, 14, 16
 - ii. Enterovirus (EV) 71, 76, 89–92

Clinical Manifestations of HFMD

1. Primarily a benign self-limiting illness of young children and infants
2. Vesicular lesions of the palms and soles
 - a. All parts of the limbs including the groin and buttocks may be involved; usually, there are oral ulcers
 - b. Acute hemorrhagic conjunctivitis may be seen

Neurologic Manifestations

1. Encephalitis:
 - a. Fever

- b. Headache
- c. Vomiting
- d. Neck stiffness
- e. Altered mental status
- f. Seizures
- g. Myoclonus
- h. ANS dysregulation

2. Poliomyelitis-like syndrome:

- a. Usually occurs in children
- b. Isolation of virus decreases with age

3. Similar manifestations have been recorded for echovirus 6

Laboratory Evaluation

1. CSF demonstrates mild lymphocytic pleocytosis

Neuroimaging

1. MRI:
 - a. Meningeal enhancement
 - b. Ventral horn (spinal cord) T2-weighted signal increase and at times gadolinium enhancement

Neuropathology

1. EVs are non-enveloped viruses that are resistant to environmental conditions and mild disinfectants
2. Transmission is through fecal-oral route although the virus has been cultured from respiratory secretions
3. There is retrograde axonal transport to the CNS; involvement occurs in:
 - a. Medulla, pons, midbrain, and cortex

West Nile Virus

General Characteristics

1. Flavivirus family
2. Mosquito-borne (crows are a common vector and may die)
3. Most patients develop a minor non-specific illness with:
 - a. Fever
 - b. Gastrointestinal dysregulation
 - c. Rash
 - d. Back pain
4. Viral transmission occurs through blood and organ transplantation

Clinical Manifestations

1. Meningitis
 - a. Occurs in less than 10/1 of infected individuals
2. Most frequent in patients older than 50 and is often associated with flaccid paralysis
3. Encephalitis
 - a. Rare seizures
 - b. Dyskinesias
 - c. Parkinsonian features
 - d. No resting tremor
 - e. Postural and action tremor
 - f. Postural instability
4. Acute flaccid paralysis:
 - a. Asymmetric muscle weakness

- b. VIIth nerve may be involved
 - c. Weakness progresses over a 3–8 day period
 - d. No sensory complaints
5. Transverse myelitis and GBS phenotypes have been described

Laboratory Evaluation

1. CSF lymphocytic pleocytosis

Electrophysiology Evaluation

1. EMG evaluation
 - a. During the acute illness (patients with flaccid paralysis)
 - i. Normal sensory nerve action potentials
 - ii. Normal or slightly reduced compound action potential amplitude
 - iii. Normal nerve conduction velocities
 - iv. Widespread fibrillation potentials

Neuroimaging

1. MRI
 - a. May demonstrate increased T2-weighted signals from the ventral horn, thalamus and basal ganglia

Neuropathology

1. Perivascular mononuclear cell infiltration of the brain and ventral horn of the spinal cord

Japanese Encephalitis (JE)

General Characteristics

1. Endemic in parts of Asia
2. Most often a disease of children
3. Similar presentation to enterovirus 30 (E30) infection
4. Adult patients are being reported with JE
5. Mosquito-borne virus of the Flavivirus family

Clinical Manifestations

1. Encephalitis/meningitis
 - a. Headache, vomiting, back pain
 - b. Fever
 - c. Altered level of consciousness (common)
 - d. Seizures (common)
2. Pediatric patients have a higher incidence nuchal rigidity, convulsions, and abnormal behavior than adults
3. Patients reported with asymmetric flaccid paralysis (polio-like syndrome)

Laboratory Evaluation

1. Increased bilirubin and aspartate transaminase
2. CSF
 - a. Lymphocytic pleocytosis with moderately elevated protein

Neuropathology

1. Direct neuronal involvement with widespread inflammatory changes

Rabies

General Characteristics

1. Canine rabies is dramatically decreasing in the USA; individual patients from Mexico, South America, Africa that are infected are seen in the USA
2. The virus is of the genus *Lyssavirus* in the *Rhabdoviridae* family
3. In the USA, the primary vectors are bats, skunks, raccoons and foxes. In Mexico and South America, it is the vampire bat

Clinical Manifestations

1. Early signs and symptoms include fever, headache, and malaise
2. In canine rabies, 20% of patients suffer pain, weakness, and sensory symptoms in the area of the bite; vampire bite victims often are unaware that they have been bitten (distal extremities are bitten while the patient is asleep)
3. Progression of the disease is associated with:
 - a. Insomnia
 - b. Anxiety
 - c. Confusion
 - d. Delirium
 - e. Polio-like flaccid paralysis
4. Symptom duration from onset to death is approximately two weeks (range 6–43 days)
5. Unusual signs include:
 - a. Severe abdominal pain
 - b. Generalized itching
 - c. Gagging sensation
 - d. Staring and unresponsiveness (lasting 10–15 seconds)
6. Classic signs of rabies:
 - a. Hydrophobia
 - b. Hallucinations
 - c. Anxiety, confusion, agitation
 - d. Hyperthermia
 - i. Usually occurs four days post-symptom onset

Neuropathology

1. Ventral roots and motor axons are inflamed, rabies virus RNA is found in AHCs
2. Perivascular cuffing

Laboratory Evaluation

1. Saliva can be tested by virus isolation or RT-PCR
2. Serum and CSF reveal antibodies to the virus

Differential Diagnosis of Poliomyelitis

1. Neurotropic Viruses:
 - a. Viral prodrome
 - b. Aseptic meningitis
 - c. Asymmetric bulbar paralysis
 - d. Differential points:
 - i. HFMD (EV71) – vesicular lesions of the palms and soles; flaccid paralysis

- ii. Heart involvement – Coxsackie A variants
- iii. Japanese encephalitis – altered mental status, seizures, and liver involvement
- 2. Guillain-Barré syndrome:
 - a. More symmetric paralysis, motor > sensory involvement (large fiber modalities)
 - b. Decreased reflexes in muscles prior to weakness
 - c. Facial paralysis
 - d. Greater incidence of ventilator dependence
 - e. Cytoalbuminologic dissociation in CSF
 - f. EMG reveals a demyelinating sensory motor neuropathy
- 3. Transverse myelitis:
 - a. More acute onset of paraparesis > quadriparesis
 - b. Band-like sensation at or above the level of weakness
 - c. Bladder and bowel involvement
 - d. MRI evidence of intraparenchymal spinal cord swelling
- 4. Botulism:
 - a. Infantile botulism occurs between 3–6 months; wound botulism; improperly canned foods
 - b. Cholinergic dysautonomia occurs with:
 - i. Non-reactive large pupils
 - ii. Constipation
 - iii. Urinary retention
 - iv. Dry mouth and eyes
 - c. Weakness is generalized and symmetric
 - d. Cranial nerve abnormalities (IX, X, XII) are prominent with dysarthria, dysphagia, and dysphonia
 - e. Frequent occurrence of diplopia and ophthalmoplegia
 - f. Areflexia
 - g. EMG pattern of dysfunction of neuromuscular transmission
 - i. Incremental increase in amplitude to 5–50 Hz repetitive stimulation (10 seconds)
- 5. Rabies
 - a. Approximately 20% of patients present with paralytic rather than encephalitic form of the illness
 - b. Prodromal symptoms of fever, chills, fatigue, irritability and insomnia
 - c. Pain, weakness, and sensory involvement may begin at the site of injury; bat bites (vampire) may be asymptomatic
 - i. Signs and symptoms may occur 1–3 months after a rabid animal bite
 - d. Anxiety, agitation and hydrophobia less common in the paralytic than encephalic form
 - e. Genitourinary and bulbar symptoms occur

Acute Intermittent Porphyria

- 1. AD with variable penetrance
- 2. Associated with severe abdominal pain and vomiting (soft abdomen)
- 3. Psychosis
- 4. Fasting, alcohol, and specific drugs are triggers

- 5. Primarily a motor predominant proximal symmetric neuropathy that may be asymmetric and accompanied by wasting in affected muscles
- 6. Autonomic neuropathy with severe abdominal pain, cardiac arrhythmia and blood pressure variation
- 7. Retained ankle jerks in an otherwise areflexia patient
- 8. Cranial nerves, including III, IV, and VI may be involved

Spinal Epidural Abscess

- 1. Occurs in a setting of:
 - a. Post-spinal surgery
 - b. Preceding discitis
 - c. SBE
 - d. Intravenous drug use (usual involvement is in the thoracic spine)
- 2. Fever, severe at level back pain and acute flaccid para- or quadriparesis (spinal shock)
- 3. Sensory level (often higher 1–2 segments in the back than the abdomen; pattern of intercostals nerve innervations)

Hypokalemia

- 1. Symmetric generalized weakness
- 2. Potassium < 2 meq/L; surprisingly little EKG change
- 3. No myotatic reflexes; deep tendon areflexia; no cranial nerve involvement (extremity rare)
- 4. Weakness is generally proximally predominant
- 5. Neck flexors and extensors may be involved
- 6. No sensory loss; muscles may feel tight

Hypophosphatemia

- 1. Occurs in a setting of diabetic ketoacidosis, burn or intravenous hyperalimentation
- 2. The serum level associated with paralysis is usually <1 mg/dl
- 3. Motor predominant neuropathy that may impair ventilation

ALS Phenotypes

- 1. Classic ALS with both UMN and LMN signs and symptoms
- 2. Genetic sporadic ALS (SALS)
- 3. Familial ALS (FALS)
- 4. Brachial amyotrophic diplegia
- 5. ALS with dementia
- 6. Monomelic (one extremity involvement)
- 7. Hemiplegic variant (Mills syndrome)
- 8. Spinal progressive muscular atrophy phenotype
- 9. Primary lateral sclerosis
- 10. Progressive bulbar palsy

Differential Diagnosis of ALS

- 1. Hereditary spastic paraparesis:

- a. Type SPG 9, 10, 14, 15, 17, 20, 22, 26 and 30 have a LMN component
- b. Pes cavus and dorsal column sensory loss are differential features
2. Distal spinal muscular atrophy type V:
 - a. Mutation of BSCL 2 gene
 - b. Pes cavus, distal amyotrophy, similar to CMT with no sensory loss
3. Structural spinal cord lesions:
 - a. AVM
 - b. Cervical spondylosis and spinal stenosis
 - c. Differential point is no bulbar symptomatology:
 - i. Spondylosis disease is most often at areas of neck movement C5-C6 whereas ALS typically affects C8-T1 initially
4. Copper deficiency:
 - a. Usually large fiber sensory loss
 - b. GI disease that may interfere with absorption
 - c. Concomitant use of zinc compounds (dental adherents)
 - d. Anemia (sideroblastic changes and nuclear maturation defects)
5. Myasthenia gravis
 - a. An important consideration of any ALS patient with a bulbar presentation:
 - i. Usual oculomotor deficits with ptosis; extremely rare in ALS
 - ii. The absence of UMN signs other than hyperreflexia in some patients (spreading acetylcholine sensitivity) and no tongue atrophy. Myasthenia gravis patients on anticholinesterase drugs may demonstrate a fasciculating tongue. This may also occur with hyperthyroidism
 - iii. Other disorders that may affect multiple lower cranial nerves are:
 1. Head and neck cancers with meningeal invasion
 2. Inclusion body myositis
 3. Oculopharyngeal dystrophy
 4. Kennedy's disease
 5. Sarcoid and Wegener's granulomatosis
6. Fazio-Londe disease
 - a. Presentation in the first decade of life
 - b. Rarely VIIth nerve and ophthalmoparesis occurs
7. Brown-Vialetto-Van Laere
 - a. Presents in the first or second decade with bulbar weakness
 - b. Sensorineural hearing loss
 - c. May also have retinal pigmentary degeneration, ataxia, seizures, and dysautonomia
8. Predominantly LMN diseases that may simulate PMA
 - a. Multiple motor neuropathy with conduction block (MMN)
 - i. Weakness without atrophy
 - ii. Nerve rather than segmental pattern of weakness
 - iii. GM1 antibodies, conduction block of motor nerves and brachial plexus swelling by MRI (1/3 of patients) are important laboratory features
9. Inclusion body myositis
 - a. The pattern of weakness is wrist and finger extensors and knee extensors. Often atrophy of the distal 1/3 of the quadriceps
10. Hirayama disease:
 - a. May be focal form of benign amyotrophic
 - b. Spread to opposite extremity in 1/3 of patients
 - c. Evidence for abnormal mobility of the cervical spine
 - d. Lower extremity form primarily described from India (Madras disease)
 - e. Dysphagia
11. Kennedy's disease:
 - a. X-linked
 - b. Gynecomastia
12. Primary lateral sclerosis
 - a. Need at least four years from disease onset of purely UMN signs to be PLS
 - i. Features that predict the evolution to ALS with UMN and LMN signs are:
 1. Focal motor weakness
 2. Bulbar onset
 3. Weight loss
 4. Reduced forced vital capacity
13. Paraneoplastic myelopathy
 - a. Rapid evolution of disease
 - b. Associated primarily with lung and breast cancer
14. HIV/HTLV-1
 - a. May produce a slowly progressive spinal cord syndrome
 - b. HTLV-1 has prominent bladder symptomatology that would be very unusual for ALS (Onuf's nucleus is usually spared)
15. X-linked adrenoleukodystrophy
 - a. Affects middle-aged female carrier
 - b. Progressive paraparesis
16. Adult acid maltase deficiency
 - a. May present with slowly progressive spinal muscle atrophy
 - b. Diaphragmatic involvement earlier than seen in ALS and more proximal muscle involvement are against an ALS diagnosis
17. Late-onset Tay-Sachs disease
 - a. Younger onset than classic ALS
 - b. Predominantly male of Ashkenazi Jewish ancestry
 - c. Balance problems and iliopsoas weakness are often early signs
 - d. All patients had cerebellar atrophy on MRI
 - e. A few patients have psychiatric and oculomotor abnormalities
18. Lyme's disease
 - a. Predominant manifestations:
 - i. Polyradiculopathy
 - ii. Rapidly progressive weakness and atrophy
 - iii. Increased reflexes

Benign Fasciculations

1. Fasciculations are benign if they are unaccompanied by weakness, wasting or reflex change
 - a. Benign fasciculations occur in the thenar eminence, eyelids, calves or orbicular muscles in normal people
 - b. They may continue for days
 - c. In general, they are more constant in location, frequent and rhythmic than those that signal denervation
 - d. Normally modeled motor neuron unit size rather than the large units typical of reinnervation (ALS or MND)
 - e. Some patients complain of fatigue and weakness

Pathologic Fasciculations

1. Occur in weak and atrophic muscles. Fasciculations in association with hyperreflexia may signify UMN and LMN degeneration or a compressive myelopathy with concomitant root involvement (cervical and lumbar spondylosis)
2. Hereditary diseases with fasciculation:
 - a. Hereditary forms of SMA and ALS
 - b. Some forms of hereditary spastic paresis with lower motor components (SPG 7, 9, 14, 15, 20, 24, 26)
 - c. Hereditary distal motor neuropathies (hSMA type V)
 - d. Bulbospinal muscular atrophy
 - e. GM2 gangliosidosis
 - f. Triple-A syndrome:
 - i. Mutation in the AAAS gene that encodes ALADIN
 - ii. Achalasia, Alacrima, and Addison's
 - iii. UMN and LMN signs (late onset form)
 - iv. Motor-sensory or autonomic neuropathy
 - v. Optic atrophy
 - vi. Cerebellar ataxia
 - vii. Parkinsonism
 - viii. Dementia

Non-Hereditary Diseases with Fasciculation

1. Fasciculation in peripheral nerve hyperexcitability syndromes include:
 - a. Isaacs' syndrome
 - b. Voltage-gated potassium channelopathy
 - c. Cramp fasciculation syndrome
 - d. Morvan's syndrome
2. Varied causes of fasciculations (neurodegenerative, autoimmune, infective mitochondrial and genetic):
 - a. Familial amyloidosis
 - b. Some spinocerebellar ataxias
 - c. Huntington's disease
 - d. Rett syndrome
 - e. L1-cell adhesion molecule (L1CAM) mutations
 - f. Fabry's disease
 - g. Gerstmann-Sträussler disease
 - h. Some mitochondrial diseases
 - i. Nerve root compression (cervical and lumbar spondylosis)

- j. Rarely in a muscular dystrophy
- k. Post-polio syndrome (formerly affected muscles)

Rare Signs in ALS

1. Extra-oculomotor abnormalities; may have decrease of vertical saccades
2. Sphincter dysfunction (may occur late in the disease in those on ventilators)
3. Sensory loss (often subtle dorsal column involvement)
4. Extrapyrimal signs in approximately 5%; impairment of postural reflexes (major confounder is age and the onset of other neurodegenerative diseases)
5. Autonomic dysregulation involving:
 - a. Blood pressure control
 - b. Heart rate variability
 - c. GI function

Associated Features

1. Sleep apnea (morning headache)
2. Sialorrhea
3. Silent and asymptomatic aspiration
4. Disturbance of sleep architecture
5. Decline of voice power with speech
6. Cachexia greater than expected from decreased nutrition
7. Absence of expected bed sores (possible changes in type III procollagen)
8. Extremely rarely the process appears to stop
 - a. There are plateaus and fluctuations of neurologic disability in some patients

Further Reading**Further Reading on Anterior Horn Cell Disease****Mechanisms in Spinal Muscular Atrophy (SMA)**

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Clinical Spinal Muscular Atrophy

(CN II–IV; Kennedy Disease Hirayama; Scapulo Peroneal (Davidow; Distal SMA; Childhood Bulbous SMA))

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Chapter 4

Spinal Cord

Overview of Spinal Cord Anatomy

The spinal cord is frequently involved in specific patterns due to varying pathologies which are extremely helpful in differential diagnosis. Recent advances in neuroimaging technology allow visualization of specific cord quadrants and Rexed nuclear layers. Due to differential growth of the vertebral column relative to the spinal cord, spinal cord segments do not correspond to vertebral segments. The spinal cord, in general, lies two segments above the vertebral level. Thus, the lumbar segments lie at the T11–T12 vertebral segment. Various congenital anomalies may also change this anatomy such as the tethered cord syndrome in which the spinal cord segments are below their expected vertebral level. The spinal cord and nerve roots move with both extension and flexion. Cervical spinal roots exit above their corresponding vertebrae while thoracic and lumbar roots exit below their corresponding vertebrae. The foramen through which the nerve root exits are canals. Nerve roots are often the subject of facet hypertrophy, synovial cysts, and root entry zone pathology. The dorsal root ganglia are within the foramen exit canals. They also possess a less tight blood-nerve barrier than the brain.

The spinal cord is surrounded by the pia mater, arachnoid and dura mater which is composed of an inner meningeal and an outer endothelial layer. The endothelial layer forms the periosteum of the vertebral canal and the epineurium of the spinal nerves (outermost covering) at the intervertebral foramina. The loose, irregular trabecular arachnoid is continuous with the cranial arachnoid. The pia mater contains large vessels, adheres to the spinal cord, and gives rise to the dentate ligaments that extend to the dura. They extend from the foramen magnum to the first lumbar vertebrae. The filum terminale is a condensation of the pia mater between the conus medullaris (S1–S5 spinal segments) and the second sacral vertebra. The leptomeninges are formed from the pia and arachnoid which surround the spinal nerves as the perineurium. The CSF, arteries and veins are contained in the subarachnoid space (between the arachnoid and pia mater). The epidural space contains a venous internal vertebral plexus (Bateson's plexus) that has no valves and connects with cerebral veins.

Anatomy of the Spinal Gray Matter

Cytoarchitecture of the spinal cord's neurons is organized by Rexed layers that have specific functions. There is great neuroplasticity of the dorsal horn after peripheral nerve and spinal cord injury and chronic pain states. This is manifest as up or down regulation of ion channels, dendritic spine synap-

tic morphologic configurations, growth factor, neurotransmitter, and cytokine concentrations. These anatomical and chemical changes underpin the physiologic behavior of neurons to produce long-term potentiation and depression, spasticity and spinal shock that are evident in specific pathologies.

Rexed Layer Classification

1. Lamina I
 - a. Posterior marginal nucleus
 - b. Pain discriminative A-delta and C-fiber afferent innervation
2. Lamina II (substantia gelatinosa)
 - a. Pain and temperature modalities:
 - i. A-delta 1–4 micron thinly myelinated afferents:
 1. Fast pain (epicritic)
 2. Cold sensation
 - ii. C-fibers:
 1. Slow conducting, burning pain
 2. Multimodal C-fiber input
 3. Heat modality and heat pain
 4. Axons of these neurons are a major component of Lissauer's zone (dorsolateral fasciculus). They synapse two spinal segments above and below their level of entry
3. Lamina III and IV
 - a. Nucleus proprius, dorsalis
 - b. Primarily receives, touch, pressure and mechanical modalities of sensation
 - c. Contribution to the lateral spinothalamic tract
4. Lamina V
 - a. Synapses with rubrospinal and corticospinal tracts
 - b. Lateral portion contains multimodal pain transmission neurons that receive:
 - i. Nociceptive-specific fibers
 - ii. Sympathetic afference
 - iii. Temperative specific fibers
 - iv. Low threshold mechano receptive neurons (LTM)
5. Lamina VI
 - a. Present in cervical and lumbosacral enlargement; absent in fourth thoracic to second lumbar segments
 - b. The lateral component contains wide dynamic range pain transmission neurons
 - c. Contributes to the lateral spinothalamic tract
6. Lamina VII
 - a. Afferents from the corticospinal (CST) and rubrospinal tract
 - b. Clark's column (origin of the dorsal spinocerebellar tract); first thoracic to the second or third lumbar segment
 - c. Intermediolateral column:
 - i. Sympathetic neurons (first thoracic to second or third lumbar segments)
 - ii. S2–S4 is parasympathetic

- d. Intermediomedial column:
 - i. Extends the length of the spinal cord
 - ii. Receives visceral afferents
7. Lamina VIII:
 - a. In the cervical and sacral enlargements
 - b. Contains commissural neurons
 - c. Afferents from:
 - i. Vestibulospinal tract
 - ii. Reticulospinal tract
 - iii. Tectospinal tract
8. Lamina IX
 - a. Contains proximal and distal motor neurons; extrafusal and intrafusal neurons
 - b. Motor neuron afference:
 - i. Excitatory (glutamatergic) from the cortico-, rubro-, reticulospinal pathways; reflex arcs
 - ii. Inhibitory (glycinergic, GABA) input from propriospinal neurons
 - iii. Motor neurons project inhibitory collaterals to Renshaw cells (inhibitory interneurons)
 - c. Somatotopic organization of alpha motor neurons:
 - i. Abductor neurons are anterior
 - ii. Flexor neurons posterior
 - iii. Extensor and adductor neurons are intermediate; some finger motor neurons are dorsolateral. Approximately 5% of descending CST fibers innervate these neurons directly
 - d. Somatotopic pattern for the lower extremity (lumbosacral segments)
 - i. Trunk neurons are medial
 - ii. Foot neurons are lateral
 - iii. Leg and thigh neurons are intermediate
 - iv. Thoracic segments:
 1. Neurons that innervate the abdominal musculature are medial to those that innervate the intercostal muscles
 2. Neurons that innervate back muscular are intermediate
 - v. Cervical segments:
 1. Hand and finger neurons are most lateral forearm
 2. Forearm and shoulder are intermediate
 3. Trunk neurons are most medial
 - vi. Tonic motor neurons:
 1. Have a low depolarization threshold and innervate Type I oxidative muscle fibers:
 - a. That stain with oxidative enzyme stains such as nicotinamide-adenine dinucleotide tetrazolium reductase (NADH-TR); succinic dehydrogenase (SDH) or cytochrome C oxidase (COX)
 - b. Are slow twitch
 - c. Fatigue resistant
 - d. Are inhibited during dynamic movement

Phasic Neurons

1. Higher firing threshold
2. Innervate fast twitch Type II muscles (myofibrillar ATPase stain)
3. Glycolytic muscle fiber metabolic profile
4. Phasic neurons project more recurrent collaterals to Renshaw cells than tonic neurons

Gamma Motor Neurons

1. Are interspersed among motor neurons
2. Discharge shorter intrafusal fibers and depolarizes motor neurons
3. Motor neurons effect movement by coactivation and modulation of the gamma loop

Ascending Spinal Tracts

1. Dorsal columns (posterior funiculus)
 - a. Somatosensory information transmitted primarily to VPL and VPM of the thalamus
 - b. Modalities encoded include:
 - i. Vibration (Pacinian corpuscles)
 - ii. Position sense
 - iii. Higher cortical sensory modalities such as stereognosis and two point discrimination
 - iv. The deepest fibers may have a role in transmitting visceral pain
 - v. The heavily myelinated fibers of the medial components of the dorsal root pass over the dorsal horn to ascend in the dorsal columns. They give rise to collaterals which terminate in Rexed layers III and IV
 - vi. Sacral, lumbar and the lower six thoracic levels lie medially in the posterior funiculus (dorsal columns) and form the fasciculus gracilis. Fibers from the upper six thoracic segments and all cervical levels are lateral and comprise the fasciculus cuneatus. They terminate in the nucleus gracilis and cuneatus of the medulla and then project to the thalamic nucleus VPL

Neospinothalamic Tract (Lateral Fasciculus)

1. Finely myelinated A-delta fibers (1–4 μ) and unmyelinated C-fibers from the lateral bundle of the dorsal root bifurcate into short ascending and descending branches (usually 2 segments) within the zone of Lissauer to terminate in the substantia gelatinosa of the dorsal horn (lamina I and outer Lamina II). They decussate through the ventral white commissure into the ventrolateral quadrant of the spinal cord to form the lateral spinothalamic tract. Neurons of Lamina I and outer lamina II are nociceptive specific
 - a. The A-delta component of the lateral spinothalamic tract encodes cold and sharp, fast pain that signals lo-

calization, intensity and affect. These fibers project to the thalamus (VPL and intralaminar nuclei) and then to the cortex (SI, SII and the insula). Collateral are given off at many levels

- b. The C-fiber component of the lateral dorsal root bundle (unmyelinated fibers) are slowly conducting and signal poorly localized burning pain. There are many subcategories of polymodal C-fibers that signal specific categories of pain. C-fibers also transmit the thermal modality of heat

Also, comprising a major component of the lateral neospinothalamic pathway are axons from wide dynamic (WDN) pain transmission neurons that arise from the deep dorsal horn in the lateral components of laminae V and VI.

These WDN neurons respond to:

1. Low threshold mechanical stimulation (LTM)
2. Thermal stimuli
3. Sympathetic innervation
4. Nociceptive-specific stimuli

They are a component of static and dynamic allodynia and hyperalgesia.

The neospinothalamic tract is topographically organized such that fibers that originate from cervical levels are dorsomedial, and sacral fibers are ventrolateral. Temperature modalities are dorsolateral, and pain fibers are ventromedial (this information is derived from cordotomies performed for intractable pain).

The Dorsal and Ventral Spinocerebellar Tracts

1. These tracts are located most laterally and originate from the neurons of Clark's column
2. They mediate unconscious proprioception from the lower extremities to the intermediate zone of the cerebellum
3. The cuneocerebellar tract from cervical segments mediates similar information from the upper extremities

Tracts in the Ventral Funiculus

1. The ventral spinothalamic tract carries fibers that transmit light touch, sexual sensation, tickle, and itch. Possible role in affective components of pain
2. The spino-olivary tract relays cutaneous modality information from Golgi tendon organs to the dorsal and medial accessory olivary nuclei
 - a. Golgi tendon organ afferents provide an estimate of muscle tendon complex length which is a component for feedback during postural and dynamic movement
3. The spinoreticular tract:
 - a. Component of the ascending reticular activating system (arousal)
 - b. Ascends through the entire spinal cord
 - c. Derived from axons of Lamina V
 - d. A role in head and eye coordination to a visual target

Descending Tracts

The Corticospinal Tract

1. The fibers of the corticospinal pathway are somatotopically organized at all levels (the exception being the medullary pyramids after their decussation)
2. The pathway takes origin from:
 - a. Primary motor cortex (BA4)
 - b. Lateral premotor cortex (BA6)
 - c. Supplementary motor cortex (BA6)
 - d. Parietal lobe (BA3, BA1, BA2)
 - e. Superior parietal lobule (BA5 and BA7)
 - f. Cingulate gyrus (small component)
3. The decussation of the pyramids occurs at C1–C2 (the arm fibers are more anterior and medial). There are approximately one million fibers in each pyramid and 90% decussate. 10% of pyramid fibers are uncrossed and descend and cross at their level of innervation (contralateral cervical and thoracic segments)
4. The primary termination of the CST is lamina IV through VII (interneurons) that then project to neurons in Lamina IX. There are direct connections (approximately 5% of CST fibers) to neurons in IX that control the digits. The termination of the uncrossed descending CST is contralateral Rexed layers VIII. Somatic organization of motor neurons that innervate the extremity are:
 - a. Axial musculature neurons are in the ventromedial portion of area IX
 - b. Limb-girdle innervating neurons are more lateral
 - c. Intrinsic extremity musculature is dorsolateral
 - d. The same topological pattern for propriospinal neurons is seen in Lamina V–VIII. These fibers project several segments from their origin and thus innervate multiple segments of proximal muscles. Propriospinal interneurons that innervate intrinsic hand muscles project minimally from their segment of origin and modulate restricted groups of distal muscle

Rubrospinal Tract

1. Originates from BA4, BA6 of the frontal cortex and BA3, BA1 and BA2 of the parietal lobe
2. Axons primarily from the magnocellular division of the red nucleus decussate and innervate flexor motor neurons

Lateral Reticulospinal Tract

1. Originates in the medullary and pontine reticular formation (ipsilaterally) and descends in the ventrolateral funiculus
2. Relay for signaling of afference to the reticular formation from the cortex, cerebellum, cranial nerves and hypothalamus to the spinal cord

Vestibulospinal Tracts

1. The lateral vestibulospinal tract (origin is Dieter's nucleus) traverses the entire cord

2. Is excitatory and is essential for vestibular nuclei afference
3. The medial, vestibular nucleus is monosynaptically inhibitory and descends to upper cervical segments

The vestibulospinal tract and the medial reticulospinal tract facilitate alpha and gamma motor neurons that project to anti-gravity musculature. The CST, rubrospinal tract, and lateral reticulospinal pathways inhibit antigravity muscles and facilitate their antagonists.

The Medial Longitudinal Fasciculus

1. Is both ascending and descending
2. Originates from vestibular and reticular neurons
3. Decussates posteriorly at the levels of the VIth nerve and ascends to innervate the contralateral IIIrd nerve. Anteriorly at the IIIrd nerve level it receives optic kinetic and adducting (medial rectus) afference
4. Coordinates III, IV, VI nerve conjugate gaze by integrating vestibular, reticular and hemispheric afference

The Fasciculus Proprius (Propriospinal Tract)

1. Comprises a large proportion of spinal cord white matter
2. An intersegmental tract that ascends and descends (crossed and uncrossed)
3. Mediates spinal cord reflexes

Spinal Cord Disease

General Characteristics

1. The spinal cord is involved in specific patterns and at characteristic levels in specific disease pathologies
2. The lamination of both the dorsal column system and spinothalamic tracts is such that sensory signs and symptoms may not reflect the true segmental levels
3. Spinothalamic lamination reveals the most lateral fibers to convey sacral sensation followed (lateral to medial) by leg, trunk, and upper extremity fibers (most medial); it is a crossed pathway (at the level of entry). Thus, a lateral cervical lesion compressing the cord (not unusual for a neurofibroma) may present with sacral and leg sensory loss. Lissauer's tract projects spinothalamic innervations two segments above and below the level of entry. Thus, a T2 lesion may present as if the level were at T4. The sensory loss is always slightly higher posteriorly than anteriorly. The lamination of the corticospinal tract places fibers innervating the legs lateral to those of the arm. Bladder fibers are between the two, but usually, bilateral involvement is required to produce symptoms (most common with compressive cord lesions)
4. For clinical and neuropathological clarity the spinal cord is divided into three spaces:
 - a. Epidural
 - b. Intraparenchymal
 - c. Intradural and extramedullary

5. Pathologies that compress the spinal cord cause ataxia (early often prior to weakness), a sensory level (best sought with pin-prick and cold), bilateral weakness below the level of the lesion and bladder involvement (retention)
6. If epidural processes are acute, such as metastasis or hematoma or fracture, there will be spinal shock. If this supervenes, all sensation, motor function, bowel and bladder control and reflexes will be lost below the level of the lesion
7. Long standing intraparenchymal spinal cord disease (multiple sclerosis) causes spasticity below the level of the lesion with a neurogenic bladder
8. In the case of a syrinx, there is segmental sensory loss with normal sensation above and below the lesion
9. Occasionally reflexes will be increased above the level of the lesion (Schiff-Sherrington reflex) from loss of ascending spinal cord inhibition
10. Cystic intraparenchymal lesions and tumors often cause minimal bladder dysfunction. Intradural, extramedullary lesions are few and comprise meningioma neurofibroma, dropped metastases and enlarged nerves and roots from congenital hereditary motor sensory neuropathies. If a neurofibroma or meningioma occurs in the thoracic or cervical segments, there is often concomitant root and spinal cord compression. In the lumbosacral areas, only roots are involved as the spinal cord ends at T12–L1 (conus medullaris)

Specific Patterns of Spinal Cord Involvement

Transverse Myelitis

1. Most often these are longitudinal rather than transverse lesions that involve two or more segments. The spinal cord is expanded
 - a. If the involvement is more ventral (enhancement of the anterior horn cells) viral infection is suspected (West Nile virus, poliomyelitis, enterovirus 71, Coxsackie A7 and ECHO 6)
 - b. Dorsal column involvement suggests syphilis, Sjögren's syndrome, B12 deficiency, and toxins
 - c. If there is complete spinal cord transection all ascending and descending tracts are disrupted which is unusual. There will be a complete loss of motor, sensory and bowel and bladder function below the level of the lesion. Most often lesions are incomplete

Differential Diagnosis of Acute Transverse Myelitis

1. Demyelinating disease
2. Trauma
3. Metastatic disease (lung, breast)
4. Lymphoma
5. Hematoma (AVM, anticoagulation)
6. Abscess (IV drug abuse)
7. Herniated disc

8. Autoimmune disease (SLE)
9. Paraneoplastic syndrome (anti-Hu)
10. Post-vaccinal (hepatitis B)
11. Longitudinal myelitis (neuromyelitis optica)

Sensory Abnormalities

1. A bandlike or squeezing sensation at the segmental level:
 - a. Cervical levels may be associated with pain radiation into the arms
 - b. With thoracic levels the pain may radiate to the chest or abdomen. May be confused with intercostal nerve neuropathy (diabetes, amyloid, syphilis) or herpes zoster (prior to the rash)
 - c. Lumbar or sacral level involvement may have leg and perineal radiations

Local Vertebral Pain

1. Particularly elicited by mechanical stimuli:
 - a. Abscess and discitis
 - b. Tumor
 - c. Pathologic fracture

Postural Induced Pain

1. Pain worse with recumbence and relieved by standing is common with malignancy. Putative mechanism is venous "engorgement"
2. Sleeping, sitting up is characteristic for spinal cord tumor or arachnoid cyst (fills with CSF and compresses the cord)

Dropped Sensory Level

1. As noted above due to the somatotopic localization of spinothalamic fibers. The lesion may also be in the medulla (PICA infarction) or lateral pons and parietal lobe

Motor Manifestations

1. Acute lesions are associated with spinal shock (flaccid paralysis, areflexia, bowel/bladder dysfunction). The weakness if below T6 may be associated with bradycardia, hypotension, and slight hypothermia. Ejaculation suggests a severe lesion
2. After four to six weeks the patient may suffer hyper-tonic, flexor and extensor spasms, hyper-reflexia, loss of abdominal and cremasteric reflexes and too easily, obtainable Babinski sign (midfoot level that often elicits flexor spasms)
3. High spinal cord lesions cause extension of the hip and knee while lower lesions cause flexion of the hip and knee
4. At the lesion level, there are signs of anterior horn cell damage that include atrophy, fasciculation, and areflexia

Autonomic Alterations

1. As noted during spinal shock there is bowel/bladder paralysis
2. Partial lesions cause urgency and urine retention. Incontinence supervenes late

3. Constipation is the earliest bowel symptom and evolves from atonia to spasticity of sphincter tone. Dyssynergia between L1–S4 intrinsic bladder contractions with the failure of external sphincter opening often occurs with partial lesions
4. Below the level of the lesion there may be anesthesia, trophic changes in skin, muscle and soft tissue and vasomotor instability
5. Sexual function may be spared if the patient can feel pinprick on the testicles. Sexually important afference appear to be ventral in the spinal cord. Sexual feelings may not be normal (painful ejaculation that may trigger a mass reflex (flexor spasm of the legs with bowel/bladder incontinence)

Brown-Séquard Syndrome (Longitudinal Division of the Spinal Cord)

1. The signs include:
 - a. Ipsilateral loss of proprioception and vibration sensibility below the lesion
 - i. Tactile sensation may be only minimally involved. Possibly from loss of function of the dorsal and ventral spinocerebellar tract rather than the dorsal column
 - ii. The cervical spinal thalamic tract (located above the CST) also carries vibration and touch sensibility as does a small portion of the spinothalamic tract
 - b. Disruption of the lateral spinothalamic tract
 - c. Usually two segments below the lesion; slightly higher in the back than anteriorly (distribution of the intercostal nerves)
 - d. Ipsilateral spastic weakness:
 - i. Interruption of the descending CST
 - e. Segmental LMN involvement
 - i. Loss of sensation at the segmental level (dorsal horn and root involvement)

The usual etiologies include trauma (knife or bullet) extramedullary lesions or X-RT therapy in which individual sulcal arteries may be involved by proliferative endarteritis.

Intramedullary Lesions

1. The spinal cord is swollen over several segments. The parenchyma usually accounts for 2/3 of the spinal canal space while the subarachnoid accounts 1/3
2. The most common causes of central cord syndrome are:
 - a. Syringomyelia
 - b. Hydromyelia
 - c. Hematomyelia

Syringomyelia

1. A slowly progressive process
2. Symptoms and signs depend on the level of involvement. Although often central, a syrinx from a congenital cause or those associated with tumors or trauma may expand asymmetrically (dorsal into the posterior columns, ventrally into anterior horn cells)

Cervical Syrinx

1. Loss of pain and temperature sensation in a capelike distribution (interruption of the decussating spinothalamic tract at C4–C6)
 - a. Light touch and proprioception are often intact
2. Segmental neurogenic atrophy and areflexia
3. Horner's syndrome may be seen if the sympathetic corticospinal center of Budge (lateral extension at C8–T1) is involved
4. Kyphoscoliosis occurs if axial muscles are denervated (represented closest to the midline) which causes a C-shaped deformity away from the involved side
 - a. S-shaped scoliosis occurs in congenital scoliosis from muscular compensation
5. Spastic paraparesis may occur from CST compression which is associated with hyperreflexia and Babinski signs
6. Sacral sparing of sensation occurs due to the lateral position of these fibers in the spinothalamic tract
7. Ventrolateral extension may involve the spinothalamic tract producing thermoanesthesia below the spinal level of the lesion
8. Neuropathic joints may be produced by loss of pain in the affected extremity
 - a. The differential diagnosis for this process includes:
 - i. DM
 - ii. Synthroid
 - iii. Syphilis
 - iv. Syringomyelia

The Differential Diagnosis of Central Cord Syndrome*Syringomyelia*

1. Often associated with Chiari type I or II and the Dandy-Walker in malformation
2. Trauma associated (often above the level of the lesions)
3. Associated tumor which includes cystic astrocytoma
 - a. Frequently an enhancing nodule is noted
 - b. Hemangioblastoma and an astrocytoma that may develop in the wall of a syrinx

Acute Cervical Central Cord Injury

1. Usually occurs after severe hyperextension neck injuries
2. The patients are acutely quadriparetic but regain leg movement within minutes to hours
3. Acute urinary retention occurs in approximately 50% of patients
4. Weakness is more pronounced in the arms, usually distal > proximal
5. Patchy sensory loss below the lesion
6. Major pathology is in the central spinal cord, but there may also be a component of brachial plexus injury
7. Usually, there is significant improvement
8. MRI imaging:
 - a. Intramedullary hyperintense signal on T2-weighted sequences
 - b. Spinal cord compression from a narrowed canal

Epidural Compression

1. Epidural spinal cord compression has a wide differential diagnosis
 - a. Destruction of the vertebral body, particularly of the peduncle is most suggestive
 - b. Bone cysts and hemangioma of the vertebral may also be symptomatic
 - c. These processes may involve only one segment. Disc involvement with concomitant enhancement suggests inflection. The anterior and posterior ligaments often enhance with this pathology
 - d. Lymphoma often starts in the epidural fat. Epidural compression occurs with myelofibrosis or any other form of extramedullary hematopoiesis. Epidural fat may be pathogenic in patients on high doses of corticosteroids
 - e. Spinal AVMs are epidural and are most often dorsal in the thoracic segments. A ventral AVM is rare (Foix-Alajouanine syndrome) is ventral and may compress the cord. Another rare ventral lesion is the neurenteric cyst
 - f. Meningitis of all forms may be most intense dorsally and invades the spinal parenchyma through draining versa or nerve exit foramina
 - g. Sarcoid often thickens the dura at cervical and thoracic levels
 - h. Processes with an expanded dura that may compress the spinal cord include:
 - i. Lymphoma
 - ii. Tuberculosis
 - iii. Cryptococcus neoformans
 - iv. Rheumatoid arthritis
 - v. Idiopathic hypertrophic pachymeningitis
 - vi. Carcinomatosis
 - vii. Amyloid

Pachymeningitis (IgG4 related) carcinomatosis of the meninges thickens the dura but rarely causes spinal cord compression. There is often enhancement with gadolinium in cerebellar and cortical sulci. Amyloid may greatly thicken the dura of both the intracranial and spinal compartment and rarely may form a compressive mass lesion.

Clinical Signs and Symptoms of Epidural Compression*Pain*

1. Radicular pain concomitant with epidural compression is lancinating, unilateral and in a dermatomal distribution. It may be exacerbated with any valsalva maneuver. Radicular pain is rare with intramedullary lesions
2. Vertebral pain is often localized to the segmental vertebra and often elicited with mechanical stimuli. It is prominent at night, particularly with malignant involvement
 - a. It is infrequent with either intraparenchymal or intradural and extramedullary pain. Neurogenic pain is not uncommon with spinal lesions that involve the spinothalamic tract

- b. It is frequently associated with dynamic and static mechano-allodynia and cold pain
 - c. It is not well localized from spinal generators and often is burning or is experienced as a deep dysesthesia
3. Motor function
- a. Both upper and lower motor dysfunction may occur with epidural lesions. Spinal shock occurs with acute lesions and increasing spasticity with chronic ones. Upper motor neuron signs occur late with intramedullary lesions

Sensory Signs

1. Compressive lesions frequently cause an ascending sensory loss that may be mistaken for polyneuropathy
 - a. It frequently is active “pins and needles” reflecting myelinated ($A\beta$ or $A\delta$ fiber pathway involvement). Intramedullary lesions more commonly express descending paresthesia or sensory loss
2. A Brown-Séquard pattern is more common with epidural lesions although it has been noted with traumatic, infectious and post-irradiation
3. A dissociated sensory loss pain and temperature more involved than position and vibration are characteristic of intramedullary lesions
 - a. Vibratory loss is often more severe than proprioceptive
 - b. Sacral sparing is a strong feature of intramedullary lesions (the most lateral fibers in the somatotopic organization of the spinothalamic tract are spared)

Sphincter Function

In general, bilateral involvement of the spinal cord is required for significant sphincter involvement. Characteristic of conus medullaris tumors is an early loss of bowel, bladder, and sexual function. Rarely demyelinating disease or a syrinx may cause dissociated sexual function. The ability to obtain an erection, but the inability to ejaculate. Saddle anesthesia also is common with conus medullaris tumors. Cauda equina lesions tend to have an asymmetric dermatomal sensory loss that is painful associated with sphincter involvement.

The advent of neuroimaging with MRI has made the use of spinal myelography rare in evaluating spine pathology. The exception to this rule is complicated cervical spine disease where the relationship of nerve roots to the exit foramen and facet, needs to be determined prior to decompression. The advantage of myelography with following CT is that contrast outlines the nerve roots and CT images bone detail. MRI images soft tissue such as disc, synovium, and ligaments clearly and contrast enhancement suggests pathology. A saw-toothed or paint brush pattern of contrast is characteristic of epidural pathology.

Intradural Extramedullary Spinal Cord Lesions

This space is the least involved with spinal cord pathology, and the differential diagnosis is restricted. The most common tumor in this space is a neurofibroma or Schwannoma. These

form “dumbbell tumors.” The neural exit foramina are expanded, and the tumor compresses the spinal cord. This is seen as a “cap” sign on myelography. Plexiform neurofibromas may involve multiple nerve roots and are characteristic of neurofibromatosis type I (chromosome 17). Other pathologies that occur in the intradural extramedullary space are:

1. Enlarged nerve roots from hereditary sensory motor neuropathies (Dejerine–Sottas neuropathy)
2. Meningiomas are characteristically found in the thoracic cord in women and are extremely rare in this location in men
3. A free fragment of a disc may migrate in this space for several cord segments
4. Arachnoid cysts may fill in a ball valve fashion and compress the spinal cord intermittently
5. Medulloblastoma (origin is often the superior medullary velum of the IVth ventricle), spinal cord metastasis and, leukemia, as well as subdural hematomas, occur in this location

Posterolateral Spinal Cord Involvement

Posterolateral column degeneration was commonly seen in advanced vitamin B12 deficiency. Patients complain of paresthesia in both hands and feet from concomitant large fiber demyelinating neuropathy. Proprioceptive and vibratory loss are most severe in the lower extremities. Patients have bilateral involvement of the corticospinal tracts with weakness, spasticity, Babinski signs and hyperreflexia. Patients frequently have involvement of cranial nerves I and II as well as ataxia from both sensory and cerebellar involvement. It may produce hyperactive reflexes in a wasted extremity (CST and peripheral nerve involvement).

HIV infection and HTLV associated myelopathy (tropical spastic paraparesis) suffer a cervical vascular myelopathy. This presents as a slowly progressive spastic paraparesis with proprioceptive and vibration loss. There is a lymphocytic CSF pleocytosis and a mild protein elevation. Mild cognitive impairment occurs with both, but bladder involvement is particularly prominent with HTLV-1. The CSF may be normal, but there may be increased IgG and antibodies to HTLV-1.

Cervical spinal stenosis with combined cervical spondylosis usually is a predominant C5–C6 and L5–S1 disease. An inverted radial reflex is common, and atrophy is prominent in the affected dermatomes. Two-point discrimination is frequently diminished in C8–T1 dermatomes while vibration sensitivity is maintained. Routine MRI secures the diagnosis. It is almost invariant that cervical and lumbar spondylosis occur concomitantly.

Posterior Column Spinal Cord Involvement

The classic posterior column disease is tabes dorsalis from neurosyphilis. The lesion is at the level of the dorsal roots with secondary degeneration of the posterior columns. Tabes dorsalis usually develops late in the course of infection (10–20 years after stage 1) and causes severe loss of propriocep-

tion, vibration, and mechanical sensibilities. Higher cortical sensory function is lost causing poor tactile localization. Patients have increased low mechanical thresholds, tactile and postural hallucinations and sensory ataxia. A Romberg sign is prominent and is anticipated by the patient's complaints of inability to walk well at night.

A stamping gait is prominent (the patient attempting to generate more tactile information. Patients may fall forward immediately after eye closure ("sink" sign).

A multitude of neurologic signs occur from neurologic involvement at several levels and include:

1. Tabetic crisis:
 - a. Lightning like lancinating pain to the extremities and the abdomen (severe enough to suggest an emergency). Usually, this phenomenon is concomitant with the development of urinary incontinence and absent patellar and ankle reflexes. The affected extremities are hypotonic but have normal strength
2. Similar crises occur in the larynx which causes stridor and in rectal and urinary sphincters (rare)
3. Proprioceptive and painless joints degenerate due to loss of their usual protective reflexes. These denervated joints are called Charcot joints. The most common is the shoulder joint, but any joint can be involved. Any proprioceptive and analgesic joint can be destroyed. The differential diagnosis is diabetes mellitus, amyloid, a syrinx, and neurosyphilis. The deep pain loss can be clinically tested by squeezing the Achilles tendon (Abadie's sign) which is innocuous to the patient
4. Hitzig zones (areas of the body surface innervated from dorsal root cutaneous collaterals) are involved in severely affected patients. Light tactile sensation is often lost in an ovoid pattern on the trunk. The usual areas of involvement are:
 - a. The mid face (probable dorsal root entry zone)
 - b. The thorax and abdomen
 - c. Ulnar side of the anus and perineal distribution in the lower extremities
 - d. Perianal area
5. Tabes dorsalis is almost always seen with an Argyll Robertson pupil. The pupil is:
 - a. Small (miotic)
 - b. Irregular
 - c. Responds to accommodation but not light
 - d. Does not dilate to mydriatics or the ciliospinal reflex (hard pinch of the trapezius muscle)
6. Optic atrophy (aspirin-like disc is common)
7. Retinitis pigmentosa. The pigment migration is adjacent to blood vessels

Sjögren's Syndrome

1. The dorsal columns may be involved specifically with characteristic symptomatology
2. Cranial nerve V may be selectively involved
3. There is a concomitant sicca syndrome (dry mouth and dry eyes)
4. Sensorimotor neuropathy

Spinal Cord Signs

1. Lhermitte's sign
 - a. Neck flexion elicits a lancinating electric shock-like sensation down the back or into the upper extremities
 - i. The usual cause is multiple sclerosis, but it may also be seen with cervical spondylosis or by progressive compressive spinal cord lesions
 - ii. Reduced threshold to fire of A δ and A β myelinated fibers. The spinal cord is pulled upward with neck flexion approximately 1.5 cm
2. Dr. Jerome Posner has pointed out that there may be early truncal and gait ataxia prior to weakness with spinal cord compression from metastatic tumors. This may occur with normal leg proprioception. The dorsal and ventral spinocerebellar tracts may be affected rather than the posterior columns. This is most common with thoracic spine lesions
3. Dorsal column lesions are frequently prominent in demyelinating disease. Some extremely large lesions have been reported that were asymptomatic

Localization of Spinal Cord Lesions at Specific Levels

Foramen Magnum

1. Suboccipital pain in the distribution of C2 may occur early. This radiation in addition to the posterior neck and scalp projects to the supraorbital area. It frequently is associated with neck stiffness. Lhermitte's sign may be prominent
2. Spastic tetraparesis, long tract sensory loss and neurogenic bladder. The pyramids decussate at C1–C2, the arm fibers anterior and medial to the leg fibers which may produce a cruciate hemiparesis (one arm and the contralateral leg)
3. Cranial nerve IX–XII may be involved
4. Downbeat nystagmus (floccular nodular lobe involvement)
5. Papilledema (CSF obstruction ventral and dorsal pathways)
6. Cerebellar ataxia
7. Patients with a usual hemiparesis (usually from compression at medullocervical C1–C2 level) also demonstrate:
 - a. Arm weakness > leg weakness
 - b. Onion skin pattern of facial sensory loss (decussation of the spinotrigeminal tract)
 - c. Respiratory dysfunction
 - d. Bladder dysfunction
 - e. Lower cranial nerve IX–XII involvement
 - f. Paresthesia in the upper extremities

C1–C4 Cervical Segment Lesions

1. Compromise of CN XI with consequent ipsilateral sternocleidomastoid and upper trapezius muscle weakness (slight head turn to the ipsilateral side and drop of the shoulder). The ipsilesional shoulder cannot be elevated normally to the ear

2. Cervical roots C2–C3 form the pre-auricular nerve with radiations both to the posterior occipital areas and the ipsilateral face. Cervical roots C3–C4 form the post-auricular nerve which radiates to the parietal bone and ear. C2 radiates to the brow and pre-auricular area at the angle of the jaw. C3 may radiate to the side of the neck and C4 to the trapezius ridge. The cap of the shoulder is a C5 radiation (also involved from diaphragmatic irritation)
3. C3–C5 innervates the diaphragm. There is poor expansion of the lower rib cage and dyspnea on exertion. High cervical lesions also interrupt descending fibers from respiratory neurons in the medulla and pons
4. Due to somatotopic segregation of both spinothalamic tracts (hands and arms represented medially) a midline C3–C4 lesion may cause a dropped sensory level to the fingertips (C6–T1) or to the thorax (band like sensation)
 - a. There may be associated clumsiness of the hands (cuneocerebellar tract involvement proprioceptive input from the upper extremity to the intermediate cerebellar zone)
 - b. Usually, cervical spondylosis affects C5–C6 muscle groups to a greater degree than the C8–T1 groups (intrinsic hand muscles). The first dorsal interosseous muscle often atrophies very early with limb-onset ALS

C5–C6 Cervical Segmental Localization

The segmental muscle involvement causes weakness and atrophy of the supra and infraspinati, the deltoid, biceps, brachioradialis, medial and lateral pectoralii, latissimus dorsi, triceps, and the extensor carpi radialis muscles.

The inverted brachial reflex is elicited by a tap of the biceps tendon. There are no biceps reflex (flexion), and no brachioradialis induced supination but increased triceps activity (C7) and finger flexion (C8–T1). The reflex, as noted above is most often seen in cervical spine compression from cervical stenosis (degenerative arthritic changes) occurring in the exit foramina (osteophytes) and cord compression at C4 (ligament disc and facet hypertrophy). The spinal cord compression would disinhibit all reflexes below the level of compression (dysfunction of the cortical spinal tract). Due to the osteophytes or other pathologies at the C5–C6 exit foramina, the sensory stimulation cannot enter the cord at this level. Sensory afference to the cord is achieved by the stimulation of the biceps tendon which induced mechanical stimulation at C4 or C8 or T1.

The spinal cord is disinhibited at C7–C8–T1 (from the C4 lesion), and finger flexion is induced as well as increased activity of the triceps muscle. Usually, as noted the cause in severe cervical spondylosis. The neck will be forward flexed, and there will be decreased movement in all planes. There will be atrophy of the deltoid caps. The spondylitic process also occurs at L5–S1, so there may be increased knee jerks (cervical compression) and absent ankle jerks. The patient will be unable to tandem walk. This process is exceedingly common. Other pathologies at this level such as meningioma, AVM, metastatic are rare.

C7 Cervical Segmental Localization

1. Extension of the arm, wrist and fingers are primarily affected. There may be some weakness of finger flexion
2. Sensory loss is most prominent in the third finger: this becomes slightly complicated as loss of sensation to pin-prick of the third digit with decreased sensation of the thumb and index finger is a lateral cord brachial plexus distribution. Loss of pin-prick sensibility of the ulnar side of the third finger in conjunction with decreased sensation of the 4th and 5th digits is a medial cord brachial plexus sensory radiation. C7 alone may cause some medial forearm sensory loss
3. Similar to lesions at C5–C6 a paradoxical triceps reflex may be elicited. A triceps jerk may elicit flexion rather than extension due to its weakness and intact C5–C6 innervated musculature (biceps and brachioradialis). Most lesions here are spondylitic but trauma, and an occasional neurofibroma can selectively involve this root (or spinal nerve)

C8–T1 Localization

1. The major motor deficits occur in intrinsic hand muscles. If there is a compressive lesion at this level, there will be an associated spastic paraparesis. C8 lesions decrease the triceps reflex (C7–C8), and finger flexor reflexes (C8–T1). A T-1 lesion preserves the triceps, but finger flexion reflexes are decreased
2. Sensory loss occurs in the 5th digit and the medial forearm. The ulnar nerve splits the 4th finger and innervates a small triangle of skin above the wrist. Brachial plexus lower trunk lesions extend from the medial forearm to the medial arm. A Horner's syndrome occurs (ciliary center of Budge) on the side of the lesion. Most lesions at this level are from cervical spondylosis or trauma. The deep muscular branch of the ulnar nerve may be involved by chronic pressure (bicycle riders, specific work injuries) with consequent intrinsic hand muscle atrophy. Rarely monomelic ALS or Hirayama's syndrome may simulate this level. Venous congestion or arterial insufficiency from higher lesions may cause glove sensory loss that can extend as high as the elbows

Pathologies of the Thoracic Spinal Cord

Inflammatory lesions at this level are usually demyelinating. Neuromyelitis optica (NMO), an autoimmune disease (antibodies to Aquaporin 4) causes a three segment spinal cord lesion associated with optic neuritis. On the other hand, most MS lesions cause shorter transverse myelitis and often lesions of the posterior columns. Sarcoid may inflame the parenchyma but usually affects the dura at times enough to cause spinal cord compression. Idiopathic hypertrophic pachymeningitis (IgG4), lymphoma, rheumatoid arthritis and tuberculosis can symptomatically compress the spinal cord. Dural AVMs that hemorrhage are usually dorsal at low cervical to high thoracic levels. The hematoma produced may

compress the cord. Subdural hematomas from trauma and from anticoagulation compress the thoracic cord. Thoracic disc disease is rare and usually occurs with severe valsalva maneuvers or trauma but are very dangerous. The spinal canal is very tight at this level (12–24 mm), so minimal protrusion may be symptomatic. In the thoracic cord, sudden compression causes very rapid paraparesis. Diabetes, a syrinx, and amyloid destroy proprioceptive and pain fibers which may cause a thoracic Charcot joint. Extremely rarely ochronosis (homogentisic acidosis) and relapsing polychondritis may affect thoracic discs. Metastatic disease may be causative (usually one level, although prostate, breast and lung cancer may affect multiple levels). Multiple myelomas affect multiple levels; eosinophilic granuloma, giant bone cysts, osteoid osteoma usually occur monostically and compress the spinal cord from a pathological fracture. Osteoporosis with anterior vertebral body fracture are extremely painful and are common in postmenopausal women but rarely compress the cord. Ganglioneuromas, and chordoma (clivus and the sacral cord) and Ewing's sarcoma are rare tumors of the thoracic cord. An astrocytoma may infiltrate over a long distance and destroy anterior horn cells that innervate the paraspinal musculature asymmetrically giving rise to a C-shaped form of scoliosis (away from the side of the lesion). An S-shaped scoliosis is congenital (with compensatory curves) which is often asymptomatic. Diastatomyelia, a fibrous band that splits the spinal cord, and reduplication of the cord (two spinal cords with their own dural coverings) are rare congenital abnormalities. The thoracic cord may be the termination of septic emboli both from IV drug abuse and SBE (T4 is frequently the involved level). A devastating infection of the thoracic spinal cord is herpes type 6, which leads to necrosis with minimal recovery. West Nile fever, enterovirus 71, Echovirus 6 and Coxsackievirus A7 as well as polio all may involve the thoracic cord during a generalized CNS infection. Paraneoplastic disease with anti-Hu, Ma2/Ta, Purkinje cell autoantibody type 1 anti-CV2 and anti-Ri have all been described to affect the entire spinal cord. HTLV-1 may involve the thoracic cord to a greater extent than the cervical cord (tropical spastic paraparesis). Usually, HIV causes a vasculitic cervical myelopathy. The many forms of hereditary spastic paraparesis affect the thoracic spinal cord severely. In uncomplicated variants, only the spinal cord is affected while complicated variants are also associated with optic nerve, cerebellar, cortical and peripheral nerve involvement. Trauma of all kinds affects the thoracic spine. Specific anatomical syndromes such as the Brown-Séquard syndrome have been reported from knife, bullet wounds, X-RT therapy and compressive thoracic spine lesions. Spondylitic changes are rare as there are no motion segments of the thoracic spine.

Clinical Features of Thoracic Spine Lesions

Lesions at this spinal level cause root or intercostal nerve-like pain. It is usually lancinating and slightly higher posteriorly than anteriorly.

If it is a compressive lesion, there will be a sensory level (usually two segments below the involved segment) accompanied by bladder/bowel alteration and paraparesis. Rarely, there is a Brown-Séquard anterior cord or a central cord presentation.

If the lesion is above T5, there is postural hypotension from loss of sympathetic innervations to the abdomen and lower extremities. Autonomic dysreflexia may occur with higher lesions. This is manifested by:

1. Hypertension
2. Cutaneous flushing
3. Severe vascular-type headache
4. Bradycardia

It is usually precipitated by a bladder catheter change, rectal distension and the lack of prophylactic guanethidine use. It has been associated with intracranial hemorrhages.

If the lesion is at T10 a Beevor's sign may be elicited with neck flexion against resistance. The umbilicus rises 0.5–1.0 cm because lower rectus abdominis muscles are weak while T8–T9 muscles are normal. Occasionally the imbalance is reversed with partial lesions, and the umbilicus is displaced downward if a spinal lesion is above T6. Supraspinal lesions above T6 cause loss of abdominal reflexes. For a lesion at or below T10, the upper and middle abdominal reflexes are maintained. All abdominal reflexes are present if the lesion is below T12.

Overview of Pathology of the Lumbar spine

The lumbar spine is most often affected by mechanical problems from degenerative disc disease or the arthritic changes of spondylosis, spinal stenosis, and spondylolisthesis. The aging process is associated with desiccation of discs (hand disc) and remodeling of bone at motion segments. Nerve roots are trapped in their exit canals by osteophytes and the restoration of facet joints in addition to the loss of disc height.

Spinal stenosis occurs with ligament hypertrophy (dentate) and facet tropism (inward rotation) and hypertrophy. It is exacerbated if the patient has congenitally short pedicles and a tight canal. This is a problem in achondroplasia and many other orthopedic syndromes. The stenosis in achondroplasia occurs at the foramen magnum and T12–L1. Severe arthritis and disc degeneration cause spondylolisthesis which is a forward or backward displacement of the vertebral body. The malalignment places the exiting nerve roots under traction at several levels. In general L5–S1, (the major motion segment and the greatest load segment) suffers the most disc disease, while L4–L5 is more frequently the site of spinal stenosis.

Synovial cysts of the facet joint is a rare cause of radiculopathy but is encountered with severe degenerative disease. Facet hypertrophy with associated tropism (rotation of the inferior facet into the foraminal exit canal) is a common cause of radicular pain in older patients.

Spondylolisthesis may be congenital (poor ossification of the pars interarticularis) with consequent vertebral malalignment. It usually occurs at L4–L5 but may occur at any lum-

bar area. There may be either anterolisthesis or retrolisthesis. In the congenital form, there is usually maldevelopment of L4–5 innervated muscles that cause poor development of the gluteus maximus musculature (a pelvic “shelf”).

In adult populations, meningocele and its variations are rare. A tethered cord, in which the filum terminale is short causes the spinal cord to be lower than its usual vertebral level at L2. It is often associated with unilateral pes cavus, a neurogenic bladder, radiculopathy, and hyperreflexia. The lateral recess component of the nerve root exit canal, particularly at L4–L5 and L5–S1, may be congenitally narrowed which causes nerve root compression. Retroperitoneal hemorrhage, usually in patients on anticoagulation, causes severe lumbosacral root pain, hyperactive reflexes and motor weakness in the effected roots.

The retroperitoneal space may contain surprisingly large benign tumors and sarcomas. The lumbar roots at high levels may be damaged directly by neuropractic injury or by retractors during abdominal surgery. Lipoma, glioma of the filum terminale, and chordoma (also occur in the clivus) are particular to the lumbosacral cord. Lymphomas may occur anywhere in the spine. They tend to envelope the nerve roots of the cauda equina at this level. Sarcomatous degeneration of a lipoma cannot be operated as it is interdigitated within the nerve roots. Plexiform neurofibromas (NF1) occur in the lumbosacral cord.

CMV infections in very ill HIV patients, (<50 CD4+ T cells/mm³) are characteristic of the lumbosacral spinal cord. Rarely a syrinx or demyelinating disease may occur in the conus medullaris.

Clinical Features of Lumbosacral Segment Disease

L1 Segmental Level

An L1 segmental lesion weakens all muscles of the lower extremity. In addition, the lower abdominal musculature (internal oblique, transverses and rectus abdominus) are involved. Palpation reveals decreased tone in the lower abdomen and Beever's sign may be positive. There is a sensory loss at the level of the groin anteriorly and slightly above the buttocks posteriorly. Chronic lesions have exaggerated tendon reflexes at the knees (L2–L4) and the ankles (S1–S4).

L2 Symmetric Level

Abdominal musculature is normal, but chronic lesions cause spastic paraparesis. The cremasteric reflex is absent. There may be slight depression of the knee-jerk (L2 involvement with exaggerated ankle jerks (S1–S2)). Sensation is intact in the upper anterior thigh

L3 Segmental Level

There is a weakness of hip flexion (L1–L3; iliopsoas and sartorius) muscle weakness of leg adduction (adductor longus, gracilis and pectineus). Sensation is intact in the upper anterior thigh. The knee reflex is depressed.

L4 Segmental Level

There is a slight weakness of hip flexion, leg adduction, knee flexion and leg extension. The leg can be stabilized which permits standing. The knee jerk may be slightly depressed, and the ankle jerks are hyperactive. There is normal sensation of the thighs and superomedial knees.

L5 Segmental Level

The patient has normal strength of the quadriceps muscles and can extend the leg against resistance. The knee jerks are active and the ankle jerks hyperactive. The patient has sensation medially in the thighs, legs, and soles.

Segmental Lesions of the First and Second Sacral Segments

There is weakness of the gastrocnemius soleus, flexor digitorum longus, flexor hallucis longus and intrinsic foot muscles. Sensory loss is apparent over the sole, heel and lateral side of the foot and ankle. There is also sensory loss in the medial side of the calf, posterior thigh, and the lateral perineum. S2 lesions primarily affect the flexor digitorum, flexor hallucis longus, and intrinsic muscles of the foot. The ankle jerk is depressed. The sensory loss occurs in the dorsal calf, the dorsolateral thigh, and the perineum.

Bladder Physiology

Storage of urine and its periodic elimination is accomplished by two functional units in the lower urinary tract: a reservoir (the urinary bladder) and the bladder neck, urethra, and the urethral sphincter. The coordination of these two units is complex and is mediated by the brain, spinal cord, and peripheral ganglia. The neural circuits that control bladder function have switch-like or phasic patterns.

Storage and voiding are coordinated peripherally by three sets of peripheral nerves that are parasympathetic, sympathetic and somatic. Afferent sensory fibers from the lower urinary tract to the lumbosacral cord are A δ (thinly myelinated 1–4 μ) and unmyelinated C-fibers. A-delta fibers innervate the detrusor smooth muscle layer and respond to stretch which is perceived as fullness. C-fibers innervate muscles adjacent to the urothelium cells.

1. The sympathetic fibers from thoracic level T11 through L2 project to the inferior mesenteric ganglion. The postganglionic fibers from the hypogastric nerve which stimulates urethral smooth muscle utilizing adrenergic receptors. It inhibits the detrusor muscle by activating B3 adrenergic receptors (NE is the ligand)
2. The parasympathetic pelvic nerves take origin from sacral neurons at S2–S4. They synapse in the pelvic ganglia and innervate (stimulate) the detrusor muscle by means of muscarinic (ACh and purinergic (P2X) receptors whose ligand is ATP and reciprocally inhibits urethral smooth muscle by nitric oxide (NO))
3. The somatic pudendal nerve stimulates the somatic striated muscle of the external urethral sphincter. Acetylcholine is the neurotransmitter

4. Glutamate is the neurotransmitter in sensory afferents from the bladder. Substance P and calcitonin gene-related peptides are additional neurotransmitter colocalized with glutamate in C-fibers

The Storage Phase

The bladder has low levels of pressure during filling due to the intrinsic viscoelasticity of the detrusor muscle. The detrusor muscle and the stimulatory parasympathetic system is inactive during filling until a critical threshold for voiding is attained. Supraspinal projections are contributory to this inhibition.

The guarding reflex (initiated by bladder distension) activates stretch mechanoreceptors in the bladder wall which synapse on sacral (S2–S4) ventral horn pudendal neurons. Efferents from the pudendal nerve stimulate the contraction of striated muscle of the external urinary sphincter which maintains continence.

As the bladder fills and distends, the thoracolumbar sympathetic nerves are stimulated which contracts the internal urethral sphincter and inhibit bladder wall contraction. These storage reflexes are maintained in the spinal cord but may be modulated supraspinally. The pontine micturition center (by means of the reticulospinal tract) activates pudendal neurons that increase urethral resistance.

Voiding Phase

Initiation and completion of voiding are dependent on brain input. Bladder efferents in the pelvic nerve synapse in the spinal cord and beyond and from these second order neurons (S2–S4) ascend to the pontine micturition center. Information from the cortex and subcortical nuclei is integrated with bladder derived sensory afference. Descending projections inhibit sympathetic and somatic neurons in the spinal cord and stimulate parasympathetic neurons. The activation of the spino-bulbo-spinal reflex relaxes the external urethral sphincter, the internal urethral sphincter, and contracts the detrusor muscle which increases bladder pressure and initiates voiding.

The role of the uroepithelium is very important in bladder pathologies from spinal cord disease but is beyond the scope of this presentation.

Clinical Localization of the Neurologic Causes of Bladder Dysfunction

1. Neurogenic spastic bladder:
 - a. Occurs with lesions above sacral bladder neurons (S2–S4) and below the pontine micturition center
 - b. Primary pathologies are spinal cord injury and demyelinating disease. Any destructive lesion at this level can be causative
 - c. Associated with quadriplegia or paraplegia
2. Due to loss of supraspinal inhibition, the detrusor muscle is hyperactive and may contract spontaneously or with coughing or changing posture. This causes:
 - a. Urinary frequency and urgency
 - b. Urge incontinence
 - c. Inability to voluntarily initiate micturition

3. The bladder capacity is small, but there is post-micturition residual from inadequate contraction

Clinical Features

1. Intact bulbocavernosus and anal reflexes
2. If the lesion is above T10 (the splanchnic hypogastric nerve) a distended bladder may produce a mass reflex:
 - a. Paroxysmal hypertension
 - b. Headache (vascular type)
 - c. Diaphoresis
 - d. Reflex bradycardia
3. Detrusor-sphincter dyssynergia:
 - a. A simultaneous contraction of the detrusor muscle and the external urethral sphincter during voiding
 - b. Occurs most often with lesions in the thoracic spinal cord but can be caused by any lesion that blocks descending control of voiding mediated by the pontine micturition center
 - c. Dyssynergia causes:
 - i. Obstructed voiding
 - ii. An interrupted urinary stream
 - iii. Increased residual urine
 - iv. High intra-vesicle pressure (the external urinary sphincter is closed during detrusor contracture)
 - v. Detrusor contraction may be poorly sustained

Spinal Cord Injury

1. Spinal shock supervenes with acute spinal cord injury. If severe there is flaccid paralysis, complete sensory loss and a paralyzed bladder below the level of the lesion. The bladder regains reflex detrusor activity usually within six weeks. Dyssynergia is common with recovery. Spinal shock may be prolonged
2. Detrusor areflexia may occur with lesions below T12 (autonomous neurogenic bladder). A lesion at this spinal level compromises the conus medullaris and the cauda equina
 - a. The bladder is insensate, and the detrusor is paralyzed
 - b. Most often there is urinary retention with bladder distension
 - c. Overflow incontinence with marked increase residual urine occurs
 - d. There is saddle anesthesia with the loss of the bulbocavernosus and superficial anal reflexes. The anal sphincter may be concomitantly paralyzed
 - e. Prolonged bladder distension may cause degenerative changes in the detrusor muscle with bladder atonia and a consequent large residual urine

Motor Paralytic Bladder

1. Injury to the pelvic nerve (innervates the detrusor) or its origin in the sacral spinal cord (S2–S4) may occur from:

- a. Spinal stenosis
- b. Lumbosacral meningocele or its repair
- c. Hysterectomy
- d. Abdominis perineal resection
- e. Trauma
- 2. Clinical features include:
 - a. Painful urinary retention
 - b. Inadequate bladder emptying
 - c. Increased residual urine
 - d. Absent bulbocavernosus and superficial anal reflexes
 - e. Intact sacral and bladder sensation

Sensory Paralytic Bladder

1. Loss of the A-delta and C-fiber innervations of the bladder has been described with spinothalamic and dorsal column spinal cord lesions
2. Urinary retention, overflow incontinence, and frequent infections are common
3. Voluntary initiation of micturition is preserved
4. Bulbocavernosus and anal reflexes may be altered
5. The usual pathologies are:
 - a. Tabes dorsalis
 - b. CMV infection in HIV patients
 - c. Syringomyelia
 - d. Diabetes mellitus
 - e. Amyloid

Fecal Incontinence

The anal sphincter complex comprises the internal and external sphincter:

1. The internal sphincter:
 - a. Accounts for 80% of resting sphincter pressure
 - b. Smooth muscular autonomic control
- c. External sphincter:
 - i. Slow twitch type I striated muscles
 - ii. Innervated by the pudendal nerves (neurons in the ventral horns of S2–S4) and the puborectalis muscle (innervated by the pelvic branches of S3 and S4)
 - iii. The external sphincter and the puborectalis muscle are the voluntary sphincter muscles. A spinal reflex causes contraction of the external sphincter with valsalva maneuvers
 - iv. Mechano stretch receptors in the pelvic floor detect stool in the rectum and are necessary for continence. The usual causes of rectal insensitivity are:
 1. Diabetes mellitus
 2. Autonomic neuropathy
 3. Pudendal neuropathy (trauma and abdominal surgical procedures)
 - v. Rectal insensitivity causes overflow incontinence
 - vi. Fecal incontinence in the elderly is most often due to constipation
2. Clinical manifestations depend on the specific etiology as fecal incontinence can be caused by dysfunction of sen-

sory and motor roots (S3–S4), compression or intrinsic or peripheral neuropathies:

- a. Reduced sphincter tone
- b. Loss of perianal sensation and the anal skin reflex
- c. Laxity of the anal sphincter from deafferentation
- d. Lesions above the conus may cause urgent defecation
- e. Spinal cord pathology often causes both urinary and fecal incontinence

Anatomy of Male Sexual Function

Many aspects of peripheral nerve and central nervous system anatomy that control erectile and ejaculation function have not been elucidated. The genitals are innervated by:

1. The sacral parasympathetic (pelvic nerves)
2. The thoracolumbar sympathetic chain at T4–L2 which protects the inferior hypogastric plexus and whose postsynaptic axons become the hypogastric nerve
3. The pudendal nerve which carries somatic sensation

The sacral parasympathetic system derived from neurons at S2–S4 whose preganglionic axons are in the pelvic nerve synapses in the pelvic plexus. Postsynaptic fibers are carried in the cavernous nerves that mediate dilatation of the corpora cavernosa by the release of nitric oxide. There is some evidence for a sympathetic component from T12 in the process. Descending pathways for erection mechanisms are in the lateral columns of the spinal cord. A spinal cord lesion above T12 impairs the psychogenic component of an erection while a complete lesion of the conus medullaris or cauda equina abolishes a reflex erection. There is some evidence that a psychogenic erection can occur from intact sympathetic innervations.

Neurons in the medial preoptic anterior hypothalamus project to the spinal cord in the median forebrain bundle (traversing the midbrain tegmentum and lateral pons) are particularly important in the erectile process. Ejaculation is proposed to occur from innervation at T12–L1. Reflex ejaculation is possible if afferent innervations (S2–S3) and efferent pathways from (T10–L2) are intact.

Conus Medullaris Syndrome

Varied pathology affects the conus medullaris. In general, there is weakness of the muscles of the pelvic floor (coccygeus, ileococcygeus and pubococcygeus) associated with bowel, bladder, and sexual dysfunction:

1. The patient has an anesthetic bladder, cannot initiate micturition and has a large volume of residual urine
2. Most often the patient is constipated
3. The patient cannot achieve an erection or ejaculate. There may be dissociated sexual function (ability to achieve an erection but inability to ejaculate). Saddle anesthesia is present
4. Pain is rare and a late complication that involves thighs, buttocks, and perineum. There is no extremity weakness or reflex change. The cauda equina and epiconus may be involved

Differential Diagnosis of Conus Medullaris Lesions

1. Demyelinating disease
2. Myxopapillary ependymoma
 - a. Most commonly occur in the conus medullaris-filum terminale
 - i. Conus medullaris syndrome occurs early with asymmetric lower extremity reflex loss
 - ii. The majority of the tumors arise in the spine, and approximately 20% occur from extramedullary sites
3. Cavernous malformation:
 - a. Approximately 1.7% intraspinal cavernous malformations arise in the conus medullaris
 - b. Most patients have a slowly progressive course but a significant proportion of patients have an acute onset with step-wise progression
 - c. Annual rate of hemorrhage is 2%
4. Sacrococcygeal development abnormalities:
 - a. Most often diagnosed in childhood
 - b. Associated with spina bifida occulta
 - c. Developmental abnormalities and tumors:
 - i. Myelomeningocele
 - ii. Meningocele
 - iii. Lipomyelomeningocele and lipoma
 - iv. Dermoid cyst
 - v. Hamartoma
 - vi. Short filum
 - vii. Hind gut cysts
 - viii. Teratoma
 - ix. Ependymomas (may be completely subcutaneous)
 - x. Neuroblastoma
 - xi. Rhabdomyosarcoma
 - d. Conus medullaris syndrome following radionuclide cisternography
 - e. Dural arteriovenous fistula

Tethered Cord Syndrome (TCS)

Tethered cord syndrome is a stretch-induced functional disorder of the spinal cord. Symptoms of a congenital tethered cord are most common in childhood, but symptoms may manifest in adulthood. Patients have an elongated spinal cord and a thick filum terminal. Three categories of TCS have been proposed:

1. A lumbosacral cord under traction from an anchored inelastic filum
2. Caudal and sacral myelomeningocele
3. Two groups of patients:
 - a. Paraplegia myelo- and lipomyelomeningocele with no functional lumbosacral neurons
 - b. Asymptomatic patient with an elongated cord and thick filum

The disease is progressive. Many adult patients suffer back and leg pain as well as bowel and bladder dysfunction. A great number of patients suffer components of spinal dysraphism in conjuncture with their tethered cord. These include:

- a. Spina bifida occulta
- b. Myelomeningocele
- c. Lipoma
- d. Lipomyelomeningocele
- e. Dermoid sinus
- f. Diastematomyelia

Clinical Manifestations

1. Backache
2. Pes cavus
3. Atrophy of the calf or thigh muscles
4. Equine VAS
5. Scoliosis
6. Bowel and bladder alterations
7. Hyperactive reflexes:
8. Cutaneous manifestations of dysraphism:
 - a. Midline hypertrichosis
 - b. Dermal sinus tract (usually a dimple in the midline spine)
 - c. Midline nevus
 - d. Subcutaneous sacral lipoma

Cauda Equina Syndrome

The usual cause is lumbar and sacral root compression below L3.

Clinical Manifestations

1. Asymmetric radicular pain in a lumbosacral root distribution
2. Bowel, bladder, and sexual dysfunction
3. Saddle anesthesia that involves the anal, perianal and genitalia
4. Flaccid, atonic, areflexic paralysis in the distribution of the involved roots
5. Characteristic L5–S1 sensory loss in the legs

Differential Diagnosis

1. Herniated disc
2. Ependymoma
3. Myxopapillary ependymoma
4. Schwannoma
5. Meningioma
6. Lymphoma
7. Metastasis

Differential Points Between Conus Medullaris Versus Cauda Equina Lesions*Conus Medullaris*

1. Early bowel, bladder and sexual dysfunction
2. Symmetric sensory loss
3. Late pain

Cauda Equina

1. Early pain
2. Asymmetric sensory loss
3. Late sphincter involvement

Epiconus Lesions (Spinal Cord Segments L4–S1)

Anatomically this area is spinal segment T10–L1. Lesions involve bladder, bowel, and sexual function as well as pain and leg weakness. A Babinski sign is present.

Trauma, congenital defects, spinal stenosis (achondroplasia) trauma, demyelinating disease and tumors (myxopapillary ependymomas, chordoma, metastasis hemangioblastoma occur at this level.

Trauma

The thoracic and lumbar junction (thoracolumbar junction) are particularly vulnerable to fracture and dislocation. High thoracic level (T1–T10) are stabilized by the rib cage and the intercostal muscle.

The lumbar vertebrae (L3–L5) are more stable because they are larger stronger and have muscular support. For these regions, the majority of thoracic and lumbar spine injuries occur at the T11–L2 level. In general, the conus medullaris terminates in the lower third of the L1 vertebra, but can vary between the lower third of T11 to the upper third of L3. Fracture at the thoracolumbar junction may damage the spinal cord, conus medullaris or the cauda equina.

Lesions of the epiconus affect the lumbar cord and the roots that supply the lower legs and feet but spare sacral roots. Trauma is rarely pure, and epiconus lesions may have conus medullaris and cauda equina components.

Neuropathy from Vertebral Fractures of the Thoracolumbar Junction Classification

1. Upper lumbar cord
2. Epiconus and lumbar roots
3. Conus medullaris and/or cauda equina

Approximately 50% of thoracolumbar junction fracture suffer epiconus lesions and present with flaccid legs and a spastic neurogenic bladder.

Congenital Spinal Defects**Overview**

In general, most of the congenital defects that affect the spinal cord involve failure of fusion of dorsal midline structures of the neural tube which occurs during gastrulation (weeks 2–3), primary and secondary neurulation (weeks 5–6). Spinal dysraphisms are characterized as open or closed:

1. Open dysraphism:
 - a. Exposure of abnormal nervous tissue through a skin defect
 - b. Include myelomeningocele myelocele and meningocele
2. Closed spinal dysraphism:
 - a. Associated with low back subcutaneous masses that include lipomyelocele, lipomyelomeningocele, meningocele, and myelocystocele

- b. Closed spinal dysraphism without a mass include:
 - i. Tight filum terminale
 - ii. Filum and intradural lipomas
 - iii. Persistent terminal ventricle
 - iv. Dermal sinus
 - v. Complex dystrophic states
 1. Defects of midline notochord integration (primarily diastematomyelia)
 2. Defects of segmental notochordal formation:
 - a. Caudal agenesis
 - b. Spinal segmental dysgenesis
- c. Abnormalities of closure of the vertebral arches:
 - i. Spina bifida occulta
 - ii. Meningocele (primarily lumbosacral)
 - iii. Meningomyelocele

Spina Bifida Occulta

1. The spinal cord remains in the canal; no external sac
2. Cutaneous signs of the defect may include a subcutaneous lipoma, dimple or area of hypertrichosis

Meningocele

1. Protrusion of the dura and arachnoid between the non-fused vertebral laminae
2. Cystic swelling in the lumbosacral area
3. The spinal cord remains in the canal

Meningomyelocele

1. More frequent than meningocele
2. The cauda equina more frequently than the cord is extruded and is attached to the cystic mass
3. Clinical features:
 - a. Primarily sacral involvement that affects sphincters
 - b. Lower lumbar and sacral involvement. The buttocks and lower leg (L4–S1) roots are more involved than the hip flexors (L1–L3) and the quadriceps
 - c. Upper lumbar involvement; the feet and legs are less involved, ankle jerks may be present as well as a Babinski response
 - d. An associated anomaly is a Chiari malformation with hydrocephalus

Congenital Defects That May Produce Symptoms in Adult Life

1. Sinus tracts (recurrent meningitis)
2. Lumbosacral lipomas with tethered cord
3. Diastematomyelia
4. Cysts
5. Tumors with spina bifida
6. Chiari malformation and syringomyelia

Sinus Tracts

1. May be associated with a dimple (usually off the midline) or by an area of hypertrichosis (midline)

2. The tract may connect to a myelocele which may be associated with a dermoid cyst or a fibrolipoma in the middle of the tract
3. Cloacal defects (no abdominal wall and no separation between bladder and rectum) occur with anterior meningoceles
4. Sinus tracts are associated with recurrent meningitis

Congenital Cysts and Lipomas

1. Associated with tethered cord

Diastematomyelia

1. A fibrous band or bony specula from the body of a thoracic or upper lumbar vertebra
2. Divides the spinal cord into halves for a variable distance
3. May be associated with a reduplicated spinal cord each with its own dura and spinal roots (diphomyelia)
4. Clinical manifestations:
 - a. Pain
 - b. Bladder (neurogenic)
 - c. Sensory loss
 - d. Weakness of leg muscles

Occult Dysraphism

1. Occurs in the lumbosacral segments
2. Due to abnormalities of the cell mass, that is caudal to the posterior neuropore
3. Associated with:
 - a. Meningocele
 - b. Lipomas
 - c. Sacrococcygeal teratomas

Caudal Regression Syndrome

1. A genesis of the sacrum (may also involve the lower lumbar vertebrae)
2. Clinical manifestations:
 - a. Flaccid paralysis of the legs
 - b. Arthrogrypotic contractures of the legs and feet
 - c. Urinary incontinence
 - d. Normal mentation
 - e. No hydrocephalus

Congenital Anomalies of the Cranial Cervical Junction

1. Congenital fusion of the atlas and foramen magnum:
 - a. If the anteroposterior diameter of the canal is <19 mm there is spinal cord compression at this level
 - b. Associated with fusion of the second and third cervical vertebrae
 - c. Associations of atlanto-occipital fusion:
 - i. Basilar invagination
 - ii. Atlantoaxial instability
 - iii. Vertebral fusion

- iv. The odontoid process may prolapse into the foramen magnum due to the decrease in vertical height of the atlas
- d. Unilateral hypertrophy of the lateral mass of the atlas:
 - i. Associated with atlanto-occipital fusion and an invaginated lateral mass of the atlas and odontoid process that protrudes into the foramen magnum
 - ii. Severe myelopathy caused by compression
- e. Congenital Atlas Hypoplasia:
 - i. Anomalies of the posterior arch of the atlas range from partial clefts to total agenesis
 - ii. May be associated with cervical canal stenosis at C1–C3

Congenital Abnormalities of the Odontoid Process

1. Complete separation of the odontoid process from the axis:
 - a. The atlas is displaced anteriorly in relation to the axial (atlantoaxial dislocation):
 - i. Acute or chronic spinal cord compression
 - ii. Sore neck with limitation of movement in all planes

Os Odontoideum

1. Os odontoideum is an independent piece of bone varying in size. It has a smooth circumferential cortical margin that is separated from a shortened odontoid peg evidence suggests it is traumatic rather than congenital
2. May be asymptomatic or a cause of myelopathy

Morquio Syndrome

1. AR; Mucopolysaccharidoses
 - a. Deficiency of N-acetylgalactosamine-6-sulfatase type IVA and type IVB (deficiency of B-galactosidase)
 - b. Defective degradation of keratan sulfate
2. Skeletal abnormalities:
 - a. Hypoplasia of the odontoid process
 - b. Short neck, pectus carinatum, thoracic kyphoscoliosis and dwarfism
3. Associated anomalies:
 - a. Joint laxity
 - b. Dental abnormalities
 - c. Deafness
 - d. Cardiac defects
 - e. Respiratory dysfunction
4. Neurologic manifestations:
 - a. Atlantoaxial subluxation
 - b. Spinal cord compression

Achondroplasia

1. Most common form of congenital short-limbed dwarfism
2. Genetics:
 - a. AD; 80% are spontaneous mutations
 - b. Mutation G380R mutation in fibroblast growth factor receptor 3 (FGFR3)

- c. Failure of conversion of fetal cartilage to bone in the growth plate. There is increased periosteal bone formation which thickens the vertebral bodies, neural arches, laminae and pedicles (shortened)
- d. Neurologic manifestations:
 - i. Craniocervical stenosis
 - ii. Tight foramen magnum; short clivus
 - iii. Medullary and upper spinal cord compression
 - iv. Lax ligaments
 - v. Hydrocephalus (in patients with stenotic foramen magnum)
 - vi. Children:
 - 1. Central apnea
 - 2. Leg spasticity
- 3. MRI evaluation
 - a. Some achondroplasia patients have a hyperintense T2-weighted signal in the cervical medulla without concomitant focal spinal cord compression. This occurs just below the craniocervical junction between C1–C2 in the gray matter

Platybasia and Basilar Impression

- 1. Platybasia is a flattening of the base of the skull measured by the angle made by the clivus and the plane of the anterior fossa. This angle should not be greater than 135 degrees
- 2. Basilar Impression or Invagination
 - a. An upward displacement of the occipital condyles above the plane of the foramen magnum
- 3. Clinical features of platybasia and basilar impression
 - a. Short neck with restriction of movement in all planes
 - b. Platybasia without basilar impression is asymptomatic
 - c. Basilar impression with indentations of the anterior medulla is associated with:
 - i. Brainstem dysfunction
 - ii. Lower cranial neuropathies
 - iii. Neurogenic dysphagia
 - iv. Hoarseness (involvement of the levator palatini and vocal cords)
 - v. Sleep apnea
 - vi. Intermittent or spastic quadriparesis
 - vii. Tussive headache (C2)
 - viii. Gait disturbance
 - ix. Syncope (with valsalva maneuvers)

Klippel-Feil Syndrome (KFS)

General Characteristics

- 1. A congenital cervical vertebral fusion due to a failure of segmentation
- 2. Associated with basicranial malformations, atlas assimilation and dens malformations
- 3. Classification of subtypes:
 - a. Type I
 - i. Single congenitally fused cervical segment
 - b. Type II

- i. Multiple non-contiguous congenitally fused segments
- c. Type III
 - i. Multiple contiguous congenitally fused segments
- d. Radiographically:
 - i. 25% are Type I
 - ii. 50% are Type II
 - iii. 25% are Type III
- 4. Neurologic manifestations:
 - a. Axial neck symptoms are associated with type I patients
 - b. Type II and III have radicular and myelopathic symptoms and signs
 - c. Mirror hand movements

Hereditary Spastic Paraplegias

Almost all of the congenital cervical spinal cord abnormalities are associated with syringomyelia.

Syringomyelia

General Characteristics

- 1. A chronic progressive degenerative or congenital disorder of the spinal cord
- 2. Cavitation of the central spinal cord although it may be asymmetrical
- 3. The cervical cord is the most common spinal segment involved, but there may be extension to the medullar and pons (syringobulbia) or into thoracic and lumbar spinal cord segments
- 4. There often are associated developmental abnormalities that include:
 - a. Thoracic scoliosis
 - b. Klippel-Feil malformation
 - c. Platybasia
 - d. Basilar invagination
 - e. Chiari I malformation

Acquired Causes of Syringomyelia

- 1. Trauma
- 2. Tumors that include:
 - a. Astrocytoma
 - b. Hemangioblastoma
 - c. Ependymoma
- 3. Hemorrhagic cord necrosis
- 4. Phase contrast MRI techniques provide excellent cerebrospinal fluid imaging that demonstrates:
 - a. Decreased absorption mechanisms of extracellular fluid
 - b. Blockage and alterations of CSF dynamics at the foramen magnum have been postulated as etiologic

Modified Barnett Classification of Syringomyelia

- 1. Type I
 - a. Obstruction at the foramen magnum and dilatation of the central canal

- i. Associated with Chiari I malformations
 - ii. Associated with other high cervical bony malformations
- 2. Type II
 - a. Syringomyelia without obstructions of the foramen magnum (congenital)
- 3. Type III
 - a. Syringomyelia with other diseases of the spinal cord (acquired)
- 4. Type IV
 - a. Pure hydromyelia (developmental dilations of the central canal with or without hydrocephalus)

Clinical Manifestations

1. Dependent on the four types particularly those with associated developmental abnormalities
2. Type I developmental or congenital type:
 - a. Onset is usually between 20–24 years of age
 - b. Insidious onset with an irregularly progressive course
 - c. Valsalva maneuvers or trauma may initiate or exacerbate signs

Neurologic Signs

1. Amyotrophy of muscles innervated by specifically innervated anterior horn cells affected by the lesion
2. Loss of pain and temperature sensation at the segmental level; normal sensation above and below the lesion (suspended sensory loss)
 - a. Disruption of the crossing fibers of the spinothalamic tract in the ventral white commissure (“cape” sensory loss)
3. Light touch, vibration, position sensibility is intact. Occasionally the syrinx is asymmetric, and the cavity expands laterally or dorsally, and other modalities may be involved
4. Claw hand in late stages (cervical syrinx) both thenar and hypothenar eminences are involved; frequently the 4th and 5th fingers are involved first; the “benediction” sign
5. Horner’s syndrome (C8–T1 involvement); destruction of the ciliary center of Budge (loss of intermediolateral column at C8–T1)
6. Bowel, bladder and impotence involvement is late
7. Loss of segmental reflexes at the involved level; hyperactive reflexes below the level
8. Babinski sign is present with corticospinal tract involvement
9. Pain may be severe early in the course of the illness; deep ache or burning quality (neuropathic central pain)
10. Associated syringobulbia may occur (rostral extension of the syrinx; this often is at the level of descending tract of the Vth cranial nerves)
11. Severe thoracic scoliosis (paraspinal muscle involvement)
12. Rarely there is extension into the centrum semiovale (syringoencephaly)

13. Charcot joints occur (shoulder, thoracic spine or hip); lack of pain (no protective reflexes). Joint destruction occurs from repeated small traumas or loss of trophic support
14. Autonomic dysregulation of the affected segment; subcutaneous neurogenic edema
15. Very commonly associated with the Chiari I malformation
16. Painless injuries; particularly burns of the hands
17. Approximately 25% of cervical syrinxes are associated with cervico-occipital malformations

Clinical Features of an Associated Chiari I Malformation

1. Nystagmus; may be down-beat in primary gaze; rotary if vestibular nuclei involved (concomitant syringobulbia)
2. Head and neck pain; lancinating C2 pain with Valsalva maneuvers particularly cough
3. Corticospinal and sensory loss in the lower extremities
4. Hydrocephalus
5. Craniocervical malformations
6. Hydrocephalus

Association of Syringomyelia with an Intramedullary Tumor

1. Clinical manifestations:
 - a. A large dissociated sensory loss
 - b. There are characteristic retinal and cerebellar hemangioblastoma if associated with Von Hippel-Lindau disease

Post-Traumatic Syrinx Clinical Manifestations

1. Delayed (at times years) spread of sensory or motor loss characteristically above the originally involved segments
2. Also associated with arachnoiditis and cord atrophy

Congenital Bony Defects That Compromise the Spinal Cord or Root Exit Foramina

Developmental Spinal Stenosis

1. General considerations
 - a. Measurements:
 - i. Cervical cord C2–C7 (24–26 mm)
 - ii. Thoracic cord (>14 mm)
 - iii. Lumbar cord L1–L5 (>24–26 mm)
2. Block vertebrae (all achondroplasia patients)
3. Short pedicles
4. Trefoil configurations of the canal (lumbosacral levels)
5. Lateral recess stenosis (primarily at the L5–S1 level)

Ossification and Ligament Abnormalities of the Axis, Atlas and Odontoid Process

1. There are five ossification centers in the axis and atlas that may have developmental abnormalities:
 - a. The body and tip of the axis

- b. The lateral mass of C1 and the central part of the axis
- c. A fracture through the most rostral ossification center of the odontoid separates the tip from the body and is frequently asymptomatic
- d. The odontoid process has three major ligaments that anchor it to the skull:
 - i. Posterior cruciate (most important)
 - ii. Two lateral ligaments
 - iii. In an adult during flexion, the atlas should not move more than 3 mm from the axis. In children, the separation may be up to 5 mm
 - iv. The tip of the odontoid process should not extend rostrally more than 3 mm above a line from the hard palate to the inner table of the skull at the foramen magnum (Chamberlain's line). Bull's and the digastric line are other measurements of this parameter that are rarely used. If the odontoid rises above this line, it invaginates (compresses) the ventral medulla
 - v. A tip of the odontoid process fracture is usually asymptomatic and can occur with violent neck flexion
 - vi. The base of the odontoid process may fail to ossify with concomitant basilar invagination
 - vii. Gorlin syndrome:
 - 1. Short atlas
 - 2. Concomitant odontoid malformations

Differential Diagnosis of Congenital Spine Defects

The general physical examination is most helpful with this differential diagnosis. A patient with a short neck with decreased movement to all planes suggests basilar impression or platybasia. Acquired causes are associated with Paget's disease, osteogenesis imperfect (blue sclera), rheumatoid arthritis (ulnar hand deviation) and rarely rickets (except in parts of Africa).

Intermittent lower cranial nerve involvement, particularly hoarseness is common from intermittent brainstem vascular insufficiency with head movement as platybasia with basilar impression causes vertebral artery occlusion. In a patient with increased reflexes induced by neck flexion, there may be excess mobility of the spine at C1–C2 atlantocervical dislocation; this is often accompanied by paresthesia of the hands. In adults, transverse cruciate destruction and laxity are most often encountered in severe rheumatoid arthritis (pannus). It may occur with congenital collagen gene defects, mucopolysaccharidoses (Morquio's type IV; absent odontoid), trisomy 21 and trauma. A short neck with low hairline and limitation of movement is common with osseous cervical congenital malformations.

Chiari I malformation have a shallow posterior fossa and are often associated with a cervical syrinx. Hoarseness and ataxia point to this diagnosis as does a C2 headache induced by a severe cough. A cervical syrinx may present with unilat-

eral hand wasting, a "cape" sensory loss and painless burns on the hands and arms.

An acquired thoracic spine scoliosis or kyphoscoliosis point to diastematomyelia, a reduplication of the spinal cord, diplomyelia or an extensive syrinx. If the scoliosis is C-shaped, there is asymmetric paraspinal muscle involvement. An S-shaped configuration is congenital with muscle compensation. An astrocytoma may also grow asymmetrically; motor neuron disease and primary muscle disease may affect paraspinal musculature asymmetrically. Severe scoliosis and kyphosis also occur with Emery-Dreifuss muscular dystrophy, fiber type disproportion, and limb-girdle muscular dystrophy type II B (LGMD11B). A syrinx may be asymmetric and extend from the cervical to the sacral cord producing a C-shaped scoliosis. Painless burns on the hands and arms, a suspended sensory loss, segmental atrophy and a "Chariot" joint identify this diagnosis.

A tethered cord may be announced in young women during delivery. The dorsal lithotomy position during a difficult birth may cause paralysis of the legs. It is usually associated with unilateral weakness and wasting of the lower extremity associated with pes cavus, bladder dysfunction, and hyperreflexia.

Tufts of hair, strawberry hemangiomas, a skin dimple, and a sacral mass often have underlying spinal and vertebral body defects. These include spina bifida occulta, A-V malformation, hemangioblastomas, and myelomeningoceles. A tuft of hair off the midline may be the marker of a neurenteric cyst or sinus tract that connects with a myelocele.

A short neck and abnormally raised and malformed shoulder and scapula is the Klippel-Feil syndrome with Sprengel's deformity.

Trauma to the Vertebral Column with Spinal Cord Injury

Overview

In civilian practice, the most common causes of vertebral trauma and spinal cord injury are:

1. Motor vehicle accidents
2. Falls
3. Gunshot and stab wounds
4. Diving accidents
5. Crushing industrial accidents
6. Birth injury

The annual incidence of spinal cord injury in the USA is five patients per 100,000 people. Males predominate at approximately 4:1. Approximately 5,000 patients per year die from their spinal injuries. There is frequently a concomitant head injury.

Vertebral Column Injuries

1. Classification
 - a. Fracture-dislocation

- b. Pure fractures
- c. Pure dislocations
- 2. The spinal cord is injured by direct compression from bony fragments or by buckling of intraspinal ligaments. Fracture dislocations of the vertebral column are most frequent and result from force applied at a distance
- 3. All three types of vertebral column injury are caused by a vertical compression with antero or retroflexion (hyperextension)
- 4. The most important parameters in the mechanics of vertebral column and spinal cord injury are:
 - a. Structure of the bones and ligaments at the site of injury
 - b. Intensity direction and point of impact of the force
- 5. Head injuries often cause concomitant cervical spine injury, may fracture the atlas and odontoid process

Acute Cervical Flexion Injury

- 1. The cervical vertebrae are jammed together at the level of the injury
- 2. The anterior inferior edge of the superior vertebra is driven into the next lower level vertebra fracturing it
- 3. The posterior portion of the fractured vertebral body is displaced backward which compresses the spinal cord
- 4. The interspinous and posterior longitudinal ligaments are torn
- 5. Less severe anterior flexion causes dislocation of adjacent vertebrae without spinal cord injury
- 6. Exacerbation of this injury occurs in association with severe cervical spondylosis, a congenital narrow canal, and ankylosing spondylitis
- 7. Extrusion of discs material has occurred with holding in patient's neck in flexion

Hypertension Injuries of the Cervical Spine

- 1. Vertical compression with the head in extension
- 2. Force is primarily on the laminae and pedicles of the mid-cervical vertebrae (C4–C6). The fractures may be unilateral or bilateral, and the anterior ligament is buckled or ruptured
- 3. The displacement compresses the cord between the laminae of the lower vertebrae and the body of the superior one
- 4. Inward buckling of the ligamentum flavum may compress the cord without misalignment of vertebrae, or they have realigned spontaneously

Severe Compression Injuries

- 1. Affects the thoracolumbar area (ski injuries and falls)
- 2. Burst vertebral bodies (a central area of compression with fracture lined radiating outwardly)
- 3. Bone splinter and disc material may extrude into the spinal cord
- 4. Anterior vertebral body wedge fracture. Common in elderly osteoporotic women from minimal trauma (opening a window). Usually only local pain with no neurologic deficit (exacerbated with breathing)

Rotational Injury

- 1. Unilateral pars interarticularis fracture or facet injury
- 2. Rotary facet dislocation. Very difficult to appreciate radiologically. Suspected from increased intraspinal distance at that level and persistent focal spine pain (rupture of an interspinous ligament) and torticollis to the ipsilesional side

Specific Vertebral Fracture and Dislocations

- 1. Rotary force to the head
- 2. Displacement of the occipital condyle in relation to lateral masses of C1
- 3. Atlantoaxial dislocation:
 - a. Flexion forces
 - b. Dislocation of C1–C2
 - c. Myelopathy
- 4. Jefferson fracture of C1:
 - a. Axial downward force on vertex of the head
 - b. Bilateral anterior and posterior arch fracture at C1
 - c. Disruption of transverse ligament
 - d. Often asymptomatic
- 5. Odontoid (dens) fracture:
 - a. Hyperflexion
 - b. C2:
 - i. Type I – tip of the dens
 - ii. Type 2 – base of the dens
 - iii. Type 3 – body of C2
 - c. Asymptomatic to severe myelopathy
 - d. Type 2 has poor healing
- 6. Hangman's fracture:
 - a. Hyperextension with axial loading
 - b. Fracture through the pedicles at C2
 - c. Often asymptomatic
- 7. Subaxial fracture dislocation:
 - a. Severe flexion
 - b. Dislocation (perched or jumped facets)
 - c. Occurs from C3–T1
 - d. Tetra- and quadriplegia
 - e. Vertebral artery dissection
- 8. Burst fracture:
 - a. Usually thoracolumbar level
 - b. Axial loading
 - c. Fracture through the vertebral body
 - d. Root compression from retropulsion of a bone fragment
- 9. Chance fracture:
 - a. Thoracolumbar level
 - b. Axial loading
 - c. Fracture through the vertebral body with facet and posterior element fracture
 - d. May be asymptomatic
- 10. Wedge fracture:
 - a. Hyperflexion
 - b. No loss of height and no subluxation

- c. Local pain; constant movement with breathing makes it difficult to heal
- d. No neurologic deficit

Fatal cervical spine fractures are due to fracture-dislocations at C1–C3 that include atlanto-occipital and atlantoaxis dislocations. Death is usually from respiratory failure.

Clinical Manifestations of Spinal Cord Injury

1. Diaphragmatic paralysis occurs with lesions of C1–C3 cervical segments
2. Quadriplegia usually occurs from a fracture dislocation of the fourth to fifth cervical vertebrae
3. If there is sparing of abduction and flexion of the arms with paralysis of the legs the lesion is at the fifth to sixth cervical vertebrae
4. Fracture at the sixth to seventh cervical levels paralyzes the hands and legs
5. Lesions below the first lumbar vertebra (the spinal cord usually terminates at the rostral edge of the L1 vertebra) cause cauda equina injury
6. Lesions of the lower cervical cord may spare sensation to the nipple line due to the infraclavicular nerves whose origin is the cervical plexus (C3–C4)
7. The somatotopic organization of the spinothalamic tract is lateral to medial. Ascending sacral and leg fibers ascend laterally so that a lateral cervical cord lesion will cause a contralateral sacral and foot loss of sensation to pin-prick and temperature (spinothalamic fibers cross at their level of entry)

Patterns of Spinal Cord Injury

1. Spinal cord concussion
2. Spinal shock
3. Complete cord transection
4. Incomplete transection:
 - a. Brown-Séquard
 - b. Central cord syndrome
 - c. Anterior cord syndrome
 - d. Associated injuries:
 - i. Vertebral artery dissection or occlusion (traverse the transcervical canals)
 - ii. Cauda injury
 - iii. Conus medullaris injury
 - iv. Mixed epiconus cones and cauda equina lesions

Spinal Cord Concussion

1. A transient loss of motor or sensory function of the spinal cord that recovers within a short time (minutes to hours). Deficits may last for days. Transient syndrome includes:
 - a. Brachial weakness (may include an element of neuropractic brachial plexus injury)
 - b. Quadriplegia and rarely hemiparesis
 - c. Isolated sensory symptoms such as “burning hands”
 - d. Hand and arm motor and sensory deficits suggest a central cord injury

Pathology

1. Destruction of gray and white matter with hemorrhage (traumatic necrosis). The changes are maximal at the site of injury but may extend in an ovoid shape 1 or 2 segments rostrally and caudally
2. Healing produces a glial scar or cavitation with hemosiderin
3. Traumatic syringomyelia may occur after a delay of months or years. It usually enlarges rostrally but may be restricted to the central cord. A central cord predominant lesion may produce segmental weakness and sensory loss in the arms with minimal long tract involvement

Radiation Spinal Cord Injury

1. In general, it follows treatment for malignancies of the neck (lymphoma) or mediastinum
2. A transitory syndrome of paresthesia of the arms may occur at 3–6 months associated with Lhermitte’s sign. There are no associated motor or sensory signs and the process resolves
3. Delayed progressive myelopathy:
 - a. May be exacerbated by hyperthermia
 - b. A delayed onset of usually 12–15 months following therapy
 - c. Insidious onset with paresthesia and dysesthesias of the feet and hands (accompanying Lhermitte’s sign with cervical X-RT)
 - d. Often a stuttering course with corticospinal and spinothalamic tract involvement
 - e. An early Brown-Séquard pattern (infarction from proliferative endarteritis) that evolves into a transverse myelitis
 - f. An anterior horn cell amyotrophy of muscles innervated by irradiated segments
 - g. The CSF demonstrate a slight increase of protein but is otherwise normal

Pathology

1. Coagulating necrosis of the irradiated segment with rostral and caudal extension for a few spinal cord segments
2. Secondary demyelination of ascending and descending tracts
3. Necrosis of arterioles
4. Delayed signs and symptoms from peripheral and cranial nerve or plexus involvement may occur 10–15 years after X-RT treatment

Neuroimaging

1. MRI may reveal early cord swelling in irradiated spinal segments. There may be heterogeneous contrast enhancement
2. There is a high T2-weighted signal from fatty infiltration of the irradiated bone marrow which identifies the level of cord involvement
3. The rostral-caudal length of the lesion is longer than that seen with demyelinating disease, tumor or vascular malformation

Electrical Causes of Spinal Cord Injury

Electrical Injury

General Characteristics

1. Approximately 1000 deaths occur annually in the USA from inadvertent electric current contact
2. The quantity of current, not the voltage determines damage to the peripheral and CNS. Modifying factors are the duration of contact and skin resistance
3. There are both immediate and delayed neurologic signs and symptoms. The delay is usually one week, but may be as long as six weeks
4. Immediate effects are from heating the cord

Clinical Manifestations

1. Spinal trophic paralysis:
 - a. Occurs weeks to years after an electric shock
 - b. Most commonly the current has passed through the cervical cord (arm to arm) or from an arm to the leg
 - c. If the head is a contact point, the patient may be rendered unconsciousness and then experience deafness, tinnitus or headaches. There may be transient pain in the involved extremity
 - d. There is early mild weakness which progresses after a latent period of weeks to months and evolves into segmental muscular atrophy. There is often mild leg spasticity
 - e. An occasional patient may suffer a cortical or brainstem syndrome

Pathology

1. Demyelination of long tracts with relating gray matter sparing from high current
2. The gray matter is affected in spinal atrophic paralysis

Lightning Injury

1. Death is from ventricular fibrillation or severe hyperthermia of the brain
2. Initial loss of consciousness; 30% fatality rate
3. Rare agitated or confusional state can last for 1–2 weeks
4. Sensorimotor dysfunction of limbs; may progress to an anterior horn cell variant
5. Chronic regional pain syndrome may evolve from affected limbs that demonstrate early autonomic dysregulation (cold extremities with livedo-reticularis and cyanosis)

Spinal Cord Vascular Disease

General Characteristics

1. Spinal cord strokes account for less than 1% of all strokes and about 5–8% of acute myelopathies
2. Infarction occurs from:
 - a. Aortic disease (clamped aorta)
 - b. Dural fistula
 - c. Bleeding (coagulopathy; anticoagulation)
 - d. Arteriovenous malformations

Vascular Anatomy of the Spinal Cord

The major blood supply of the spinal cord is derived from a series of segmental branches from the aorta and branches of the subclavian and internal iliac arteries.

Segmental Artery from the Aorta

1. Divides into an anterior and posterior ramus
2. A spinal arteriole from the posterior ramus passes through the vertebral foramen to supply the dorsal root ganglia and roots by anterior and posterior radicular branches
3. Anterior radicular arteries supply much of the blood to the spinal cord. Its branches irrigate the vertebral bodies and ligaments
4. Venous drainage is to the posterior veins that form the spinal venous plexus

Anterior Spinal Artery

1. The anterior medullary arteries arise from the distal vertebral artery to form the anterior spinal artery. The artery usually extends the full length of the cord from the spinomedullary junction at the foramen magnum to the filum terminale in the anterior sulcus
2. The anterior spinal artery is also formed by approximately ten unpaired segmental arteries that originate from the distal vertebral arteries and the aorta and its branches
3. Radicular medullary arteries from the anterior spinal artery are divided into three groups:
 - a. Upper cervicothoracic branches from the anterior spinal artery and branches of the thyrocervical trunk and costovertebral arteries
 - b. Middle thoracic branches derived primarily from a T7 radicular artery
 - c. Thoracolumbar artery whose origin is from T10–L1 (the great radicular artery of Adamkiewicz) which supplies the lower 2/3 of the spinal cord
 - d. The posterior medullary arteries form the paired posterior spinal arteries on the dorsal spinal cord surface. The dorsal spinal arteries are also fed by posterior radicular arteries that enter with nerve roots at every spinal level
 - e. Additional segmental arteries from the vertebral, aorta and iliac arteries supply paraspinal structures
4. The most lateral white matter of the ventral 2/3 of the spinal cord is supplied by a pial radial network from the anterior spinal artery
5. Posterior spinal artery penetrating branches supply:
 - a. The posterior columns
 - b. Uppermost Rexed layers of the dorsal horn (I–IV)
 - c. Circumflex anastomotic vessels (the anastomosing plexus of small arteries between the anterior and posterior vessels) supply the superficial white matter

Venous Drainage of the Spinal Cord

1. Radial veins drain the inner cord to form a coronal plexus

2. Deep parenchymal veins drain into central sulcal veins
3. Parenchymal veins drain both sides of the cord
4. Sulcal veins anastomose intrasegmentally
5. Anterior median spinal vein:
 - a. Drains the sulcal vein
 - b. There may be two veins instead of one
6. Extramedullary venous channels:
 - a. Common on the dorsum of the spinal cord
 - b. Eight to twelve anterior radicular veins arise:
 - i. Drain the anterolateral anastomosis from the coronal venous plexus
7. The junction of the anterior radicular vein and the coronal venous plexus is at the nerve roots prior to their exit through the dura
8. The lumbar enlargement is drained by the reticularis magna vein
9. Posterior radicular veins are most prominent in the cervical cord
10. Spinal cord venous blood drains into:
 - a. Epidural and paravertebral plexi (a valveless system)
 - b. Extends from the occipital bone to the sacrum (Bateson's plexus)
 - c. Valsalva maneuvers increase the pressure in the system and are a route for pelvic cancers to metastasize to the posterior fossa (rarely the cerebral hemisphere)
- b. Infarction of the artery is caused by:
 - i. Atherosclerosis of extra vertebral collateral arteries
 - ii. Aortic pathology:
 1. Severe atherosclerosis
 2. Dissecting aneurysm
 3. Intraoperative surgical procedures (segmental artery occlusion)
 4. Cardiac and aortic surgery with cross-clamping for >30 minutes
 5. Aortic arteriography
2. Polyarteritis:
 - a. Occlusion of a spinal medullary artery
 - b. Systemic cholesterol emboli
3. Origin from atherosclerotic aorta:
 - a. Following surgical procedure
 - b. Angioplasty
 - c. Cardiopulmonary resuscitation
 - d. Delayed onset in some instances
4. Extracranial vertebral artery dissection:
 - a. Causes cervical cord infarction:
 - i. Anterior spinal artery territory
 - ii. Central cord ischemia
 - b. Clinical manifestation:
 - i. Vertigo
 - ii. Asymmetric brachial diplegia
 - iii. Suspended sensory loss
 - iv. Radicular and neck pain
5. Other aortic pathologies:
 - a. Cord ischemia:
 - i. Dissection
 - ii. Traumatic rupture
 - iii. Thromboembolic occlusion
 - iv. Ulcerative aortic plaque disease
 1. Obstruction of the orifices of radicular arteries
6. Aortic Dissection:
 - a. Dissection of the arch:
 - i. Associated with sudden pain in the face
 - ii. Contralateral, hemiparesis
 - iii. Brachial artery ischemia (sensorimotor neuropathy)
 - b. Dissection below the subclavian artery:
 - i. Severe interscapular and chest pain
 - ii. Ischemia of arms or legs
 - iii. Hypotension if above T6
 - iv. Paralysis of the sphincters and both legs; sensory loss below the dissection
 - v. Myoclonus and leg spasms
 - vi. Aortic aneurysm surgery:
 1. Paraplegia occurs in approximately 5% of patients with thoracoabdominal aneurysm surgery; rarely after infrarenal procedures
 - a. Delayed occurrence
7. Rare complication of vertebral arteriography:
 - a. High cervical infarction

Spinal Watersheds

1. The longitudinal watershed of the spinal cord is between T2–T4
2. The spinal cord is perfused at a much lower pressure 60–70 mmHg than the brain
3. Infarction of the spinal cord is frequently overshadowed by cerebral signs and symptoms
4. Internal watershed zones in the spinal cord are the:
 - a. Corticospinal tract
 - b. Rexed layers V–VI
5. Selective segmental gray matter necrosis does occur due to thoracic watershed infarction:
 - a. Cross-clamping of the aorta >30 minutes
 - b. Intraoperative surgical occlusion of the segmental spinal arteries at their origin
 - c. Spinal cord infarction after surgical procedures may be delayed for up to three weeks. There may be widespread embolization in this circumstance
6. Systemic hypotension
7. Cardiac arrest
8. Anoxia
9. Aortic dissection
10. Vertebral artery occlusion
11. Carbon monoxide poisoning

Causes of Spinal Cord Ischemia

1. Usually involves the anterior spinal artery distribution:
 - a. Atherosclerosis and thrombotic occlusion of the anterior spinal artery are rare

- b. Immediate sensorimotor paralysis
- c. Painful segmental spasm
- d. Spinal myoclonus and rigidity
- e. Putative vasoconstriction from older contrast agents
8. Progressive ischemic necrosis from arteriovenous malformation
9. Cocaine abuse:
 - a. Infarction may be preceded by spinal transient ischemic attacks
 - b. Signs and symptoms may be immediate or develop over several hours
 - c. Radicular pain may occur
 - d. Paralysis is usually bilateral
 - e. Those with transverse myelopathy:
 - i. Flaccid and areflexic paralysis
 - ii. Spasticity supervenes after weeks
 - iii. Some return of bladder control
10. Heroin Injection:
 - a. Signs occur after the patient regains consciousness
 - b. May be associated with acute pulmonary edema
 - c. Myelopathy occurs after a period of abstinence
 - d. Possible autoimmune reaction to adulterants or vasospasm
11. Embolism
 - a. Common causes of spinal cord embolism with infarction are:
 - i. Bacterial endocarditis
 - ii. Atrial myxoma
 - iii. Non-bacterial thrombotic emboli (most often in cancer patients)
12. Fibrocartilaginous emboli:
 - a. Arises from disc herniations
 - b. Young women > men
 - c. Primarily affects the cervical cord
 - d. Precipitants include minor trauma, sudden neck motion lifting, and prolonged spinal flexion
 - e. Clinical manifestations:
 - i. Pain in the neck or upper back: Radicular pain
 - ii. Rapidly progressive often asymmetric spinal cord syndrome
 - iii. MRI usually fails to demonstrate the herniated disc
13. Angiography
 - a. Catheterization for dural AVM
14. Fat emboli:
 - a. Broken bones (long bones in young patients)
 - b. Hip replacement in older patients
 - c. Diabetic ketoacidosis
15. Tumor cells
16. Nitrogen bubbles (Caisson's disease)
17. Air bubbles:
 - a. Diving accidents
 - b. Cardiac surgery
 - c. Surgical procedure in sitting position (ENT and neurosurgery)
18. Therapeutic renal artery embolization
19. Spinal cord infection and inflammation that cause infarction
 - a. Most common organisms are:
 - i. Tuberculosis
 - ii. Syphilis
 - iii. Cryptococcosis
 - iv. Coccidioidomycosis
 - v. Lyme's disease
 - b. Inflammation of the meninges spreads to the spinal arteries which may cause acute infarction
 - c. *Schistosoma mansoni*
 - i. Parasites invade cord blood vessels primarily in the conus medullaris and cauda equina
20. Chronic adhesive arachnoiditis
 - a. Scarring and obliteration of spinal penetrating arteries primarily affecting the central cord
21. Surfer's myelopathy
 - a. Novice surfers that are prostate for a long time
 - b. Standing with vigorous movements
 - c. Approximately one hour from surfing:
 - i. Severe upper lumbar or thoracic pain followed by paraparesis or paraplegia with urinary retention
 - d. MRI suggestive of ventral spinal cord ischemia

Arterial Spinal Cord Infarction Syndromes

Anterior Spinal Artery Ischemia

1. At the origin of the anterior spinal artery from the vertebral artery:
 - a. Usually severe atherosclerosis of the vertebral arteries
 - b. Medial medullary syndrome:
 - i. Ipsilateral XII nerve palsy
 - ii. Contralateral proprioceptive and vibratory deficit
 - iii. Contralateral weakness of the arm and leg (above the decussation of the pyramidal tract at C2)
 - iv. Crural plegia (arm ipsilateral and leg contralateral)
2. Low anterior spinal artery infarction:
 - a. Involvement of the ventral 2/3 of the spinal cord
 - b. Weakness of the extremities below the lesion
 - c. Loss of temperature and pain below the lesion
 - d. Bladder retention in approximately 50% of patients
 - e. Intact dorsal column sensory function

Differential Diagnosis of Anterior Spinal Artery Syndrome

1. Atherosclerosis of the artery (rare) or its feeding vessel (vertebral arteries)
2. Vertebral artery dissection
3. Aortic dissection
4. Surgical procedures of the aorta
5. Arteriography of the aorta

6. Hypotension (cross-clamped aorta >30 minutes)
7. Emboli:
 - a. Atrial myxoma
 - b. Arrhythmia
 - c. Fibrocartilage embolus
 - d. Air embolus
 - e. Nitrogen embolus
 - f. Cholesterol emboli
8. Infections:
 - a. Syphilis
 - b. Cryptococcus
 - c. Tuberculosis
 - d. Fungi
 - e. Schistosoma
9. Arachnoiditis
10. Idiopathic pachymeningitis (IgG4)
11. Cardiopulmonary and aortic surgical procedures
12. Vasculitis:
 - a. Polyarteritis nodosa
 - b. Sarcoid
 - c. Takayasu's disease
13. Systemic hypotension
14. Cocaine abuse
15. Intravenous heroin abuse

Ischemia of the Lower Thoracic Cord and the Lumbar Enlargement by Involvement of the Artery of Adamkiewicz

1. Renal arteriogram
2. Surgical procedures (cross clamping the aorta)
3. Aortic dissection
4. Atherosclerosis
5. Emboli

Posterior Spinal Artery Ischemia

General Characteristics

1. Extremely rare
2. Atherosclerosis or occlusion of the vertebral arteries
3. Cocaine abuse (vasoconstriction)
4. Trauma
5. Surgery

Clinical Manifestations

1. Severe sensory ataxia (may be acute with arm levitation)
2. Loss of posterior and vibration sensibility

Neuroimaging of Spinal Cord Infarction

1. MRIs obtained in the first hours or even days from the infarction may be normal
2. T2-weighted sequences reveal edema over several segments
3. Slight enhancement with gadolinium
4. Chronic lesions demonstrate an atrophic cord

Venous Infarction of the Spinal Cord

General Characteristics

1. Venous infarction without hemorrhage is hard to distinguish from arterial patterns of infarction
2. Differential diagnosis of venous infarction of the spinal cord:
 - a. Extension of thrombophlebitis of pelvic veins
 - b. Associated with chronic obstructive pulmonary disease
 - c. Polycythemia vera
 - d. Thrombophlebitis of the lower extremities:
 - i. Propagates into the cord via the paravertebral venous plexus
 - e. Subacute necrotizing myelitis:
 - i. Associated with spinal cord thrombophlebitis
 - ii. No systemic foci
 - iii. Associated with chronic obstructive pulmonary disease
 - f. Associated with epidural abscess
 - g. Endoscopic sclerotherapy (esophageal varices)
 - h. Coagulopathy
 - i. Cancer (breast and pancreas)
 - j. Subacute necrotizing myelopathy (paraneoplastic)
 - k. Birth control pills
 - l. Pregnancy
 - m. Disseminated intravascular coagulation

Hemorrhagic Disease of the Spinal Cord

Malformations and of the Spinal Cord and Dura Fistulas

General Characteristics

1. These lesions cause both ischemia and hemorrhage
2. Distinguishing features are:
 - a. Size of the nidus between an artery and vein
 - b. Size and location of feeding and draining vessels
 - c. Newer classification:
 - i. Medullary arteriovenous malformations that involve surrounding structure to a limited extent
 - ii. Intradural perimedullary fistulas (pial and subpial surface of the cord)
 - iii. Dural fistulas

Dural Arteriovenous Fistula

General Characteristics

1. Primarily located in the low thoracic cord and conus medullaris
2. Limited venous drainage system
3. A proportion of dural arteriovenous fistulas is in a dural root sleeve which drains into the perimedullary coronal venous plexus
4. Men > women

Clinical Manifestations

1. Slowly progressive “signs” but may have intermittent exacerbations precipitated by valsalva maneuvers or postural changes
2. Gait imbalance
3. Paresthesia
4. Slowly progressive asymmetric leg weakness
5. Some low back and sciatic pain
6. Urinary involvement
7. Claudication syndrome

Neuropathology

1. Rare bleeding
2. Venous congestion and edema

Neuroimaging

1. MRI reveals swelling of one or more adjacent spinal segments
2. Usually, there is no SAH; those that do bleed are primarily cervical and located near the cervicomedullary junction
3. Thoracic, lumbar and sacral fistulas rarely cause epidural hemorrhage

Intramedullary AVM*General Characteristics*

1. Located on the dorsal surface of the lower spinal cord
2. May occur at any location and at any age but is most often seen in middle-aged or elderly females

Clinical Manifestations

1. Acute lancinating pain often in a sciatic nerve distribution may be the presenting feature; the pain appears in clusters and may be worse in recumbency over weeks
2. Weakness and paresthesias are usually present in the same distribution as weakness
3. An apoplectic or slowly progressive weakness may be its course
4. Gait alteration is frequently by six months

Neuropathology

1. Dorsal surface of the spinal cord demonstrates enlarged veins that may involve roots and penetrate the spinal cord
2. Intramedullary ischemic changes
3. Thrombosis of venous vessels
4. CSF demonstrates elevated protein

Neuroimaging

1. MRI reveals serpiginous flow voids on the dorsal spinal cord
2. Hematomyelia and subarachnoid hemorrhage are rare

Intradural Perimedullary AVMs*General Characteristics*

1. Least frequent malformation
2. Possibly related to Foix-Alajouanine malformation
3. Involves the lower thoracic, upper lumbar or the cervical enlargement

Clinical Manifestations

1. Young patients and men and women are equally affected
2. Evolution may be slowly progressive (spinal cord compression), or it may present apoplectically
3. Mechanism for apoplectic onset:
 - a. Thrombosis of a vessel
 - b. Hemorrhage from a draining vein
4. Compressive myelopathy
5. Sudden onset consistent with transverse myelopathy

*Neuroimaging of Spinal Malformations***Dural Fistulas**

1. Enlargement of the spinal cord at the lesion level
2. T2-weighted MRI signal of the swollen cord over several segments
3. Draining vessels are infrequently imaged
4. Rare gadolinium enhancement
5. Arteriography which demonstrates the fistula in the dura; early draining vein
6. Rarely a fistula or high flow AVM may be in an organ outside of the spinal cord and cause pathology by increasing venous pressure

Rare Vascular Spinal Cord Malformations**Klippel-Trenaunay-Weber Syndrome (KTWS)***General Characteristics*

1. Associated with a cutaneous vascular nevus that overlies the AVM or is in the limb supplied by the affected segment

Clinical Manifestations

1. If the segmental malformation is at cervical levels:
 - a. Upper extremity is enlarged
 - b. Telangiectasia and tortuous veins are prominent
2. Segmental and tract lesions occur from infarction and hemorrhage

Aneurysm of a Spinal Artery with Coarctation of the Aorta and Telangiectasia of the Spinal Cord*General Characteristics*

1. May be associated with Osler-Weber-Rendu (hereditary hemorrhagic type)

Clinical Manifestations

1. Acute spinal cord hemorrhage
2. Acute hemorrhagic lesions with myelopathy

Foix-Alajouanine Syndrome*General Characteristics*

1. Congestive myelopathy due to spinal arteriovenous fistulas described by Foix-Alajouanine in 1926 (named it a necrotizing myelopathy)
2. Increased intramedullary venous pressure that causes an increased arteriovenous pressure gradient and concomitant decrease of cord perfusion

Clinical Manifestations

- a. Lower part of the cord is affected
- b. Gait difficulty
- c. Dysesthesia and non-dermatomal sensory loss
- d. Wasting and weakness of the lower extremities
- e. Sphincter involvement

Cavernous Hemangioma of the Spinal Cord (Cavernoma)*General Characteristics*

1. Benign vascular lesions that are common in the skin, liver and soft tissue
2. Arise from abnormal development of periradicular vessels
3. Most common in the cerebral hemispheres, but can be found anywhere in the neuraxis
4. Incidence is not known:
 - a. Possibly 1% of spinal masses
5. Men > women
6. Lower thoracic and lumbar cavernous hemangiomas are most frequent
7. May be associated with arteriovenous fistula of the lung

Clinical Manifestations

1. Onset with pain, weakness, and sensory symptoms
2. Later bowel and bladder dysfunction
3. Cervical lesions produce earlier symptoms
4. Severe weakness in 20% of patients by six months after presentation
5. Pain may be local or radicular
6. A combination of upper and lower motor weakness

Associations with Onset of Signs and Symptoms

1. Exercise
2. Pregnancy
3. Menstruation
4. May bleed during sleep
5. In 50% of patients, the onset of the first symptoms to diagnosis is three years

Neuropathology

1. Large dilated hyaline vascular channels which are in diffuse patterns. They are associated with thrombosis, perivascular hemosiderin (old bleeds with macrophage ingested hemosiderin) and calcification
2. Histologically the irregular vascular spaces are lined by a single layer of endothelium
3. A capillary hemangioma is a plexus of small capillary-sized vessels
4. The large sinusoid-like vascular channels have few or no intervening neurons or glial cells. They are separated by thin fibrous adventitial tissue

Neuroimaging

1. MRI reveals a heterogeneous well-circumscribed lesion or lesions

2. T2-weighted sequences may reveal a high-intensity signal (more recent bleed) or the lesion may have T1-weighted decreased signal. There is a hemosiderin ring. The lesions may show a homogeneously enhanced lesion on T1 and hypointense on T2-weighted sequences

Epidural Cavernous Hemangioma**Pure Spinal Epidural Cavernous Hemangiomas (PSECH)***General Characteristics*

1. Most spinal cavernous hemangiomas are vertebral in origin with or without epidural extension; pure epidural cavernous hemangiomas not originating from a vertebra are extremely rare
2. Reported incidence of spinal cavernous hemangiomas is 22 cases/million/year
3. 70% of pure spinal epidural cavernous hemangioma (PSECH) are women
4. Average age at diagnosis is 40 years
5. Most commonly located in the thoracic spine, posterolaterally and may extend into the neural foramina (19%)

Clinical Manifestations

1. Slowly progressive paraparesis (71%)
2. Radiculopathy (10%)
3. Rare acute paraparesis from possible intralesional thrombosis or hemorrhage and compression from an epidural hematoma

Neuropathology

1. PSECHs are dynamic lesions due to:
 - a. Intralesional hemorrhage
 - b. Thrombosis
 - c. Cyst formation
 - d. Involution
2. Hemorrhages are less common than what occurs with intra-axial cavernous hemangiomas

Neuroimaging

1. MRI:
 - a. High T2 signal intensity
 - i. Homogeneous, strong contrast enhancement
 - ii. Rarely there is heterogeneous signal intensity after recurrent bleeding
 - iii. No low signal hemosiderin rim whose putative mechanism is the easier removal of blood products because they are outside of the blood-spinal cord barrier

Differential Diagnosis of PSECH

1. Meningioma
2. Lymphoma
3. Metastasis
4. Schwannoma
5. Neuroma

Cobb's Syndrome*General Characteristics*

1. A vascular malformation that is metameric
2. Involves both the spinal and dermatomal segment

Clinical Manifestations

1. Segmental cutaneous angiomatous skin lesions
2. Often at a thoracic level
3. Spastic paraparesis

Bannayan-Zonana Syndrome*General Characteristics*

1. Autosomal dominant; A few sporadic patients

Clinical Manifestations

1. Macrocephaly
2. Multiple lipomas
3. Hemangiomas
4. Spastic paraparesis
5. Intracranial lesions
6. Male > female

Coarctation of the Aorta*General Characteristics*

1. Decreased circulation to the lower spinal cord
2. Weakness of the legs, sensory loss, and sphincter alternations

Subarachnoid Hemorrhage in the Spinal Cord*General Characteristics*

1. Spinal SAH < 1% of all SAH
2. Most common cause is bleeding from a spinal vascular malformation

Clinical Manifestations

1. Acute onset
2. Severe back pain at the level of the hemorrhage
3. Pain quickly becomes diffuse with signs of meningeal irritation
4. Radiculopathy at the site of the lesion
5. If blood diffuses above the foramen magnum:
 - a. Headaches
 - b. Cranial neuropathy (rare)
 - c. Depressed level of consciousness (rare)
6. Over time, there are decreased ankle jerks with increased knee and upper extremity reflexes
7. Increased intracranial pressure with papilledema (rare)
8. CSF evaluation:
 - a. RBC (1,000,000/mm³)
 - b. Within days there may be hypoglycorrachia (severely depressed glucose level < 20 mg%)
 - c. Xanthochromia

Hematomyelia*General Characteristics*

1. Most bleeding is caused by vascular malformations
2. The differential diagnosis of hematomyelia is:
 - a. Vascular malformation:
 - i. Intradural, perimedullary and subpial AVM
 - ii. Intramedullary AVM
 - iii. Dorsal arteriovenous fistula
 - iv. Trauma:
 1. Direct injury to the spine (penetrating and non-penetrating)
 2. Hyperextension and flexion of the cervical spine
 - v. Hemorrhage into a tumor
 - vi. Hemorrhage into a syrinx
 - vii. Coagulopathy
 - viii. Anticoagulation
 - ix. Venous infarction

Clinical Manifestations

1. Presents as spinal shock associated with severe back pain
2. Autonomic instability (postural hypotension if the lesion is above T6)
3. Gray matter is more affected than white matter
4. Spasticity develops below the level of the lesion
5. Atrophy and fasciculation of affected segments occur with time
6. Babinski sign is prominent
7. Sensory level:
 - a. Two segments lower than the lesion (if thoracic)
 - b. Higher posteriorly than anteriorly (follows pattern of intercostal nerves)
 - c. Dropped sensory level to T4–T6 following cervical lesions due to lamination of the spinal thalamic tract
 - d. Rare suspended sensory loss (destruction of the segmental dorsal horn at the level of injury with preserved long tract sensory function)
 - e. Mass reflex after stimulation late in the course of the illness

Disabled Cardiovascular Control After Spinal Cord Lesions*General Characteristics*

1. Lesions of the spinal cord damage autonomic pathways that alter cardiovascular homeostasis
2. The higher the level of the lesion and its severity increases cardiovascular dysfunction
3. Abnormalities of blood pressure control increase the patient's risk of heart disease and stroke

Acute Phase Following Spinal Cord Lesions

1. Bradyarrhythmia
2. Hypotension

3. Enhanced vasovagal reflexes
4. Supraventricular and ventricular ectopy
5. Vasodilation and venous stasis
6. Hypothermia and hyperthermia
7. Neurogenic shock

Chronic Phase of Spinal Cord Lesions

1. Orthostatic hypotension (lesions at or above T6)
2. Impaired cardiovascular reflexes
3. Autonomic dysreflexia:
 - a. Lesions above T6
 - b. Sudden uncontrolled sympathetic response (a stimulus below the level of the injury; urinary catheter replacement; treatment for fecal impaction)
 - c. Abrupt rise in blood pressure that may cause ICH
 - d. Erythema of the upper chest wall
 - e. Severe pounding headache
4. Urinary autonomic dysfunction that includes hyperreflexia or areflexia of the detrusor and/or the external bladder sphincter
5. Reduced sensation of cardiac pain
6. Loss of reflex cardiac acceleration
7. Quadriplegic cardiac atrophy:
 - a. Loss of ventricular mass
 - b. Pseudo-myocardial infarction
8. Spinal cord lesions lead to:
 - a. Atherosclerotic disease from:
 - i. Obesity
 - ii. Lipid disorders
 - b. Metabolic syndrome
 - c. Diabetes
 - d. Predisposed to thrombotic emboli due to venous stasis and hypercoagulability
 - e. Cardiovascular dysfunction during sexual activity and exercise

Epidural Hematoma

General Characteristics

1. Epidural hemorrhage occurs with greater frequency than subdural hemorrhage
2. Peak occurrences are during childhood and the fifth to sixth decade
3. Cervical lesions are more common in childhood; thoracic and lumbar lesions in adults
4. Spontaneous epidural hematomas occur in approximately 40% of patients:
 - a. Pathogenesis of spontaneous bleeding is thought to be venous:
 - i. Valveless epidural venous plexus is subject to pressure from the abdominal and thoracic cavities
 - ii. Hematomas are usually located posteriorly, which is consistent with the anatomical location of the venous plexus. Ventral hematomas are rare (less than 5%)

Clinical Manifestations

1. Sudden onset of back pain at the segmental area of the bleeding
2. Signs of nerve root or spinal cord compression
3. Thunderclap headache has been described when the bleeding is in the cervical spinal cord
4. Horner's syndrome occurs in approximately 10% of cervical lesions
5. May have a pain free interval that can last for days, following which there are signs of a progressive myelopathy

Neuropathology

1. Associated with anticoagulation, spinal anesthetic procedures, trauma, chronic renal failure and hepatitis C

Neuroimaging

1. MRI:
 - a. Oval lesions
 - b. Shifts in the spinal cord in the canal
2. Hyperintense T2-weighted sequences in the parenchyma are associated with poor recovery

Spinal Subdural Hematoma

General Characteristics

1. Comprise approximately 6% of all spinal hematomas
2. Rarely occurs in association with a cranial subdural hematoma
 - a. Concomitant cranial and spinal SDH, the spinal SDH is located below the thoracic levels
 - b. May develop in patients with intracranial hypotension from ventriculoperitoneal shunt placement

Clinical Manifestations

1. Similar to epidural signs and symptoms

Subarachnoid Hematoma

General Characteristics

1. Usual age is between 55 and 70 years old

Clinical Manifestations

1. Meningitic
2. Alteration of consciousness
3. Epileptic seizures

Neuroimaging of Epidural Hematoma

1. T1-weighted sequence:
 - a. Signal intensity of the epidural hematoma is primarily isointense to the spinal cord
 - b. T2-weighted sequences of epidural hemorrhages:
 - i. Heterogeneous hyperintensity as compared to the spinal cord
 - ii. Focal hypointensity (acute blood; deoxyhemoglobin)
2. Direct continuity with adjacent osseous structure

3. Spontaneous spinal epidural hematomas may be located ventrally to the cord:
 - a. Premembranous hematoma
 - b. Posterior longitudinal ligament hematoma

Neuroimaging of Spinal Subdural Hematoma

1. Subdural collection of blood with smooth borders

Laboratory Evaluation of Spinal Subdural Hematoma

1. CSF:
 - a. Motor oil color
 - b. Methemoglobin
 - c. Some RBCs

Differential Diagnosis of Spinal Hematomas

1. Epidural anesthetic procedures
2. Anticoagulation
3. Trauma
4. Vascular malformations
5. Lumbar puncture
6. Neoplasm
7. Thrombocytopenia
8. Following heparinization after lumbar surgery

Differential Diagnosis of Specific Spinal Cord Malformations

1. AVM:
 - a. Dural arteriovenous fistula
 - b. Intraparenchymal
 - c. Intradural perimedullary and subpial
2. Hemangioblastoma
3. Cavernous hemangioma
4. Bannayan-Zonana syndrome
5. Klippel-Trenaunay-Weber syndrome
6. Foix-Alajouanine syndrome
7. Occult vascular malformation of the spinal cord

Hemangioblastoma

General Characteristics

1. May arise in isolation
2. A major manifestation of Von Hippel-Lindau disease (VHL)
 - a. Prevalence of 1/36,000 in the population

Von Hippel-Lindau Syndrome (VHL)

General Characteristics

1. Autosomal dominant; chromosome 3p25-3p26 mutation in gene; deletions or mutations
2. Associated central nervous system hemangioblastomas:
 - a. Cerebellum
 - b. Retinal
3. Associated systemic manifestations:
 - a. Renal cysts
 - b. Renal carcinoma
 - c. Pheochromocytoma (specific alleles of VHL)
 - d. Increased levels of vascular endothelial growth factor

Clinical Manifestations

1. 80% are in the cerebellum
2. 20% in the spinal cord
3. 55% of patients with hemangioblastoma have VHL disease:
 - a. 60% are symptomatic when less than 30 years of age
4. Spinal hemangioblastoma:
 - a. Relationship to VHL is greater when in an infratentorial location
5. VHL patients are younger than sporadic patients
6. VHL patients develop endolymphatic sac tumors:
 - a. Tinnitus and deafness
7. Spinal hemangioblastoma:
 - a. Are often associated with cerebellar hemangioblastoma
 - b. May be multiple
 - c. May be extramedullary in a spinal root location
 - d. Renal cell carcinoma may metastasize to the hemangioblastoma

Neuropathology

1. Associated tumors:
 - a. Renal cell carcinoma
 - b. Pheochromocytoma
 - c. Paragangliomas
 - d. Endolymphatic sac tumors
 - e. Pancreatic neuroendocrine tumors (PNET)
 - f. Papillary cystadenomas of the epididymis
 - g. Adrenal papillary tumors (mesonephric origin)
2. Germline mutation of tumor suppressor gene on short arm of chromosome 3:
 - a. 30% of these patients have large deletions of VHL
 - b. May involve other genes
3. The VHL tumors arise from embryologic hemangioblasts that form endothelial cells and blood cells
4. Distribution of hemangioblastomas in a series of 225 patients:
 - a. Supratentorial (1%)
 - b. Cerebellum (45%)
 - c. Brainstem (7%)
 - d. Spinal cord (36%)
 - e. Cauda equina (11%)
 - f. Nerve roots (3%)
5. Hemangioblastoma growth:
 - a. Increased tumor burden:
 - i. Partial deletions in VHL gene
 - ii. Male sex
 - b. Three new tumors/year associated with:
 - i. Younger age
 - ii. More initial tumors
 - c. Growth:
 - i. No growth in 51%
 - ii. 49% grew in solitary pattern
 - iii. Linear growth in 6%
 - iv. Exponential pattern in 22%
 - d. Faster growth associated with:

- i. Male sex
- ii. Symptomatic tumors
- iii. Tumors associated with cysts

Angiographically Occult Vascular Malformations of the Spinal Cord (AOVMS)

General Characteristics

1. May occur with a dural arteriovenous fistula between a radicular feeding artery and the venous system at the dural sleeve of the nerve root
2. Spinal cord cavernous malformations are the most common lesion

Clinical Manifestations

1. Sensory and motor loss below the level of the lesion
2. Clinical cause:
 - a. Neurologic decline due to repeated episodes of relapse and remission
 - b. Linear neurologic functional decline
3. Cavernous hemangiomas are often intramedullary and may not have characteristic radiographic signs

Neuroimaging

1. Flat panel catheter angiotomography (IFCA) during spinal digital subtraction angiography if standard angiography fails to detect a clinically suspected malformation
2. Surgical microscope-integrated intraoperative near-infrared indocyanine green angiography:
 - a. Rapidly identifies a draining vein as it enters the spinal canal if catheter-based digital subtraction angiography fails

Differential Diagnosis of Angiographically Occult Vascular Malformation of the Spinal Cord

1. Primary hemorrhagic tumors of the spinal cord:
 - a. Ependymoma
 - b. Astrocytoma
 - c. Medulloblastoma
2. Hemorrhagic transverse myelitis:
 - a. Lung metastasis (small cell)
3. Paraneoplastic spinal cord hemorrhagic necrosis:
 - a. Small cell lung cancer
 - b. Anti-Hu antibody syndrome
 - i. Often occurs at the thoracic level
4. Bleeding diathesis:
 - a. Coagulopathy
 - b. Anticoagulation (Coumadin/heparin; status of Xa and direct thrombin inhibitors in this regard has not been established)
 - c. Platelet disorders
 - d. Leukemia/lymphoma
 - e. Hemorrhagic leukoencephalitis
 - f. Spinal SDH
 - g. Parenchymous bleed (trauma)

5. Systemic conditions affecting the spinal cord:
 - a. Whipple's disease
 - b. Gluten-sensitive enteropathy
 - c. Kohlmeier-Degos disease
 - d. Sjögren's disease
 - e. B12 deficiency
 - i. Acute following nitrous oxide anesthesia (cobalamin deficiency)
 - ii. High serum B12 level noted with leukemia and lymphoma
 - f. Vitamin E deficiency
 - i. Dietary
 - ii. Alpha-tocopherol transporter defect
 - g. Copper deficiency
 - i. Genetic
 - ii. Zinc excess (paste in dental adherents)
 - h. Pure spinal angitis
6. Werner's syndrome
 - a. General characteristics:
 - i. AR; WRN gene is located on chromosome 8
 - ii. Encodes a helicase and an exonuclease
 - b. Accelerated aging
 - c. Childhood age of onset
 - d. Clinical manifestations:
 - i. Balding
 - ii. Atherosclerosis of all circulations
 - iii. Premature graying
 - iv. Osteosclerosis
 - v. Diabetes mellitus
 - vi. Juvenile cataracts
 - vii. Hypogonadism
 - viii. Rare spastic paraparesis
 1. Many patients have increased reflexes

Spinal Pseudoathetosis

General Characteristics

1. Occurs after protracted severe loss of proprioception
2. Secondary to:
 - a. Lesions of the dorsal columns or their nuclei
 - b. Lesions of the dorsal root ganglia (DRG)
 - c. Lesions of the dorsal root entry zone

Clinical Manifestations

1. Lateral and up drift of the upper extremities with polymyoclonus
2. Rare flinging of the arms and legs
 - a. Acute lesions that can occur with cocaine abuse
3. Severe proprioceptive loss is partially compensated by the excess movement
4. Pain may precede the pseudoathetosis

Differential Diagnosis of Spinal Pseudoathetosis

1. Spinal trauma (dorsal column destruction)
2. Tabes dorsalis

3. Cocaine abuse:
 - a. Acute signs (putative mechanism in vasospasm of the posterior spinal arteries)
4. Demyelinating disease
5. Syringomyelia
6. Sjögren's disease
7. Friedreich's ataxia
8. SLE
9. Migrated disc
10. Cervical spondylosis
11. B12 deficiency
12. Vascular lesion with hemipseudoathetosis

Spinal Cord Veno-Occlusion

Venous Spinal Cord Infarction

General Characteristics

1. Associated with:
 - a. Vascular malformations
 - b. Hematoma
 - c. Epidural abscess
2. Hemorrhagic venous occlusive disease:
 - a. Back pain at the level of involvement
 - b. Progression is subacute (days to weeks)
 - c. Multiple spinal segments are involved
3. Non-hemorrhagic venous occlusive disease
 - a. Course is over weeks
 - b. Less pain
 - c. Fewer spinal segments are involved
4. Embolic venous infarction:
 - a. Fibrocartilaginous
 - b. Sudden onset
 - c. Pain at the level of involvement (often cervical)
 - d. Asymmetric deficit
5. Venous infarction associated with vascular malformations:
 - a. Subacute neurologic syndrome
 - b. Foix-Alajouanine syndrome
 - i. Congestive myelopathy
 - ii. Stepwise dysfunction due to thrombosis of supplying vessels
 - iii. Intramedullary hypertension due to spinal dural arterial fistula
6. Sclerotherapy:
 - a. Direct penetration of epidural veins
 - b. Occlusion of the anterior spinal artery
 - c. Cirrhosis (acquired or congenital) is often the systemic defect:
 - i. Related AV shunts
 - ii. Inadvertent arterial access following esophageal vein injection
 - iii. Putative mechanism is congestion of the abdominal epidural venous plexus

Varices Increases Thoracoabdominal Pressure – Neuroimaging

1. Small intramedullary high signal intensity is known as “snake-eye appearance”
 - a. Small cystic necrosis of the central gray matter of the ventrolateral posterior columns
 - b. Neuronal loss in the flattened anterior horn
 - c. Described in patients with compressive myelopathy from cervical spondylosis or ossification of the posterior longitudinal ligament

Hereditary Spastic Paraplegia

Overview

There are more than 50 genetic causes of hereditary spastic paraplegia. It is a clinical diagnostic classification for neurologic syndromes the major feature of which is bilateral lower extremity weakness and spasticity and for which a gene has been identified. There is great variation in severity and often associated neurologic and systemic features. There is a wide clinical spectrum between and within genetic types of HSP that include the age of symptom onset and degree of progression.

In general, HSP is classified as “uncomplicated,” which is characterized by lower extremity spasticity, weakness, and slight dorsal column dysfunction.

Complicated forms are associated with:

1. Dementia
2. Ataxia
3. Cognitive impairment
4. Neuropathy, amyotrophy
5. Visual loss
6. Ichthyosis
7. Many genetic forms are associated with both “uncomplicated” and “complicated” syndromes. Genotype-phenotype correlation has not been well defined in many genetic types of HSP which is another cause of clinical variability. The identical gene mutation in a family can cause both “complicated” and “uncomplicated” form of the disease

Clinical Manifestations

1. General features that apply to core elements in HSP. “Complicated” patients have major other system involvement:
 - a. Most patients present with lower extremity weakness and spasticity which impairs gait
 - b. Urinary urgency is an early or even presenting symptom
2. General recognized syndromes:
 - a. Uncomplicated HSP (limited to lower extremity weakness, spasticity, minimal dorsal column involvement and gait alteration)
 - b. Spastic paraplegia with:

- i. Motor neuropathy and/or distal wasting
- ii. Cognitive impairment
- iii. Ataxia
- iv. Neuroimaging abnormalities (thin corpus callosum)
- v. Neurologic and systemic abnormalities
- c. Age of symptom onset
 - i. Variable within a genetic type
- d. Progression may be static, progressive or after a variable period may stabilize:
 - i. Early onset form (SPG3A and SPG4) has a relative non-progressive course
 - ii. More rapid progression during adolescence and decreased progression after 5–10 years of disease are common patterns
- e. HSP gene mutations may be associated with syndromes that are not phenotypically HSP
 - i. SPG3/Atlastin mutation may be associated with a hereditary sensory neuropathy 1 (HSN1)
 - ii. BSL2/seipin mutations when heterozygous cause:
 - 1. AD, HSP (SPG17)
 - 2. Charcot-Marie-Tooth type 2
 - 3. Distal hereditary neuropathy type V
 - 4. Homozygous mutations cause:
 - a. Congenital generalized lipodystrophy type 2
 - iii. SPG11/spastin mutations
 - 1. May present as levodopa responsive juvenile parkinsonism
 - iv. SPG20/spartin (Troyer syndrome)
 - 1. Also a biomarker for colorectal cancer

Neurologic Examination

1. “Uncomplicated” HSP:
 - a. Muscle weakness greater in the iliopsoas, hamstring, and tibialis anterior muscles
 - b. Spasticity is most prominent in the hamstrings, quadriceps, adductor and gastrocnemius soleus muscles
 - c. Easily obtainable (1/2 lateral foot stimulated) Babinski response associated, with hyperactive KJs, AJs and crossed adductor and puboadductor reflexes
 - d. Mild vibration loss in distal lower extremities
 - e. Hyper-reflexia without weakness or spasticity occurs in the upper extremities
 - f. Usual but not invariant pes cavus deformity
2. “Complicated” HSP:
 - a. Core features of weakness, spasticity, hyper-reflexia, subtle vibration loss
 - b. Associated neurologic and systemic features that include:
 - i. Dementia
 - ii. Cognitive impairment
 - iii. Optic atrophy
 - iv. Retinitis pigmentosa
 - v. Extrapyrarnidal features

- vi. Peripheral neuropathy
- vii. Ataxia
- viii. Distal wasting (amyotrophy)
- ix. Cataracts

Genetic Classification

There are dominant, recessive X-linked and mitochondrial forms of HSP that have been designated by the order of their discovery. There are also other inherited disorders with a similar phenotype of lower extremity weakness spasticity and hyperreflexia. SPG7 paraplegia may manifest both as an autosomal dominant or recessive disorder. Genetic penetrance in autosomal dominant HSP is age dependent. There are rare reports of genetic anticipation in SPG3A and SPG4 apparently without trinucleotide repeat expansions.

Putative Molecular Mechanisms

An analysis of the function of HSP encoded proteins surmised by their dysfunction in patients with specific mutations, have given insights into the molecular mechanisms that may be operative in these diseases. The deficits incurred include:

1. Alterations in axonal transport (SPG30/KIFA; SPG10/KIFA; SPG4/spastin)
2. Endoplasmic reticulum alterations (SPG12/reticular; SPG3AA/atlastin, SPG4/spastin and SPG31/Reep)
3. Mitochondrial dysfunction (SPG13/chaperonin 60/heat shock protein 60, SPG7/paraplegia and mitochondrial ATP6)
4. Primary myelin alterations (SPG21 proteolipid protein, SPG42/connexin 47)
5. Protein conformation defects initiating the ER-stress response (SPG16/NIPA1, SPG8 SPG7/BSCL2/Seipin)
6. Neurodevelopment dysfunction of the corticospinal tract (SPG1/L1 cell adhesion molecule, SPG22)
7. Vesicle formation and membrane trafficking (SPG47, K1AA, SPG48, SPG50, SPG51, SPG52, SPG53)
8. Disturbances of lipid metabolism:
 - a. A subset of HSP patients have defects in phospholipid, sphingolipid, and fatty acid metabolism. A major area of present interest is the degree of “cell” autonomous alterations (due to intrinsic abnormalities only in the neurons that are degenerating) versus “non-cell autonomous” (degeneration depends on interaction with other cells). It is clear from the genetic deficits and their functional analysis that corticospinal tract axons are selectively vulnerable in these diseases

Genetic Forms of SPG

1. SPG3A:
 - a. Genetics:
 - i. Chromosome 4q4
 - ii. Protein encoded
 1. Atlastin
 - b. Clinical manifestations:

- i. Uncomplicated
 - ii. Onset primarily childhood; may be in adolescence or adulthood
2. SPG4:
 - a. Genetics:
 - i. Chromosome 2p22; AD
 - ii. Protein encoded
 1. Spastin
 - b. Clinical manifestations:
 - i. Uncomplicated
 - ii. Onset all age groups
 - iii. Most common cause of AD forms
 - iv. Some patients have late cognitive impairment
3. SPG6:
 - a. Genetics:
 - i. Chromosome 15q11.1
 - ii. Protein encoded
 1. NIPA1 (not impaired in Prader-Willi and Angelman syndrome)
 - b. Clinical manifestations:
 - i. Uncomplicated
 - ii. Onset late adolescence and early adulthood
 - iii. Rarely associated with epilepsy or peripheral neuropathy
4. SPG8:
 - a. Genetics:
 - i. Chromosome 8q23-q24
 - ii. Protein encoded
 1. Strumpellin
 - b. Clinical manifestations:
 - i. Uncomplicated
5. SPG9:
 - a. Genetics:
 - i. Chromosome 10q23-q24.2
 - ii. Protein encoded
 1. Not identified
 - b. Clinical manifestations:
 - i. Complicated
 - ii. Cataracts, gastroesophageal reflex, motor neuropathy
6. SPG10:
 - a. Genetics:
 - i. Chromosome 12q13
 - ii. Protein encoded:
 1. KIF5A kinesin heavy chain
 - b. Clinical manifestations:
 - i. Uncomplicated
 1. Distal muscle atrophy
7. SPG12:
 - a. Genetics:
 - i. Chromosome 19q13
 - ii. Protein encoded
 1. RTN2 protein
 - b. Clinical manifestations
 - i. Urinary symptoms
- ii. Distal sensory impairment
8. SPG13:
 - a. Genetics:
 - i. Chromosome 2q24-34
 - ii. Protein encoded
 1. Chaperonin (heat shock protein 60)
 - b. Clinical manifestations:
 - i. Adolescent and adult onset
 - ii. Uncomplicated
9. SPG19:
 - a. Genetics:
 - i. Chromosome 11q12-q14
 - ii. Protein encoded
 1. BSCL2/seipin
 - b. Clinical manifestations:
 - i. Complicated
 - ii. Associated with amyotrophy of hand muscles (Silver syndrome)
10. SPG19:
 - a. Genetics
 - i. Chromosome 9q33-34
 - ii. Protein encoded
 1. Not identified
 - b. Clinical manifestations:
 - i. Uncomplicated
11. SPG29:
 - a. Genetics:
 - i. Chromosome 1q31, 1-21.1
 - ii. Protein encoded
 1. Not identified
 - b. Clinical manifestations:
 - i. Complicated
 - ii. Hearing impairment and hiatal hernia
12. SPG31:
 - a. Genetics:
 - i. Chromosome 2q12
 - ii. Protein encoded
 1. Receptor expression enhancing protein (REEP)
 - b. Clinical manifestations:
 - i. Uncomplicated
 - ii. Rarely associated with peripheral neuropathy
13. SPG33:
 - a. Genetics:
 - i. Chromosome 10q24.2
 - ii. Protein encoded
 1. Proteins contain ZFYE zinc fingers
 - b. Clinical manifestations:
 - i. Uncomplicated
14. SPG36:
 - a. Genetics:
 - i. Chromosome 12 q23-24
 - ii. Protein encoded
 1. Not identified
 - b. Clinical manifestation:
 - i. Onset adolescence to 28 years

- ii. Complicated
 - iii. Associated with sensory motor neuropathy
 - 15. SPG37:
 - a. Genetics:
 - i. Chromosome 8q21, 1-q13.3
 - ii. Protein encoded
 - 1. Not identified
 - b. Clinical manifestations:
 - i. Uncomplicated
 - 16. SPG38:
 - a. Genetics:
 - i. Chromosome 4q16-15
 - ii. Protein encoded
 - 1. Not identified
 - b. Clinical manifestation (1 family)
 - i. Onset 16–21 years
 - ii. Complicated
 - iii. Associated with severe hand atrophy (1 patient)
 - 17. SPG40:
 - a. Genetics:
 - i. Chromosome (locus unknown)
 - ii. Protein encoded
 - 1. Not identified
 - b. Clinical manifestations:
 - i. Onset after 33
 - ii. Uncomplicated
 - 18. SPG41:
 - a. Genetics:
 - i. Chromosome 11q14.1-p11.2
 - ii. Protein encoded
 - 1. Not identified
 - b. Clinical manifestations:
 - i. One Chinese family
 - ii. Adolescent onset
 - iii. Complicated
 - iv. Associated with mild weakness of intrinsic hand muscles
 - 19. SPG42:
 - a. Genetics:
 - i. Chromosome 3q24-q26
 - ii. Protein encoded
 - 1. Acetyl CoA transporter (SLC33A1)
 - b. Clinical manifestations:
 - i. Uncomplicated (one kindred)
 - ii. Onset 4–40 years of age
- Autosomal Recessive HSP*
- 1. SPG5:
 - a. Genetics:
 - i. Chromosome 8p
 - ii. Protein encoded
 - 1. CYP7B1
 - b. Clinical manifestations:
 - i. Complicated with associated with axonal neuropathy
 - c. MRI
 - i. White matter changes, distal or generalized muscle atrophy
2. SPG7:
 - a. Genetics:
 - i. Chromosome 16q
 - ii. Protein encoded
 - iii. Paraplegin
 - b. Clinical manifestation:
 - i. Uncomplicated or complicated
 - ii. If complicated associated with dysarthria, dysphagia, optic atrophy, axonal neuropathy, cerebellar and cerebral atrophy, MRI evaluation suggestive of vascular lesions
3. SPG11:
 - a. Genetics:
 - i. Chromosome 15q
 - ii. Protein encoded
 - iii. Spatacsin (KIAA1840)
 - b. Clinical manifestations:
 - i. Uncomplicated form
 - ii. If complicated associated with thin corpus callosum, cognitive impairment, upper extremity weakness, dysarthria nystagmus
 - iii. Kjellin syndrome:
 - 1. Childhood onset
 - 2. Spastic paraplegia
 - 3. Retinitis pigmentosa
 - 4. Cognitive impairment
 - iv. Some patients have ALS
4. SPG14:
 - a. Genetics:
 - i. Chromosome 3q27-28
 - ii. Protein encoded
 - 1. Not identified
 - b. Clinical manifestations:
 - i. One Italian family
 - ii. Onset approximately 30 years of age
 - iii. Complicated and associated with cognitive deficits, distal motor neuropathy
5. SPG15:
 - a. Genetics:
 - i. Chromosome 14q
 - ii. Protein encoded
 - 1. Spastizin/ZFYVE26
 - b. Clinical manifestations:
 - i. Complicated
 - ii. Associated with:
 - 1. Pigmented maculopathy
 - 2. Distal amyotrophy
 - 3. Dysarthria
 - 4. Cognitive impairment
 - 5. Kjellin syndrome
6. SPG18:
 - a. Genetics:

- i. Chromosome 8p12-p11-21
 - ii. Protein encoded
 1. Endoplasmic reticulum lipid raft associated protein 2 (ERLIN2)
 - b. Clinical manifestations:
 - i. Two families described
 - ii. Complicated
 - iii. Associated with thin corpus callosum, cognitive impairment
 - iv. ERLIN2 mutations associated with juvenile ALS
7. SPG20:
 - a. Genetics:
 - i. Chromosome 13q
 - ii. Protein encoded
 1. Spartan
 - b. Clinical manifestations:
 - i. Complicated
 - ii. Associated with distal muscle wasting (Troyer syndrome)
8. SPG21:
 - a. Genetics:
 - i. Chromosome 15q21-q22
 - ii. Protein encoded
 1. Maspartin
 - b. Clinical manifestations:
 - i. Complicated
 - ii. Associated with:
 1. Dementia
 2. Cerebellar and extrapyramidal signs
 3. Thin corpus callosum
 4. White matter abnormalities on MRI
 5. Mast syndrome
9. SPG23:
 - a. Genetics:
 - i. Chromosome 1q24-q32
 - ii. Protein encoded
 1. Not identified
 - b. Clinical manifestations:
 - i. Complicated
 - ii. Childhood onset
 - iii. Associated with:
 1. Vitiligo
 2. Premature graying
 3. Dysmorphisms
 4. Lison syndrome
10. SPG24:
 - a. Genetics:
 - i. Chromosome 13q14
 - ii. Protein encoded
 1. Not identified
 - b. Clinical manifestations:
 - i. Complicated
 - ii. Childhood onset
 - iii. Associated with spastic dysarthria and pseudobulbar signs
11. SPG25:
 - a. Genetics:
 - i. Chromosome 6q 23-q24.1
 - ii. Protein encoded
 1. Not identified
 - b. Clinical manifestations:
 - i. One consanguineous Italian family
 - ii. Adult onset (30–46)
 - iii. Complicated
 - iv. Associated with:
 1. Disc herniation
 2. Peripheral neuropathy
12. SPG26:
 - a. Genetics:
 - i. Chromosome 12p11.1-12q14
 1. Protein encoded
 - a. Not identified
 - b. Clinical manifestations:
 - i. Single Bedouin family
 - ii. Childhood onset
 - iii. Complicated
 - iv. Dysarthria
 - v. Distal amyotrophy in both upper and lower extremities
 - vi. Mild cognitive impairment
13. SPG27:
 - a. Genetics:
 - i. Chromosome 10q22.1-q24.1
 - ii. Protein encoded
 1. Not identified
 - b. Clinical manifestations
 - i. Complicated and uncomplicated forms
 - ii. Uncomplicated form:
 1. Onset age: 25–45
 - iii. Complicated form:
 1. Childhood onset
 2. Associated with:
 - a. Ataxia
 - b. Dysarthria
 - c. Cognitive impairment
 - d. Sensorimotor neuropathy
 - e. Short stature
 - f. Facial dysmorphisms
14. SPG28:
 - a. Genetics:
 - i. Chromosome 14q21.3-q22.3
 - ii. Protein encoded
 1. DDHD
 - b. Clinical manifestations:
 - i. Uncomplicated form with onset in infancy, childhood or adolescence
 - ii. Complicated form associated with axonal neuropathy, distal sensory loss, cerebellar eye movement disorder
15. SPG29:

- a. Genetics:
 - i. Chromosome 14q
 - ii. Protein encoded
 1. Not identified
 - b. Clinical manifestations:
 - i. Childhood onset
 - ii. Uncomplicated
16. SPG30:
- a. Genetics:
 - i. Chromosome 2q37.3
 - ii. Protein encoded
 1. RIFA
 - b. Clinical manifestations:
 - i. Complicated
 - ii. Associated with:
 1. Distal wasting
 2. Defective
 3. Smooth pursuit
 4. Cerebellar signs
 5. Peripheral neuropathy
17. SPG32:
- a. Genetics:
 - i. Chromosome 14q:2-q21
 - ii. Protein encoded
 - iii. Not identified
 - b. Clinical manifestations:
 - i. Complicated
 - ii. Associated with:
 1. Cognitive dysfunction
 2. Brainstem defects
 3. Asymptomatic cerebellar atrophy
18. SPG35:
- a. Genetics:
 - i. Chromosome 16q21-q23
 - ii. Protein encoded:
 1. Fatty acid 2-hydroxylase (FA2H)
 - b. Clinical manifestations:
 - i. Complicated
 - ii. Childhood onset
 - iii. Associated with:
 1. Extrapyrarnidal signs
 2. Dysarthria
 3. Dementia
 4. Seizures
 - iv. White matter alterations and brain iron accumulation
19. SPG39:
- a. Genetics:
 - i. Chromosome 9q13
 - ii. Protein encoded
 1. Neuropathy target extremities (NTE)
 - b. Clinical manifestations:
 - i. Complicated
 - ii. Wasting of distal upper and lower extremities
20. SPG43:
- a. Genetics:
 - i. Chromosome 19q13.11-q12
 - ii. Protein encoded
 1. C 6, 12, or 19
 - b. Clinical manifestations:
 - i. One family from Mali (sisters)
 - ii. Complicated
 - iii. Associated with intrinsic hand muscles atrophy in 1 sister
21. SPG44:
- a. Genetics:
 - i. Chromosome 1a41
 - ii. Protein encoded
 1. Gap junction protein GJA 12/GJC2 also known as connexin (cxH7)
 - b. Clinical manifestations:
 - i. Merzbacher-like disease
 - ii. GJA/GJC2 mutations
 1. Later onset (first and second decades)
 2. Complicated and associated with dysarthria and upper extremity involvement
 3. MRI and MR spectroscopy compatible with hypomyelination and leukoencephalopathy
22. SPG45:
- a. Genetics:
 - i. Chromosome 10q24.3-q25.1
 - ii. Protein encoded
 1. Not identified
 - b. Clinical manifestations:
 - i. One consanguineous family linked from Turkey
 - ii. Complicated
 - iii. Associated with cognitive impairment contractures. Optic atrophy and one patient with pendular nystagmus
23. SPG46:
- a. Genetics:
 - i. Chromosome 9p21.1-q21.2
 - ii. Protein encoded
 1. Not identified
 - b. Clinical manifestations:
 - i. Complicated
 - ii. Associated with:
 1. Dementia
 2. Thin corpus callosum
 3. Ataxia
 4. Congenital cataracts
24. SPG47:
- a. Genetics:
 - i. Chromosome 1p 13.2-1p12
 - ii. Protein encoded
 1. AB4B1
 - b. Clinical manifestations:
 - i. Consanguineous Arab family
 - ii. Complicated; childhood onset
 - iii. Associated with:

1. Mental retardation
 2. Seizure
 3. Thin corpus callosum
 4. Periventricular white matter hyperintensities
25. SPG48:
- a. Genetics
 - i. Chromosome 14q 32.31
 - ii. Protein encoded
 1. TECPR2
 - b. Clinical manifestations
 - i. Complicated
 - ii. Jewish Bukharin ethnicity
 - iii. Associated with:
 1. Infantile onset dysmorphisms
 2. Severe gait alterations
 3. Gastroesophageal reflex
 4. Recurrent apneic episodes
 5. 2 patients with thin corpus callosum
 6. Cerebellar atrophy
26. SPG50:
- a. Genetics:
 - i. Chromosome 7q22-1
 - ii. Protein encoded
 1. AD4MI
 - b. Clinical manifestations:
 - i. One consanguineous Moroccan family; infantile onset
 - ii. Complicated
 - iii. Associated with:
 1. Cognitive impairment
 2. Adducted thumbs
 3. Ventriculomegaly
 4. White matter abnormalities
 5. Variable cerebellar atrophy
27. SPG51:
- a. Genetics:
 - i. Chromosome 15q21.2
 - ii. Protein encoded
 1. APE1
 - b. Clinical manifestations:
 - i. Complicated
 - ii. Palestinian-Jordanian family
 - iii. Associated with:
 1. Microcephaly hypotonia
 2. Psychomotor issues
 3. Facial dysmorphisms
 4. Seizures
 - iv. MRI revealed atrophy and diffuse white matter hyperintensities (WMH)
28. SPG52:
- a. Genetics:
 - i. Chromosome 14q12
 - ii. Protein encoded
 1. AP4S1
 - b. Clinical manifestations:
 - i. Complicated
 - ii. Consanguineous Syrian family
 - iii. Associated with:
 1. Neonatal hypotonia
 2. Cognitive impairment
 3. Microcephaly
 4. Short stature
 5. Facial dysmorphism
29. SPG53:
- a. Genetics:
 - i. Chromosome 8q22
 - ii. Protein encoded
 1. USP37A
 - b. Clinical manifestations:
 - i. Complicated (2 Arab families)
 - ii. Associated with:
 1. Upper and lower extremity spasticity
 2. Kyphosis and pectus carinatum
 3. Cognitive impairment
 4. Hypertrichosis
 5. Decreased vibration sensibility
30. SPG54:
- a. Genetics
 - i. Chromosome 8p11.23
 - ii. Protein encoded
 1. C120RI65
 - b. Clinical manifestations:
 - i. Complicated
 - ii. Associated with:
 1. Psychomotor delay
 2. Cognitive deficits
 3. Foot contracture
 4. Dysarthria
 5. Dysphagia
 6. Strabismus
 7. Optic hypoplasia
 - iii. MRI
 1. Thin corpus callosum
 2. Periventricular WMH
31. SPG55:
- a. Genetics:
 - i. Chromosome (note identified)
 - ii. Protein encoded
 1. C120RF65
 - b. Clinical manifestations:
 - i. Complicated
 - ii. Japanese consanguineous family (2 brothers reported)
 - iii. Associated with central scotoma and optic atrophy, decreased upper extremity strength and motor sensory neuropathy
32. SPG56:
- a. Genetics:
 - i. Chromosome 4q25
 - ii. Protein encoded

1. CYP201
- b. Clinical manifestations:
 - i. Complicated (early childhood onset)
 - ii. Associated with upper extremity dystonia, cognitive deficits, and axonal neuropathy
 - iii. MRI evaluation:
 1. Thin corpus callosum
 2. Basal ganglia calcification
 3. WMH
33. Cerebral Palsy, Spastic Quadriplegic 1 (CPSQ1)
 - a. Genetics:
 - i. Chromosome 2q31.1
 - ii. Protein encoded
 1. Glutamate Decarboxylase 1 (GAD1)
 - b. Clinical manifestations:
 - i. Consanguineous Pakistani family
 - ii. Spastic cerebral palsy
 - iii. Moderate to severe cognitive impairment
34. Spastic Paraplegia Associated with Optic Atrophy (SPOAN)
 - a. Genetics:
 - i. Chromosome 11q23
 - ii. Protein encoded
 1. Not identified
 - b. Clinical manifestations:
 - i. Complicated
 - ii. Associated with optic atrophy
35. Chaperonin containing t-complex polypeptide 1, subunit 5 (CCT5)
 - a. Genetics:
 - i. Protein encoded
 1. Epsilon subunit of the cytosolic chaperonin containing +-complex peptide 1 (CCT5)
 - b. Clinical manifestations:
 - i. Complicated
 - ii. Associated with sensory neuropathy
36. Sjögren-Larsson syndrome
 - a. AR
 - b. Clinical manifestations:
 - i. Short stature
 - ii. Seizures
 - iii. Retinal degeneration
 - iv. Ichthyosis
37. Hematologic abnormalities with spastic paraparesis
 - a. AD (autosomal dominant)
 - b. May-Hegglin anomaly
 - i. Cytoplasmic inclusions in leukocytes
 - ii. Giant platelets
 - iii. Thrombocytopenia
38. Evan's syndrome
 - a. Spastic paraparesis
 - b. Coombs-positive hemolytic anemia
 - c. Immune thrombocytopenia
 - d. AR

X-Linked HSP

1. SPG1:
 - a. Genetics:
 - i. Chromosome Xq28
 - ii. Protein encoded
 1. L1 cell adhesion molecule (LICAM)
 - b. Clinical manifestations:
 - i. Complicated
 - ii. Associated with:
 1. Mental retardation
 2. Aphasia
 3. Adducted thumbs
 - c. MRI
 1. Hydrocephalus
2. SPG2:
 - a. Genetics:
 - i. Xq28
 - ii. Protein encoded
 1. Proteolipid protein
 - b. Clinical manifestations:
 - i. Complicated
 - ii. Associated with peripheral neuropathy
 - c. MRI
 - i. White matter abnormalities
3. SPG16:
 - a. Genetics:
 - i. Chromosome Xq11.2-q23
 - ii. Protein encoded – Not identified
 - b. Clinical manifestations:
 - i. Uncomplicated and complicated
 - ii. Complicated form associated with:
 1. Aphasia
 2. Nystagmus
 3. Decreased visual acuity
 4. Dysfunction of bowel and bladder
 5. Mental retardation
4. SPG22:
 - a. Genetics:
 - i. Chromosome Xq21
 - ii. Protein encoded
 1. Monocarboxylate transporter 8 (MCT8)
 - b. Clinical manifestations:
 - i. Complicated (Allan-Herndon-Dudley syndrome)
 - ii. Congenital onset
 - iii. Associated with:
 1. Dysarthria
 2. Mental retardation
 3. Ataxia
 4. Facial dimorphisms
5. SPG34
 - a. Genetics:
 - i. X-chromosome mutation
 1. Protein encoded: not identified
 - b. Clinical manifestations:
 - i. Uncomplicated

6. Mitochondrial (Maternal) Inheritances

- a. Genetics:
 - i. Mitochondrial ATP 6 gene
- b. Clinical manifestations:
 - i. Complicated; adult onset
- c. Associated with:
 - i. Axonal neuropathy
 - ii. Dementia (late)
 - iii. Cardiomyopathy

Differential Diagnostic Signs in Complicated HSP

1. Peripheral Neuropathy
 - a. SPG Types: SPG2, 5, 6, 7, 10, 25, 27, 30, 31, 55, 56, SPOAN CCT5, mitochondrial ATP 6 gene
2. Distal amyotrophy
 - a. SPG Types: SPG3A, 4, 5, 10, 14, 15, 17, 20, 26, 30, 38, 39, 41, 43, 55
3. Mental retardation
 - a. SPG Types: 1, 11, 14, 16, 18, 20, 22, 26, 27, 32, 44, 45, 47, 49, 50, 51, 52, 53, 54, 56, GSD1 mutation
4. Dementia
 - a. SPG Types: SPG4, 15, 21, 35, 46 and ATP 6 gene mutation
5. Vision impairment
 - a. SPG Types: SPG15, 16, 45, 54, 55, and SPOAN
6. Deafness
 - a. SPG Types: SPG29
7. Skeletal abnormalities or dysmorphic features
 - a. SPG Types: SPG25, 49, 50, 51, 52, 53
8. Extrapyramidal movement disorders
 - a. SPG Types: SPG21, 35, 56
9. Epilepsy
 - a. SPG Types: SPG6, 35, 42, and 51
10. Dysarthria
 - a. SPG Types: SPG7, 15, 22, 24, 27, 35, 43, 44, 54
11. Ataxia
 - a. SPG Types: SPG7, 21, 22, 27, 30, 32, 46, and 49
12. Spastic Paraparesis and MRI abnormalities
 - a. SPG Types: SPG1, 2, 5, 7, 11, 15, 18, 21, 32, 35, 44, 46, 47, 49, 50, 54, and 56
13. Spastic paraplegia and skin abnormalities
 - a. Types: Sjögren-Larsson syndrome
14. Childhood onset with skin pigment abnormality
 - a. AR
15. Endocrine abnormality
16. Kallmann syndrome
 - a. Spastic paraplegia
 - b. Hypogonadotropic hypogonadism and anosmia

Neuropathology of the Hereditary Spinal Paraplegias (HSP)

1. Axon degeneration involving the corticospinal tracts and to a lesser degree the posterior columns:
 - a. Most severe at the distal end of the long tracts
 - b. Long tracts CST degeneration may extend rostrally to the pons, cerebral peduncle and internal capsule

2. Neuronal loss and gliosis in upper and lower motor neural pathways
3. Particular vulnerability of the longest fiber tracts in the CNS and spinal cord
4. Predominant distributions of axon degeneration are the distal ends of cortical spinal tracts and the fasciculus gracilis fibers
5. Lower motor neuron involvement is demonstrated by distal wasting and amyotrophy in many genetic forms of HSP
 - a. It is particularly severe in SPG11 (similar to juvenile ALS)
 - b. It is also predominant in SPG17 (Silver syndrome) and SPG20 (Troyer syndrome)
 - c. Hyaline inclusions, mitochondrial alterations, and abnormalities in cytoskeletal protein have been noted in AD SPG4
6. Myelin abnormalities in HSP are noted in SPG2 proteolipid protein and SPG42. The mutated genes in these forms of HSP are in oligodendroglia. Abnormal myelin as demonstrated by MRI is seen in many forms of HSP
7. Neurons in other systems, cerebellar, basal ganglia, cranial nerves are also frequently involved
8. Developmental factors as clinically demonstrated by a small spinal cord diameter, white matter hyperintensities and thin corpus callosum are seen in many forms of complicated HSP

Differential Diagnosis of Hereditary Forms of Spastic Paraplegia***Machado-Joseph Disease (Spinocerebellar Ataxia Type 3)****General Characteristics*

1. The most common spinocerebellar ataxia worldwide
2. Clinical heterogeneity among different families and within families
3. Chromosome 14; ATXN3 gene
 - a. Unstable CAG repeat expansion in the coding region of the MJD1 gene (now termed ATXN3)

Clinical Manifestations

1. Core clinical feature is a progressive ataxia. Ataxia never occurs in isolation. Clinical features demonstrate deficits in the brainstem, oculomotor system, extrapyramidal and pyramidal tracts, lower motor neurons and peripheral nerves
2. Presents in young adults and middle-age patients. Prominent early features are gait ataxia, vestibular and speech problem
3. Clinical categories:
 - a. Type 1 disease:
 - i. Age of onset young adult
 - ii. Spasticity, rigidity, bradykinesia, and minimal ataxia

- b. Type II disease:
 - i. Onset in young to mid-adult years; the most common form
 - ii. Progressive ataxia and upper motor neuron signs
- c. Type III disease:
 - i. Late-onset form (mean age at onset approximately 50 years)
 - ii. Ataxia and peripheral nerve involvement with amyotrophy
- d. Type IV disease
- 4. Parkinsonism is prominent
- 5. Bradykinesia, rigidity, and dystonia

Neuropathology

- 1. Neurodegeneration of the basal ganglia, various brainstem nuclei, and the cerebellum
- 2. Disease protein in MJD accumulates within inclusions (ubiquitin-positive intranuclear spheres)

X-Linked Adrenoleukodystrophy

General Characteristics

- 1. X-chromosome mutation
- 2. ABCD1 gene mutations
 - a. Encodes the membrane protein ALDD which is involved in the transmembrane transport of very long chain fatty acids (VLCFA > L22)

Clinical Manifestations

- 1. Involves a clinical spectrum that ranges from isolated adrenocortical insufficiency and slowly progressive myelopathy to severe cerebral demyelination
- 2. Phenotype in male X-linked ALD patients
 - a. Addison only
 - b. Cerebral myeloneuropathy
 - i. Effects almost all patients who reach adulthood:
 - 1. Gradually progressive spastic paraparesis
 - 2. Sensory ataxia with vibratory loss
 - 3. Sphincter disturbance (bladder > fecal)
 - 4. Pain in the legs
 - 5. Impotence

Neuropathology

- 1. Non-inflammatory distal axonopathy that involves the long tracts of the spinal cord and to some extent the peripheral nerves

Neuroimaging

- 1. MRI
 - a. High signal intensities of the pyramidal tract at all levels on FLAIR and T2 sequences

Women with X-Linked ALD (Carriers)

Clinical Manifestations

- 1. Many patients develop AMN signs
- 2. Onset occurs in the 4th and 5th decade
- 3. Sensory ataxia, fecal incontinence, and leg pain may be prominent

Laboratory Evaluation

- 1. Plasma concentrations of very long chain fatty acids are increased in 99% of males and greater than 85% of female carriers

Krabbe's Disease (Globoid Cell Leukodystrophy)

General Characteristics

- 1. Chromosome 14q31
- 2. The deficient lysosomal enzymes are galactocerebrosidase
 - a. Degrades galactocerebroside to ceramide and galactose

Clinical Manifestations

- 1. Approximately 15 variants of globoid leukodystrophy have been reported several with long survival
- 2. Adult Variants
 - a. Progressive quadriparesis
 - b. Mild pseudobulbar signs
 - c. Progressive memory loss
 - d. Dystonic arm posturing and preserved sphincter control
 - e. CSF can be normal although it is usually elevated
- 3. Variant reported by Kolodny:
 - a. 15 patients with onset between 4–73 years
 - b. Pes cava
 - c. Optic pallor
 - d. Progressive spastic quadriparesis
 - e. Demyelinating sensorimotor neuropathy

Neuropathology

- 1. Infantile forms:
 - a. Accumulations of galactocerebroside and a metabolite psychosine destroy oligodendrocytes
 - b. Atrophy of parieto-occipital lobes and periventricular white matter

Neuroimaging

- 1. Symmetrical non-enhancing areas of increased signal in the basal ganglia and internal capsule
- 2. Enlargement of prechiasmatic optic nerves
- 3. Adults demonstrate parieto-occipital atrophy

Laboratory Evaluation

- 1. CSF has protein between 70–450 mg/dl. Adult patients may have normal protein
- 2. Adult patients retain more of the functioning enzyme

Werner's Syndrome

General Characteristics

- 1. Mutations of WRN gene
 - a. AR that maps to chromosome 8p12
- 2. Encodes helicase and exonuclease

Clinical Manifestations

- 1. Severe atherosclerosis

2. Premature aging
3. Premature balding
4. Osteoporosis
5. Hypogonadism
6. Juvenile cataracts
7. DM
8. Peripheral neuropathy
9. Increased reflexes in some patients

Neuropathology

1. Generalized severe atherosclerotic changes in large vessels; often calcification
2. WMH (small vessel disease)

Neuroimaging

1. Topographic strokes in large vessels
2. Generalized WMH

Metachromatic Leukodystrophy

General Characteristics

1. AR; maps to chromosome 22q13.33
2. Deficiency in arylsulfatase A
 - a. Impaired degradation of sulfate

Clinical Manifestations

1. Adult MLD presentation
 - a. Behavioral abnormalities
 - b. Spastic paraparesis
 - c. Late in the disease
 - i. Optic atrophy
 - ii. Intention tremor
 - iii. Brainstem signs

Neuroimaging

1. Severe periventricular white matter involvement
2. Frontal lobe atrophy and white matter involvement

Laboratory Evaluation

1. Elevated protein (75 to 250 mg/dl)
2. Sulfatide in the urine
3. Absence of arylsulfatase in white blood cells
4. Pseudodeficiency of the enzyme
 - a. PD allelic variants
 - b. 10% of enzyme activity is present
 - c. No clinical manifestation

Adult-Onset Leukoencephalopathy with Neuroaxonal Spheroids and Pigmented Glia (ALSP)

General Characteristics

1. Mutation in colony-stimulating factor 1 receptor (SF-1R) gene

Clinical Manifestations

1. Adult onset (3rd–4th decades)
2. Progressive spastic paraparesis
3. Dementia

Neuropathology

1. Neuroaxonal spheroids and pigmented glia

Neuroimaging

1. Frontal lobe involvement with white matter hyperintensities
2. Multiple diffuse white matter involvement without enhancement
3. Corpus callosum involvement

Laboratory Evaluation

- a. Normal CSF

Hyperlysinemia

General Characteristics

1. Chromosome 7q31.3 mutation; AR
2. Gene defect in AASS (alphaaminodic semialdehyde synthase)
3. Defect is in the major catabolic pathway for L-Lysine; the pathway leads to the production of acetyl-CoA

Clinical Manifestations

1. Intellectual impairment
2. Epilepsy
3. Progressive spastic paraparesis
4. The relationship of hyperlysinemia to phenotype has been questioned. Clinical symptoms may require the loss of PTPRZ1 (protein tyrosine phosphatase Receptor-Type IZ Polypeptide1)

Neuroimaging

1. MRI is normal

Laboratory Evaluation

1. Elevated plasma lysine levels ($>600 \mu\text{mol/L}$)

Adult Onset Alexander's Disease

General Characteristics

1. Mutation is in the glial fibrillary acidic protein gene that maps to chromosome 17
 - a. An alternatively spliced GFAP isoform (GFAP-epsilon) may be modulatory

Clinical Manifestations

1. Onset 3rd to 5th decade
2. Spastic paraparesis
3. Brainstem signs including palatal myoclonus and nystagmus
4. Cerebellar intention tremor and ataxia
5. Hyperreflexia
6. Urinary incontinence

Neuropathology

1. Destructive changes in cerebral white matter with frontal lobe predominance

2. Eosinophilic hyaline bodies below the pia and within blood vessels are noted in the cortex, brainstem and spinal cord (Rosenthal fibers)

Neuroimaging

1. White matter hyperintensities throughout the frontal lobe, cerebrum, and middle cerebellar peduncles
2. Atrophy of the medulla that extends caudally to the cervical spinal cord

Metabolic Disorders Affecting the Spinal Cord

Homocarnosine (gamma-amino-butyryl-histidine)

General Characteristics

1. A histidine-containing dipeptide abundant in the CNS and muscle
2. Quenchers of reactive cytotoxic carbonyl species; detoxify 4-hydroxy-trans-2,3-no neural HNE
3. AR; maps to chromosome 18

Clinical Manifestations

1. Spastic paraparesis
2. Mental retardation

Laboratory Evaluation

1. Increased homocarnosine in the CSF

Vitamin B12 (Cobalamin) Deficiency

General Characteristics

1. Conditional deficiency:
 - a. Failure to transfer cobalamin across the intestinal mucosa due to the absence of intrinsic factor and hydrochloric acid (both secreted by parietal cells of the gastric mucosa). It is transported to the ileum and absorbed into the portal circulation
2. Malabsorption Disorders leading to Deficient Cobalamin
 - a. Poor nutrition (elderly patients)
 - b. Atrophic gastritis
 - c. Celiac sprue
 - d. Gastric or iliac surgery
 - e. Overgrowth of intestinal bacteria
 - f. Fish tapeworm infestation
 - g. Exposure to nitrous oxide:
 - i. Depression of methionine synthetase (methylcobalamin dependent enzyme)
 - ii. Operating room personnel, dentists, and abusers (whippets)
 - iii. Chronic exposure may produce complete combined degeneration syndrome
 - iv. Approximately six hours of exposure is required for those that are not B12 deficient prior to exposure; symptoms may occur 2 to 6 weeks after exposure

- v. Methylcobalamin is a cofactor for methionine synthetase; deficiency causes failure of conversion of homocysteine to methionine
- vi. Antibodies that destroy gastric parietal cells may accompany autoimmune disorders

Clinical Manifestations

1. Mild general weakness
2. Active paresthesia of the hands more than feet; constant and progressive
3. Unsteady gait with leg weakness
4. Late manifestations are an ataxic spastic paraplegia

Neurological Signs

1. Loss of vibration sensibility is the most consistent sign (legs > hands) and may occur on the trunk
2. Reflexes are usually increased but rarely the neuropathy may predominant, and they are lost
3. Rare Lhermitte's sign
4. Cognitive impairment
5. Optic, neuropathy

Neuropathology

1. White matter degeneration of the spinal cord with some brain involvement. Swelling of the myelin sheaths with intramyelinic vacuoles and separation of myelin lamellae
2. Late stage – gliosis
3. Rare spongy degeneration in the optic nerves and chiasm
4. Methylcobalamin is a critical cofactor in the conversion of homocysteine to methionine that leads to a failure of DNA synthesis
5. B12 is essential for methylamine-CoA mutase reactions. It is necessary for myelin synthesis. Lack of B12 causes a decrease of the conversion of methylmalonyl-CoA to succinyl-CoA. An accumulation of methylmalonyl-CoA causes a decrease in normal myelin synthesis and the incorporation of abnormal fatty acids into neuronal lipids

Neuroimaging

1. The most consistent MRI pathology finding in B12 deficiency is a symmetrically increased signal of the posterior and lateral columns. Primarily evident in the cervical and thoracic spinal cord
2. In acute patients, the spinal cord may appear to be swollen
3. DWI sequences reveal restriction of water diffusion congruent with intramyelinic edema
4. Rare enhancement of lesions with gadolinium
5. FLAIR and T2-weighted sequences demonstrate high-intensity signal in periventricular white matter

Copper Deficiency

General Characteristics

1. Usually caused by the failure of absorption after bowel surgery or gastric bypass. Excess zinc absorption from dental fixatives can also be causative
2. Associated anemia with ringed sideroblasts, leucopenia, and vacuolated bone marrow myeloid precursor cells

Clinical Manifestations

1. Women > men
2. Presenting complaint is often imbalance
3. Posterior column signs
4. Gait ataxia
5. Spasticity with Babinski sign
6. Reduced ankle reflexes

Neuropathology

1. Antioxidant SOD1 and subunit 2 of cytochrome oxidase may be decreased in blood cells and muscles (5 patients studied)
2. In muscle, deficits of ferritin (iron storage) was detected in the face of normal serum levels
3. Heme proteins including cytochrome C and myoglobin are depressed
4. Muscle expression of the copper transporter CTR1 is up-regulated along with the copper chaperone CCS while the antioxidant protein 1 is decreased

Neuroimaging

1. MRI
 - a. Increased signal intensity in the posterior and lateral columns of the spinal cord similar to that of B12 deficiency

Hyperparathyroidism*General Characteristics*

1. Approximately 100,000 cases of primary hyperparathyroidism occur/year in the USA
2. A multisystem disorder with skeletal, renal, neuropsychological, cardiovascular and rheumatological signs and symptoms
3. Most patients are asymptomatic
4. Changes in calcium homeostasis and the development of bone cysts contribute to neurological spinal cord symptomatology
5. Neurological manifestations occur with primary and secondary hyperparathyroidism (hemodialysis and renal failure)

Clinical Manifestations

1. Dialysis patients may develop brown bone cysts and collapsed vertebrae with spinal cord compression
2. Tetraparesis and severe muscle atrophy may occur
3. Proximal muscle weakness and fatigue
4. Fibrillating tongue, urinary frequency, and generalized hyperreflexia had been described
5. Neurocognitive alterations

Neuroimaging

1. MRI
 - a. Erosion of the radial side of the index fingers and the acromial head of the clavicle

Laboratory Evaluation

1. Elevated serum calcium, PTH and alkaline phosphatase

Neuropathology

1. Severe disruption of bone metabolism

Hyperthyroidism*General Characteristics*

1. Thyroid disease may present first with neurologic signs and symptoms
2. May present concurrently with other neurologic disorders that are most often autoimmune

Clinical Manifestations

1. Amyotrophic lateral sclerosis presentation
2. Presenting as pyramidal tract disease
3. A constellation of nystagmus, spasticity and Babinski signs
4. Associated neurologic complications:
 - a. Encephalopathy
 - b. Hypokalemic periodic paralysis
 - c. Myopathy
 - d. Ophthalmopathy
 - e. Cognitive dysfunction

Portocaval Shunt*General Characteristics*

1. Portosystemic encephalopathy
 - a. Complications of portal hypertension
 - i. Caused by ammonia that is usually removed by the liver
 - ii. Surgical portosystemic anastomosis (PSA) the collateral vessels bypass the liver

Clinical Manifestations

1. Portosystemic encephalopathy (PSE)
2. Portosystemic myelopathy:
 - a. Paresis primarily of the lower extremities
 - b. Spasticity and Babinski signs, no sensory loss or sphincter involvement
 - c. Intervals between surgical shunt and neurological signs
 - i. Total portocaval shunts (median of 16 months)
 - ii. Partial non portocaval shunts (median 60 months)
 - d. Portosystemic encephalopathy develops prior to the myelopathy in most patients
 - e. Myelopathy occurs with splenorenal shunts
 - f. Relationship with type II Alzheimer astrocytes

Neuropathology

1. Loss of anterior horn cells
2. Localized degeneration of the lateral columns

Neuroimaging

1. MRI may be normal in the spinal cord
2. Associated increased T2-weighted signal in the caudate and putamen

Laboratory Evaluation

1. High serum and CSF ammonia concentrations

Hepatic Encephalopathy*General Characteristics*

1. Hepatic encephalopathy may complicate all forms of liver disease and is not related to jaundice or ascites
2. Encephalopathy may be worsened by dietary protein or gastrointestinal hemorrhage. Other precipitating factors are:
 - a. Hypoxia
 - b. Hypokalemia
 - c. Metabolic alkalosis
 - d. Diuresis
 - e. Hypnotic sedatives
 - f. Valproic acid

Clinical Manifestations

1. Mental slowing and confusion that may progress to stupor or coma
2. Asterixis
3. Rare patients exhibit fluctuating rigidity of the trunk and limbs, asymmetry of reflexes and cortical reflexes (suck and grasp)
4. Spinal signs and symptoms (spastic paraplegia) similar to portocaval shunting are common
 - a. These may occur without jaundice and ascites (portal-systemic encephalopathy)
5. Those patients who have suffered multiple episodes of hepatic coma may develop acquired hepatolenticular degeneration (AHLT)
 - a. Clinical features include:
 - i. Dementia
 - ii. Falling backwards
 - iii. Dysarthria
 - iv. Tremor
 - v. Ataxia of gait
 - vi. Choreaathetosis
 - vii. Spastic paraplegia

Clinical Stages of Hepatic Encephalopathy

1. Acute I:
 - a. Personality change (confusion to active psychosis)
 - b. Acute increased intracranial pressures
 - c. Reye's syndrome (increased ICP, vomiting, low glucose, decortication)
2. Subacute stage II:
 - a. Brainstem involvement
 - b. Reversible decerebration
 - c. Spasticity of all extremities
 - d. Pupils <1 mm but reactive to light
 - e. Babinski signs are present
3. Stage III:
 - a. Coma
 - b. Feterhepation
 - c. Failure of Doll's eyes and ice-water colonic

Neuropathology

1. Increased numbers and sizes of protoplasmic astrocytes in the deep layers of the cortex, substantia nigra, dentate and pontine nuclei. These are Alzheimer type II astrocytes
2. Increase in both mitochondria and enzymes that metabolize ammonia
3. Cerebral edema occurs in rapidly evolving patients

Neuroimaging

1. Increased signal intensity of T1-weighted sequences in the globus pallidus from possible manganese deposition in chronic patients
2. Acute hepatic encephalopathy
3. Diffuse cortical edema demonstrated on T2-weighted and FLAIR sequences
4. Diffuse weighted images (DWI) high signal intensity with low signal intensity on apparent diffusion coefficient (ADC) maps
5. High signal intensity alone in the hemispheric white matter in or around the corticospinal tract on FLAIR T2-weighted images

Laboratory Evaluation

1. Increased blood ammonia levels
2. EEG
 - a. Classic triphasic waves

Selected Toxins That Affect the Spinal Cord**Lathyrism***General Characteristics*

1. Due to the consumption of Lathyrus sativus (vetch pea, or grass pea)
2. Common in parts of India and Africa particularly during periods of famine when wheat and other grains are not available

Clinical Manifestations

1. Gradual leg weakness accompanied by cramps, active paresthesias, and urgency of micturition, impotence and sphincter spasms
2. Upper extremity demonstrates coarse tremors and involuntary movements
3. Affects primarily young men; may have a sudden onset

Neuropathology

1. B-ODAP (B-N-oxalyl-dlB-diamino propionic acid) in grass pea is thought to be etiologic
2. A diet of grass pea is deficient in essential sulfur amino acids methionine and cysteine that are important in maintenance of redox homeostasis
3. Loss of ascending and descending spinal cord tracts that include the corticospinal and direct spinocerebellar tracts; loss of posterior column and lateral spinothalamic tract myelination

4. Loss of Betz cells in the cortex but anterior horn cells appear unaffected
5. Gliosis and thickened blood vessels in the degenerated tracts

Konzo

General Characteristics

1. Caused by consumption of improperly processed cassava (*Manihot esculenta*) roots
2. Primarily in remote rural areas of southern Africa and Ethiopia
3. Cyanogenic glycosides are etiologic
4. The disease occurs during famines and droughts as the plant is drought resistant and becomes the major part of the diet
5. May occur suddenly in young mothers after childbirth

Clinical Manifestations

1. Similar to lathyrism
2. Abrupt onset of a non-progressive symmetric spastic para/tetraparesis
3. Clinical signs and symptoms may be precipitated by manual labor or a long walk
4. Paresthesia of the legs, cramping, and pain in the back can precede and accompany the paraparesis. It frequently abates in weeks
5. Upper limb involvement varies from loss of fine movement to spastic quadriparesis
6. Some patients suffer:
 - a. Optic atrophy
 - b. Rotary nystagmus
 - c. Pseudobulbar dysarthria
 - d. Signs of upper motor neuron damage (increased reflexes and Babinski sign) can occur in the absence of paraparesis
 - e. Second attacks occur in approximately 10% of patients
 - f. Contracture occurs in severe patients

Neuropathology

1. Hydrogen cyanide is liberated from cyanogenic glycosides (cyanogenesis)
2. Cyanide is:
 - a. Mitochondrial oxidative phosphorylation blockers
 - b. Derived from the conversion of linamarin
 - c. Possible role for glutathione deficiency

Ethylene Oxide

General Characteristics

1. Ethylene oxide (ETO) is a reactive species and a potent biocide
2. Used widely in the sterilization of hospital equipment. It is in sterilization packs for the operating room
3. Approximately 75,000 health care workers have potential exposure

4. May cause chromosome aberrations
5. Exposure has been associated with leukemia
6. The byproduct ethylene chlorohydrin (EC) may be the toxic agent

Clinical Manifestations

1. Neuropathy
2. Mild cognitive impairment
3. Generalized spasticity
4. Shunt malfunction in children (possible autoimmune reaction)

Neuropathology

1. Sural nerve biopsy
 - a. Axonal damage

Neuroimaging

1. MRI
 - a. Some patients with cerebral atrophy by MRI

Subacute Myelo-Optic Neuropathy

General Characteristics

1. Likely due to the iron chelator
2. Most patients between 1957–1970 in Japan had taken chelator for a prolonged period of time

Clinical Manifestations

1. Optic neuropathy
2. Proprioceptive and vibratory loss
3. Depression
4. Spasticity and gait ataxia
5. Dysesthesia of the lower extremities

Neuropathology

1. Axonal degenerations and gliosis in the cervical spinal cord (fasciculus gracilis)

Neuroimaging

1. MRI
 - a. T2-weighted hyperintensities in the cervical spinal cord
 - b. Volume loss in the dorsal columns
 - c. FLAIR and tractography are normal

Autoimmune Causes of Spinal Cord Dysfunction

Overview

Almost all autoimmune diseases may involve the spinal cord some time in their course. This involvement is frequently overshadowed by cerebral and cerebellar signs and symptoms. Spinal cord involvement in the various forms of MS may be the most prominent etiology of autoimmune disease of the spinal cord. The neuromyelitis-optica spectrum disorder (NMOSD) specifically affects the spinal cord over

many segments with concurrent optic nerve involvement. The spinal cord is less often the predominant pathology in acute disseminated encephalomyelitis in which multiple lesions develop simultaneously. A significant proportion of these patients evolves into a form of multiple sclerosis. Acute hemorrhagic encephalomyelitis has the propensity to involve the left side of the neuraxis and is explosive in onset. Systemic lupus erythematosus may present with transverse myelitis or affect the spinal cord sometime during its evolution. Sjögren's syndrome may preferentially affect the posterior columns, but also causes transverse myelitis. All autoimmune diseases may affect the spinal cord. Sarcoid involves the dura but has an inflammatory component that involves the parenchyma and blood vessels. Graft-versus-host disease most often causes peripheral neuropathy, but may involve the CNS including the spinal cord. Chronic demyelinating inflammatory polyneuropathy overlaps rarely with CNS involvement. Transverse myelitis is the usual spinal cord pathology.

Autoimmune Demyelinating Diseases with Prominent Spinal Cord Involvement

1. Multiple sclerosis
2. Neuromyelitis optica
3. Acute disseminated encephalomyelitis
4. Acute hemorrhagic encephalitis
5. Systemic lupus erythematosus
6. Sjögren's disease
7. Sarcoid
8. Idiopathic hypertrophic pachymeningitis (IgG)
9. Graft-versus-host disease

Multiple Sclerosis

General Characteristics

1. Peak age is approximately 30 years and risk is high in the fourth decade. The risk is low in the sixth decade
2. Spinal cord abnormalities determine a great deal of the clinical disability in MS. The cross-sectional area of the upper cervical spinal cord is a significant spinal cord parameter in determining the expanded disability score
3. Spinal cord gray matter abnormalities are associated with secondary progression and physical disability
4. Some evidence that HLA-DRB1 alleles may have a role in determining the severity and extent of spinal cord involvement

Clinical Manifestations

1. Paresthesias of the palms rather than the fingers (the latter is more characteristic of nerve or brachial plexus sensory loss)
2. Sensory level often to all modalities at the T4 (variants occur with cape like or abdominal presentations)
3. Gait instability and ataxia

4. Spasticity of the lower extremities with easily electable Babinski response, hyperactive reflexes and clonus
5. Loss of superficial abdominal reflexes
6. In almost invariant bladder dysfunction:
 - a. Neurogenic
 - b. Dyssynergia between detrusor contraction and sphincter opening
7. Bowel involvement is usually constipation
8. Focal amyotrophy in the upper extremities may occur
9. Associated neurologic signs:
 - a. Intranuclear ophthalmoplegia
 - b. Afferent papillary defect
 - c. Bilateral cerebellar ataxia
 - d. Bilateral cortical spinal tract dysfunction
 - e. Cognitive decline

Neuropathology

1. Lesions vary in the spinal cord from less than a millimeter to several centimeters. Lesions are sharply demarcated
2. Rarely does a lesion extend past the root entry zone
3. Myelin sheath destroyed early with relative axonal sparing
4. Some anterior horn cell involvement
5. Inflammatory changes predominate early; signs of defective remyelination and gliosis are later manifestations

Neuroimaging

1. MRI:
 - a. Focal cord lesions are evident in > 82% of patients; numbers of plaques are maximal in the cervical cord and increase with disease duration
 - b. Focal lesions are usually round or oval; 35% of patients may have subpial wedge-shaped lesions. Diffuse cord involvement may occur in 10% of patients

Laboratory

1. Approximately 30% of patients with acute onset or during an exacerbation have CSF:
 - a. Mononuclear pleocytosis (<50 cells/mm³)
 - b. IgG and oligoclonal bands are positive in a majority of patients

Neuromyelitis Optica Spectrum Disorder (NMOSD) or Devic's Disease

General Characteristics

1. Prevalence is approximately 0.3–4.4 per 100,000 of the population. It accounts for approximately 1–2% of demyelinating disease in Caucasians, but approximately 20–45% of Asian patients
2. It appears to be more prevalent in black patients in the USA
3. Women are preferentially affected 10:1 over men
4. The age of onset varies with approximately 1% of patients being children or elderly. The median age of onset is 40 years

5. Several HLA variants and polymorphisms have been identified
6. Associated autoimmune diseases occur in 10–40% of patients and include:
 - a. SLE
 - b. MG
 - c. Sjögren's syndrome
 - d. Celiac disease

Clinical Manifestations

1. Approximately 50% of NMO patients present with isolated optic neuritis (ON) of which 20% are bilateral (extremely rare in MS)
2. Profound loss of visual acuity is common (VA 20/200) which differs from MS. Severe visual acuity loss occurs in 80% of NMO patients and 36% of MS during an acute attack
3. NMO optic neuritis is distinguished from MS ON by MRI imaging and functional studies:
 - a. NMO lesions are more extensive and more likely to involve the chiasm
 - b. Due to involvement of the optic chiasm, patients may develop a bitemporal or homonymous visual field deficit
 - c. Optical coherence tomography (OCT) demonstrates a severe peripapillary retinal nerve fiber layer (RNFL) loss in NMO > than that seen with MS

Current Criteria for NMO

1. ON and transverse myelitis
2. Two of three supportive findings
 - a. Contiguous spinal cord 3 vertebral levels
 - b. Brain MRI is not diagnostic of MS
 - c. Aquaporin-IgG 4 seropositivity
3. Seropositive patients with isolated ON or TM have NMO spectrum disorders. This designation carries a high risk of evolution to NMO

Neuropathology

1. A complement-mediated humoral immune reaction against Aquaporin4-expressing astrocytes
2. The target antigen of NMO-IgG is astrocytic foot processes AQP4 (is the most abundant water channel protein in the CNS). The foot processes are expressed primarily at the blood-brain barrier, subpial and subependymal areas
3. Perivascular deposition of immunoglobulins with complement activation occurs within axons

Neuroimaging

1. MRI:
 - a. Longitudinal 3 segment spinal cord involvement with swelling and gadolinium enhancement
 - b. Long optic nerve lesions that may extend into the chiasm and optic tracts

Laboratory Evaluation

1. Immunofluorescence assays for AQP4-IgG have a sensitivity of 2.3–77% and approximately 100% specificity
2. Autoantibodies to myelin oligodendrocyte glycoprotein may be seen in some pediatric patients with aquaporin 4 antibodies
3. GFAP may be elevated in the CSF during acute exacerbations

Acute Disseminated Encephalomyelitis (ADEM)

General Characteristics

1. An acute encephalitic, myelitic or encephalomyelitic process that is most common after an infection in children
2. Usually follows a febrile illness by 2 weeks in children. These are usually uncomplicated respiratory illnesses. The documented viral illnesses that appear to be associated with ADEM are:
 - a. CMV
 - b. HIV
 - c. Epstein-Barr
 - d. Mycoplasma
3. It has also followed vaccination

Clinical Manifestations

1. The encephalitic form is more common in children than adults
2. Abrupt onset as the infection is resolving or after a short latent period
3. Children may have seizures and headache accompanied by ataxia, choreoathetosis, and myoclonus. Rarely decerebration and coma occur
4. New lesions may continue to form after the initial onset (rare)
5. The myelitic form:
 - a. Acute transverse myelitis:
 - i. Partial or complete paraplegia
 - ii. Bowel and bladder involvement
 - iii. A form that simulates anterior spinal artery infarction with primarily ventral cord involvement
 - iv. Sacral variant with severe back pain
 - v. In younger patients, the neurological deficits may be accompanied by slight fever
 - vi. Recovery in adults is the usual

Postvaccinal ADEM

General Characteristics

1. Post-rabies vaccination with older vaccine preparations may cause severe encephalomyelitis similar to that which occurs after measles infection
 - a. The illness may be initiated (after rabies vaccine with neural tissue) into an MS clinical picture
 - b. The process evolves over 2–4 weeks
2. Rarely presents with peripheral nerves and roots involved as with Guillain-Barré syndrome

Neuropathology

1. An acute inflammatory and demyelinating disease
2. Numerous areas of demyelination are seen throughout the hemispheres and spinal cord of approximately the same age. However, there are some evolving and new lesions after the initial event
3. Lesions vary from 1 mm to several millimeters that surround small and medium-sized veins
4. Axons and nerve cells are minimally involved
5. Perivascular lymphocytic and mononuclear cell reaction is frequent
6. Multifocal meningeal infiltration is characteristic

Neuroimaging

1. Multiple T2-weighted high signal intensity plaques throughout the neuraxis of approximately the same age. Many enhance with gadolinium, the lesions have blurred margins
2. Serial MRIs have shown the evolution of new lesions over time in some patients. Lesions may be confluent
3. ADEM patients with corpus callosum lesions:
 - a. Lesions may occur in the corpus callosum (primarily the splenium)
 - b. Usually in the setting of all lesions occurring simultaneously (they all enhance or are non-enhanced)

Laboratory Evaluation

1. CSF
 - a. Lymphocytic pleocytosis; slight protein elevation

**Acute Necrotizing Hemorrhagic Encephalomyelitis
(Weston-Hurst Disease)**
General Characteristics

1. Affects children and young adults
2. Probably the most severe form of ADEM (a variant)
3. Often follows a viral infection of undetermined cause

Clinical Manifestations

1. Abrupt onset accompanied by a headache, stiff neck, fever, and confusion
2. Evolves rapidly to seizures, hemiplegia or quadriplegia, bulbar signs, and coma

Neuropathology

1. The white matter of the hemispheres is severely involved. Severe changes are noted in the brainstem, cerebellum, and spinal cord
2. Widespread neurosis of small blood vessels and the brain tissue around the blood vessels
3. The intense inflammatory cellular reaction, small hemorrhages and an inflammatory meningeal reaction
4. Fibrin is deposited in the vessel wall
5. Fibrin exudation in the spinal cord of a patient with fatal encephalomyelitis has been described

Neuroimaging

1. Bilateral asymmetric extensive hypointensities with mass effect and microhemorrhages in the frontal and mesiotemporal lobes
2. Massive edema on T2-weighted and FLAIR sequences
3. Cortical ribbon may be spared
4. Gray and white matter microhemorrhages are noted

Laboratory Evaluation

1. CSF:
 - a. Acutely there is increased intracranial pressure
 - b. Variable cell counts from a few lymphocytes to a polymorphonuclear count of up to 3,000 cells/mm³; may have RBC's
 - c. Protein is increased
 - d. Glucose is normal

**Differential Diagnosis of Acute Hemorrhagic
Leukoencephalitis**

1. Brain abscess
2. Subdural empyema
3. Focal embolic encephalomalacia
4. Type 1 herpes simplex encephalitis

Graft-Versus-Host Disease*General Characteristics*

1. Neurologic complications after allogeneic hematopoietic stem cell transplantation are common and often severe
2. The incidence of neurologic complications may be related to the degree of human leukocyte antigen (HLA) disparity and the underlying disease
3. Intense immunosuppression regimes (use of fludarabine, busulfan, melphalan, cyclophosphamide or low dose body irradiation in the setting of allogeneic hematopoietic stem cell transplantation)
4. Graft-versus-host prophylaxis consists of cyclosporine A combined with methotrexate

Clinical Manifestations

1. Non-focal encephalopathy
2. Meningoencephalitis
3. Stroke
4. Intracranial hemorrhage
5. Mononeuritis and polyneuropathy
6. Sepsis-related encephalopathy in mechanically ventilated patients

Neuropathology

1. Mechanisms of disease:
 - a. Macrophage induced development of Th17 cells
 - b. Release of S100 proteins that amplify inflammation
 - c. Donor macrophages may be pivotal by secreting CSF1 and CSF-1R in the skin and lung
 - d. No human T-cells

Neuroimaging

1. No MRI CNS studies have been reported

Laboratory Evaluation

1. There is no standardized non-invasive diagnostic method to evaluate graft-versus-host disease
2. Immunologic assay monitors intracellular adenosine triphosphate (ATP) levels in stimulated T-cells

Spinal Cord Involvement in SLE*General Characteristics*

1. CNS is affected in approximately 75% of patients
2. Often neurologic features of SLE develop in the late stage of the illness. They may occur early and be the presenting feature
3. Some neurological features may be secondary to HCVD and Libman-Sacks endocarditis. TTP may complicate the terminal phase of the disease

Clinical Manifestations

1. Psychosis
2. Proximal Myopathy
3. Seizures
4. Choreoathetosis
5. Conducting vessel strokes
6. Features of antiphospholipid antibody syndrome

Clinical Manifestations of Spinal Cord Involvements

1. Patients with extensive longitudinal involvement (4 segments):
 - a. 77% are females with mean age of 29 years
 - b. 23% of patients may be the presenting manifestation
 - c. Sensory > motor > sphincter disturbance
 - d. Cervical to mid-lower thoracic levels are involved
2. Signs and symptoms of acute transverse myelitis

Neuropathology

1. White matter changes in the cerebral hemispheres
2. Longitudinal involvement of the spinal cord of several segments (similar to AQP-4 of Devic's disease)
3. Widespread microinfarcts in the cerebral cortex and brainstem
4. Destructive and proliferative changes in arterioles and capillaries
5. No cellular vascular infiltrate; immune complexes are attached to the endothelium
6. Hypertensive changes and those from emboli of Libman-Sacks endocarditis

Neuroimaging

1. Increased T2-weighted signal intensity in the involved segments (cervical to mid thoracic) that are affected longitudinally
2. Cord swelling and contrast enhancement
3. Rarely transverse myelitis with similar imaging features

Laboratory Evaluation

1. Antibody to double-stranded DNA (anti-dsDNA) is sensitive
2. Coexistent lupus anticoagulant and anticardiolipin antibodies

Wegener's Granulomatosis*General Characteristics*

1. A subacutely evolving vasculitis with necrotizing granulomas of the upper and lower respiratory tract
2. The orbits, heart, skin, and joints may be concomitantly involved along with the nervous system
3. Necrotizing glomerulonephritis follows sinus disease. Overtime, neurologic manifestations occur in 1% to 50% of patients
4. Orbits are involved in 20% of patients and may simulate orbital pseudotumor, cellulitis or lymphoma

Clinical Manifestations

1. Polyneuropathy or mononeuritis multiplex
2. Multiple cranial neuropathies from direct extension of the nasal and sinus granulomas into the upper cranial nerves
3. Episodic hemicrania with periorbital ecchymosis; lower cranial nerve involvement from pharyngeal lesions
4. Rare Neurologic Complications
 - a. Seizures
 - b. Celebritis
 - c. Temporal Arteritis
 - d. Horner's syndrome
 - e. Papilledema
 - f. Ischemic stroke
 - g. Meningitis
5. Spinal Cord involvement with paraparesis:
 - a. Compression from dural thickening (granulomas)
 - b. The spread of inflammation to adjacent areas of the spinal cord

Neuropathology

1. Vasculitis of small arteries and veins
2. Fibrinoid necrosis of vessel walls with infiltrates of neutrophils and histiocytes

Neuroimaging

1. Epidural granulomatous masses that compress the cord (biopsy positive necrotizing granuloma)
2. Minimally hyperintensive epidural lesions on T1-weighted sequences and hypointense on T2-weighted images; minimal contrast enhancement peripherally
3. Intraparenchymal contrast enhancement at the lesion level

Laboratory Evaluation

1. Elevated sedimentation rate, rheumatoid and antiglobulin antibody levels
2. Elevated C-ANCA titers (antineutrophil cytoplasmic antibodies); increased titers of antimyeloperoxidase (MPO)
3. CSF:
 - a. Increase of IgA, IgM and IgG (one patient)

Sjögren's Syndrome*General Characteristics*

1. May occur at any stage of the illness; during the development of the full sicca complex or just with involvement of the minor salivary glands
2. The neurologic symptomatology may precede the other manifestations of the disease
3. Women > men

Clinical Manifestations

1. Posterior root ganglionopathy
2. Sensory peripheral neuropathy
3. Myelopathy
4. Optic neuritis

Neuropathology

1. Lymphocytic infiltration of the exocrine glands, particularly the parotid and lacrimal glands
2. May have associated arthritis, lymphoma, vasculitis, IgM paraproteinemia and renal tubular defects

Neuroimaging

1. Multiple foci of high signal intensity on T2-weighted sequence
2. Transverse myelitis
3. Longitudinal long segment involvement
4. Posterior column involvement

Laboratory Evaluation

1. Positive anti-Ro (SSA) and anti-La (SSB) antibodies
2. Monoclonal IgM immunoglobulins
3. Lip biopsy

Neuro-Sarcoid*General Characteristics*

1. Most involved organs are the mediastinal and peripheral lymph nodes, lungs, liver, skin, phalangeal bones, parotid glands
2. CNS and PNS involvement occurs in approximately 5–50% of patients

Clinical Manifestations

1. Cranial neuropathy (VII); optic neuropathy and retinal vasculopathy; cranial nerve V
2. Mononeuropathy and mononeuropathy multiplex; sensory predominant peripheral neuropathy; lumbar or brachial plexopathy; cauda equina and polyradiculopathy
3. Brain lesions:
 - a. Nodular masses (simulating MS)
 - b. Perivascular infiltration
 - c. Posterior pituitary and perichiasmatic involvement
 - d. Dural involvement of the brain and spinal cord
4. Spinal cord:
 - a. Granulomatous meningomyelitis
 - b. Pachymeningitis

Neuropathology

1. Granular infiltration of the meninges and parenchyma
2. The lesion consists of a focal collection of epithelial cells surrounded by a rim of lymphocytes; giant cells may be seen, but no caseation

Neuroimaging

1. MRI
 - a. Dural involvement
 - b. Nodular masses on T2-weighted or FLAIR sequences that are multifocal
 - c. Thickened spinal dura (Pachymeningitis)
 - d. Posterior hypothalamus and pituitary involvement
 - e. Lesions may enhance with gadolinium and be longitudinally extensive
 - f. Swollen cord at the level of involvement

Laboratory Evaluation

1. Mild anemia, hypercalcemia, slightly elevated sed rate, slight hyperkalemia
2. Angiotensin-converting enzyme (ACE) may be increased in the serum (approximately 2/3 of patients with lung involvement) and the CSF in many with neurologic involvement
3. CSF evaluation:
 - a. Lymphocytic pleocytosis
 - b. Glucose of 30–40 mg/dl
 - c. Protein slight to moderate elevation

Differential Diagnosis of Sarcoid Myelitis

1. Demyelinating disease
2. SLE
3. Wegener's disease
4. Lymphomatoid granulomatosis (if there is lung involvement)
5. Cryptococcus and other deep fungi
6. Syphilis
7. Whipple's disease (large joint arthritis, GI involvement)

Infections of the Spinal Cord**Epidural Abscess***General Characteristics*

1. Staphylococcus aureus is the organism most frequently. The other organisms are:
 - a. Streptococci
 - b. Gram negative bacilli
 - c. Anaerobic organisms
2. Injuries, skin and wound infection or bacteremia are the primary causes
 - a. Bacteremia may seed the epidural space directly or cause vertebral body osteomyelitis with consequent spread to the epidural space
 - b. Following spinal procedures

Bacterial Infection

General Characteristics

1. The most often cause is an infected disc:
 - a. Epidural anesthesia and lumbar puncture give direct access to the epidural space. Prolonged epidural anesthesia for severe pain problems may be associated with catheter infection. This may be exacerbated by steroid epidural infection (may cause cauda equina epidural abscess)

Clinical Manifestations

1. Early there may be low-grade fever and local intense back pain which progresses to:
 - a. Severe radicular pain within a day or two
 - b. Rapidly progressive paraparesis with a sensory level and bowel and bladder dysfunction
 - c. Spine percussion at the infectious site is extremely painful
 - d. Subdural abscess is indistinguishable clinically

Neuropathology

1. Abscess formation with cord compression
2. Following spinal cord decompression, there may be signs of a slowly progressive myelopathy. This is caused by a fibrous and granulomatous reaction at the operative site
 - a. Fever, leukocytosis, elevated sedimentation rate and C-reactive protein suggest continued infection
3. Long standing infection or inadequate therapy may cause adhesive meningomyelitis
4. Venous ischemia of the cord

Neuroimaging

1. Increased signal from the disc space on T2-weighted sequences is often the first manifestation of discitis
2. Enhancement of the posterior and anterior longitudinal ligament, para-spinal muscles and the rim of the abscess itself
3. CT myelography that demonstrates a blurred margin and greater vertical extent in post-surgical incomplete abscess drainage

Laboratory Evaluation

1. CSF:
 - a. Neutrophilic pleocytosis usually less than 100/mm³ and lymphocytosis
 - b. Protein is between 100 mg–400 mg/dl
 - c. Normal glucose
2. Peripheral elevation of the sed rate, C-reactive protein, and leukocytosis

Spinal Cord Abscess

General Characteristics

1. Systemic bacterial infection septicemia, endocarditis, and bed sores are common causes of infection. In this instance,

(bed sores) there may be a subcutaneous fistula that allows bacteria to access the cord through an intervertebral foramen

2. Dorsal fistulous tract

Clinical Manifestations

1. Severe mechanically sensitive back pain at the infected level
2. Radicular pain
3. Paraparesis, sensory level, sphincter dysfunction

Neuropathology

1. Acute bacterial infection

Neuroimaging

1. T2-weighted sequences that demonstrate an edematous swollen cord at, above and below the infected segments

Laboratory Evaluation

1. Similar to those of epidural abscess

Vertebral Body Osteomyelitis

General Characteristics

1. Hematogenous spread of infection or following neurosurgical spine procedures:
 - a. Stabilization instrumentation
 - b. Catheter use
2. Post-surgical procedure organisms:
 - a. Coagulase-negative staphylococci
 - b. Propionibacterium
3. Organisms from bacteremia:
 - a. Low virulence
 - b. May be due to multiple organisms
 - c. May have delayed symptoms and signs (gram negative organisms) up to one month to six weeks following the procedure
 - d. Staphylococcus
4. Bacteremia source:
 - a. Immunocompromised patient (Brucella)
 - b. Uncontrolled diabetes
 - c. Intravenous drug use
 - i. Often at T4–6 a watershed spinal level
 - d. Renal dialysis
 - e. Endocarditis
5. Approximately 20% have associated epidural abscess and in 50% of patients, the source cannot be identified

Clinical Manifestations

1. Fever may not be present
2. Severe local mechanosensitive back pain (pounding on the back), especially if there is associated discitis

Neuropathology

1. In general cancerous involvement does not cross the disc space. Disc involvement most often is an infection
2. Inflammatory exudates and bone infection demonstrated by biopsy

Laboratory Evaluation

1. Elevated peripheral white count, sed rate, and C-reactive protein

Neuroimaging

1. MRI:
 - a. High T2-weighted signal in the vertebral body
 - b. Associated ligament involvement and discitis

Tuberculosis Spinal Osteomyelitis (Pott Disease)*General Characteristics*

1. Tuberculous osteomyelitis of the spine with kyphosis:
 - a. Still prevalent in endemic parts of developing countries
 - b. Children and young adults are most often affected
 - c. Reactivation of tuberculosis from hematogenesis spread

Clinical Manifestations

1. Angulated kyphotic deformity; with additional rotary instability causes a Gibbus Deformity
2. Active manifestations of tuberculosis are often concurrent
3. Compressive myelopathy occurs from:
 - a. The deformity (infrequently)
 - b. Tuberculous abscess
 - c. In USA lumbar > thoracic > cervical segments affected. In Asia, cervical segments are most involved

Neuropathology

1. Infectious endarteritis causes bone necrosis with collapse of a thoracic or lumbar vertebrae
2. Pus or caseous granulation tissue from the infected vertebra compresses the spinal cord
3. Tuberculous meningitis may cause a pial arteritis and consequent spinal cord infarction
4. Tuberculomas are exceedingly rare

Neuroimaging

1. MRI:
 - a. Endplate disruption
 - b. Paravertebral soft tissue (cold abscess)
 - c. High signal intensity of the intervertebral disc
 - d. High sensitivity but low specificity is bone marrow edema

Laboratory Evaluation

1. Organisms may be identified directly in the CSF
2. PCR is positive in the CSF or from bone biopsy

Enterovirus Group A and B*General Characteristics*

1. Selective attack on neurons of the spinal cord and brainstem
2. Non-polio enteroviruses are associated with acute flaccid paralysis in polio endemic areas of Africa and East Asia

3. Enteroviruses are members of the genus enterovirus family Picornaviridae
4. Spread by the fecal-oral route
5. Enterovirus A is divided into two groups:
 - a. Hand, foot and mouth disease group (herpangina; self-limited)
 - b. A group with severe autonomic dysregulation
6. HEV-B species are predominant in many areas

Clinical Manifestations

1. Brainstem encephalitis is characterized by three stages with HEV-71:
 - a. Uncomplicated
 - b. Autonomic nervous system dysregulation
 - i. Pulmonary edema
 - ii. Nucleus tractus solitarius and medullary involvement
 - c. Acute flaccid paralysis

Neuropathology

1. Immunopathogenesis plays a major role in the illness. Regulatory T-cells control the expansion of effector T-cells and modulate inflammation
2. Destruction of vasomotor and respiratory centers in the medial, ventral and caudal medulla (similar to polio)
3. Destruction of anterior horn cells
4. Release of proinflammatory cytokines (hypercytokinemia)
5. Inflammatory cells, necrosis, was found in clusters in the spinal cord. Inflammatory cells were CD 68 positive and CD 15 negative

Neuroimaging

1. Enterovirus 71-related acute flaccid paralysis in patients with hand-foot-mouth disease:
 - a. Anterior horn regions and ventral roots of the cervical spinal cord and below the T9 level are often affected
 - b. High signal in T2-weighted images and low signal T1-weighted sequences in all patients with acute flaccid paralysis. Mild enhancement of anterior horn areas and ventral roots
 - c. Involvement of the central midbrain, posterior portion of the medulla and pons, and bilateral dentate nuclei

Laboratory Evaluation

1. CSF:
 - a. Lymphocytic pleocytosis
 - b. Slight protein elevation

Coxsackie A and B*General Characteristics*

1. Immunosuppressive drugs that target the humoral immune response (rituximab for B-cell lymphoma) may lead to reactivation and increased replication of persistent HEV in the CNS

Clinical Manifestations

1. A cause of hand-foot-mouth disease without neurologic complications
2. Acute disseminating myelitis and transverse myelitis
3. Purpuric and petechial rashes may occur

Neuropathology

1. Anterior horn cell inflammation and neuronal necrosis in those patients with flaccid paralysis

Laboratory Evaluation

1. CSF:
 - a. Lymphocytic pleocytosis
 - b. Mild protein elevation

Poliomyelitis*General Characteristics*

1. Occurs in developing countries and those endemic areas without vaccination programs
2. Polio is an RNA virus of the picornavirus family. Humans are the only known hosts
3. Fecal, oral route of entry; the virus replicates in the pharynx and intestinal tract
4. Only 1–5% of infected patients have nervous system complication

Clinical Manifestations

1. Asymptomatic
 - a. Pharyngitis or gastroenteritis which occurs during viremia
2. Non-paralytic poliomyelitis:
 - a. Fatigue, headache or fever (100–104 degrees)
 - b. Stiff and aching muscles
 - c. Sore throat
 - d. Symptoms may subside which is then followed by recurrence in 3–4 days with an increase of initial symptomatology
 - e. Aseptic meningitis or evolves into the paralytic phase
3. Paralytic phase:
 - a. Weakness occurs with fever
 - b. Muscle weakness may develop over 48 hours or 7–8 days
 - c. Fasciculations are seen in stricken muscles
 - d. Reduced or loss reflexes occur with flaccid paralysis
 - e. Paresthesias without sensory signs are seen in the paralyzed limbs
 - f. Bladder dysfunction may occur early
 - g. Atrophy of affected muscles starts at three weeks and is maximum at 3–4 months
 - h. Involvement of the nucleus ambiguus and n. tractus solitarius respiratory and autonomic control

Neuropathology

1. Lesions in the precentral gyrus, brainstem, and spinal cord. The anterior horn cells and those of the intermediolateral column are severely affected

2. Neuronophagia, leukocyte inflammatory reaction, and perivascular monocyte accumulation occurs
3. Central chromatolysis of motor neurons
4. Mild inflammatory changes in the meninges and dorsal root ganglion

Neuroimaging

1. T2-weighted signal hyperintensities in the ventral spinal cord

Laboratory Evaluation

1. Difficult to isolate the virus from the CSF during the infection (in counter distinction to Coxsackie and echoviruses)
2. CSF findings of aseptic meningitis usually 50–150 lymphocyte/mm³

Differential Diagnosis of Non-Poliovirus Infection with Phenotypic Poliomyelitis

1. RNA viruses:
 - a. Echoviruses
 - b. Coxsackie enteroviruses (A9 and B5)
 - c. Enterovirus 70 (associated conjunctivitis)
 - d. Enterovirus 71 (brainstem and spinal cord)

Herpes Zoster*General Characteristics*

1. An exclusive human neurotropic alpha-herpes virus
2. Primary infection causes chicken pox
3. Latent infection in dorsal root, autonomic and cranial ganglia
4. Reactivation with a decline in cell-mediated immunity in elderly and immune compromised patients

Clinical Manifestations

1. Herpes Zoster
2. Post-herpetic neuralgia
3. Vasculopathy (MCA infarction with V1 root infection)
4. Retinal necrosis
5. Cerebellitis
6. Zoster sine herpete (pain radiculopathy without rash)
7. Herpes Zoster ophthalmicus:
 - a. Skin lesions extend to medial side of the nose (Hutchinson's sign)
 - b. Optic nerve involvement
 - c. Ophthalmoplegia (III and VI, rarely IV)
8. Zoster oticus:
 - a. Rash in the external auditory canal and VIIIth nerve palsy (Ramsay Hunt syndrome); tinnitus with VIIIth cranial nerve involvement

Varicella Zoster Virus Myelopathy*General Characteristics*

1. Cervical or lumbar distribution causes anterior horn cell involvement in the arm and leg

2. Rarely thoracic zoster causes abdominal anterior horn cell necrosis (consequent abdominal herniations)
3. Two major variants:
 - a. "Post-infectious-myelitis"
 - i. Self-limiting monophasic spastic paraparesis
 - ii. Minimal sensory loss and sphincter disturbance
 - iii. Occurs in immune competent patient days to weeks after acute varicella or zoster infection
 - b. Insidious progressive myelitis
 - i. Immunocompromised patients
 - ii. AIDS is the most common medical problem associated with VZV myelitis
 - iii. May have recurrent form

Neuropathology

1. In immune compromised patients:
 - a. Invasion of VZV into the spinal cord parenchyma and adjacent nerve roots
 - b. VZV myelitis may develop with rash
 - c. VZV spinal cord infarction

Neuroimaging

1. AIDS associated VZV myelitis
 - a. Longitudinal serpiginous enhancing lesions

Laboratory Evaluation

1. CSF in immune competent patients:
 - a. Mild mononuclear pleocytosis with normal or slightly elevated protein
- b. CSF in immune compromised VZV patients:
 - i. Mild predominately mononuclear pleocytosis
 - ii. VZV DNA (PCR) or anti-VZV IgG or both in the CSF

HIV

General Characteristics

1. The frequency of spinal cord involvement in AIDS is approximately 20%. Often overshadowed by neuropathy or opportunistic infection

Clinical Manifestations

1. Asymmetric leg or arm weakness, sensory and sphincter disturbance that may develop over weeks
2. Sensory ataxia

Neuropathology

1. White matter of the spinal cord is vacuolated (ballooning of myelin sheaths of long tracts)
2. Some involvement of axons
3. The most severe changes are seen in the posterior and lateral tracts at thoracic levels
4. Rarely similar changes in the brain
5. Lipid-laden macrophages are noted
6. Pathology resembles that which occurs in B12 deficiency

Neuroimaging

1. Transverse myelitis with gadolinium enhancement
2. Long segment involvement with bilateral T2 signal weighted hyperintensity in the thoracic cord without enhancement and with posterior column predominance

Laboratory Evaluation

1. Low lymphocyte count
2. Slight protein elevation
3. Occasional bizarre giant cells

Tropical Spastic Paraparesis (Human T-Cell Lymphotropic Virus Type I) HTLV-1

General Characteristics

1. Primarily found in the Caribbean islands, southern Japan, South America and Africa
2. Transmission occurs from:
 - a. Transfer of infected lymphocytes (CD4+)
 - i. Perinatal
 - ii. Breast feeding
 - iii. Blood transfusions
 - iv. Sexual contact
 - v. Intravenous drugs
3. Both HTLV-1 and HTLV-2 utilize GLUT-1 and NRP1 cellular receptors to gain entry
4. HTLV-1
 - a. Conclusively associated with leukemia/lymphoma (approximately 5% of infected individuals)
 - b. Approximately 5% of infected individuals develop HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP)
5. HTLV-2
 - a. Is associated with elevated lymphocytic and platelet counts
 - b. An increase in cancer mortality
 - c. Rarely associated with a myelopathy
 - d. Approximately 10–20 million people are infected worldwide

Clinical Manifestations

1. Primarily occurs in adults
2. Insidious onset with gait alteration and bladder dysfunction as the presenting signs
3. Spasticity and hyper-reflexia of the lower extremities
4. Lower extremity muscle weakness
5. 50% of patients have back pain
6. No cranial nerve involvement
7. Progressive course without remission
8. Associated medical complications
 - a. Uveitis
 - b. Myositis
 - c. Infective dermatitis
9. Coinfected patients (with HIV)
 - a. Present at an earlier age
 - b. <40 years of age
 - c. Present to hospital sooner

Neuroimaging

1. Long segment involvement with bilateral T2 signal weighted hyperintensity in the thoracic cord without enhancement and with posterior column predominance
2. White matter hyperintensities are seen in the brain on T2-weighted sequences
3. Mild atrophy of the thoracic spinal cord

Laboratory Evaluation

1. Low lymphocyte count
2. Slight protein elevation
3. Occasional bizarre giant cells
4. High levels of antibody titers against HTLV-1 antigens in the blood and CSF
5. High HTLV-1 proviral load is found in the blood
6. Moderate increase of CSF protein is seen in the CSF accompanied by intrathecal production of specific HTLV-1 antibody

Neuropathology

1. Chronic inflammation with perivascular lymphocytic cuffing
2. Some parenchymal lymphocytic infiltration
 - a. CD4(+) lymphocytes in early disease
 - b. CD8(+) in later stages
3. Pyramidal tract destruction with both demyelination and axonal loss primarily in the lower thoracic spinal cord
4. Focal spongiform demyelination, destruction of gray matter
5. The posterior columns may be prominently involved

Rabies*General Characteristics*

1. Rare now in the USA; bats, raccoons, skunks, foxes and dogs are the reservoir
2. India has high prevalence and small pockets of disease occur in developing countries
3. Approximately 20–30,000 people receive rabies vaccine/year
4. Inoculation is primarily by the bite of a rabid animal

Clinical Manifestations

1. Incubation period is usually between 20–60 days; face and neck bites may have a very short incubation period (14 days)
2. Tingling and numbness at the site of the bite (which may occur after healing of the wound)
3. 2–4 day prodromal period that includes:
 - a. Fever, headache malaise
 - b. Apprehension
 - c. Dysarthria and dysphagia
 - d. Behavioral alterations
 - e. Severe spasms of muscles of deglutition when attempting to swallow water

- f. Facial numbness and spasms
 - g. Diplopia
4. A spinal form may occur without behavioral alterations or concomitantly
 - a. May follow bat bites
 5. Coma follows the encephalitic phase which evolves to death in 4–10 days

Neuropathology

1. Negri bodies
 - a. Predominately in pyramidal cells of the hippocampus and cerebellar Purkinje cells:
 - i. May be seen in nerve cells of the brain and spinal cord
 - ii. Perivascular cuffing with lymphocytes and monocytes
 - iii. Intense brainstem inflammatory response
 - iv. Focal microglial nodules

Neuroimaging

1. MRI:
 - a. Predilection for midline gray matter
 - b. T2 and Flair sequences involve the dorsal brain stem, thalamus and basal ganglia
 - c. Involvement of central gray matter of the spinal cord
 - d. Involvement of the hippocampus and subcortical white matter occurs

Laboratory Evaluation

1. RT-PCR (100% sensitivity)
2. The direct immunofluorescence test detects rabies viral antigen in 83.3% of rabies positive patients

Epstein-Barr Virus*General Characteristics*

1. Epstein-Barr virus (EBV) is a member of the herpes virus family
2. EBV is a herpes virus that is detectable in >90% of the general population
3. Maybe associated with infectious mononucleosis
4. AIDS patients have 10–20 times as many circulating EBV-infected B-cells than control patients

Clinical Manifestations

1. Meningitis
2. Encephalitis
3. Cranial nerve involvement
4. Peripheral neuropathy
5. Radiculitis
 - a. Myelitis with EBV is rare: May present as Brown-Séquard syndrome
 - b. Transverse myelitis

Neuropathology

1. Neuronal loss in anterior horn cells
2. Lymphocytic perivascular cuffing

3. Inflammatory changes
4. Involvement of white matter long tracts
5. Infiltration of cytotoxic CD8+lymphocyte
6. Deposition of antibody-antigen complexes

Neuroimaging

1. Cervical and thoracic segmental involvement with expansion of the cord; mild gadolinium enhancement

Laboratory Evaluation

1. Lymphocytic pleocytosis
2. Moderately elevated protein
3. Diagnosis by PCR of DNA in the CSF

Cytomegalovirus (CMV)

General Characteristics

1. CMV is a member of the ubiquitous Herpes Virus family
2. Primary infection is usually asymptomatic or mononucleosis-like
3. Reactivation of the virus may have severe consequences in immunosuppressed patients; transplant and AIDS patients

Clinical Manifestations

1. Pneumonitis
2. Hepatitis
3. Uveitis
4. Retinitis
5. Hepatosplenomegaly
6. Colitis
7. Graft rejection
8. Neurologic manifestations:
 - a. Encephalitis
 - b. Myeloradiculitis
 - c. Myelitis
 - d. Conus medullaris and cauda equina involvement in immunosuppressed patients is common
 - e. Brown-Séquard syndrome

Neuropathology

1. Direct cytolysis of neurons
2. Vascular thrombosis
3. Uveitis retinitis, corneal endotheliitis and papillitis

Neuroimaging

1. MRI
 - a. Swelling and gadolinium enhancement of the conus characteristic medullary and the cauda equina

Laboratory Evaluation

1. Anti-CMV IgM antibodies primarily
2. Seroconversion of IgG antibody titer during the illness

Herpes Simplex

General Characteristics

1. A cause of lymphoproliferative disease in immunocompromised patients

2. Herpes virus type 1 (HSV-D and VZV are the most frequent cause of sporadic encephalo/myelitis)

Clinical Manifestations

1. Encephalitis
2. Myelitis
3. Retinitis

Neuropathology

1. Bilateral and asymmetric necrosis of the temporal lobes
2. Leptomeningeal infiltration by lymphocytes, plasma cells
3. Perivascular cuffing and neuronophagia

Neuroimaging

1. MRI: Transverse myelitis

Laboratory Evaluation

1. CD19 and CD20 B-cells in those that have undergone organ transplantation
2. Viral DNA detected in the CSF by PCR

Herpes Virus Type II

Clinical Manifestations

1. Myelitis
2. Encephalitis with posterior uveitis
3. Meningitis and vasculopathy

Differential Diagnosis of Herpes Virus Infections with Transverse Myelitis

1. VSV 1 (Herpes virus)
2. VZV
3. Beta and gamma herpes virus
4. Epstein-Barr virus
5. HHV6 – 8 viruses
6. Hepatic viruses
7. SV 70

Japanese Encephalitis

General Characteristics

1. Endemic virus in Southeast Asia
2. A single-stranded RNA virus belonging to the Flaviviridae family
3. Arthropod-borne

Clinical Manifestations

1. Severe encephalitis
2. Acute flaccid paralysis (spinal cord syndromes)

Neuropathology

1. Perivascular infiltrate is mononuclear
2. Foci of rarefaction and necrosis
3. Gray matter is affected in the thalamus, substantia nigra, cerebral cortex, and hippocampus
4. Spinal cord anterior horn cell involvement

Neuroimaging

1. MRI: Ventral cord hyperintensity on T2-weighted sequences

Laboratory Evaluation

1. Rapid microneutralization test (MNT); neutralizing human antibodies
2. Seroconversion of IgM and IgG by ELISA

West Nile*General Characteristics*

1. Almost all states in the USA have reported patients
2. Migrating birds apparently spread the virus, crows are important reservoir in the eastern USA
3. Virus of the family Flaviviridae
4. Incidence is highest in the Midwest from mid-July to early September; mosquito bite transmission

Clinical Manifestations

1. Meningitis
2. Encephalitis
3. Acute flaccid paralysis
 - a. Approximately 2/3 of patients that have developed paralysis have permanent weakness of the affected extremities

Neuropathology

1. Microglial nodules and perivascular chronic inflammation
2. Neuronal loss with necrosis or neuronophagia

Differential Diagnosis of Arbovirus-Flavivirus with Transverse Myelitis

1. Eastern, Western and Venezuelan equine encephalitis
 - a. The spinal cord is generally spared. If involved the upper cervical cord is affected
2. St. Louis Encephalitis:
 - a. The pathology is usually in the cortex, basal ganglia and cerebral white matter
 - b. Cerebellar infiltration and inflammation is more severe in St. Louis than Western Equine encephalitis
3. Japanese Viral Encephalitis
4. West Nile Fever
5. Tick Born Viruses:
 - a. Ixodes ricinus is the vector
 - b. Reindeer are a reservoir (Scandinavia)
 - c. Clinical manifestations:
 - i. Primarily viral encephalitis
 - ii. Spinal cord may be involved

Myelitis from Bacteria, Fungal and Parasitic Diseases***Mycoplasma Pneumonia****General Characteristics*

1. Children are primarily affected with atypical pneumonia

2. CNS involvement occurs in approximately 2–5% of patients
3. Associated autoimmune disorders include:
 - a. Hemolytic anemia
 - b. Arthritis
 - c. Carditis

Clinical Manifestations

1. Usually, the onset of neurological manifestations is one week after the respiratory illness and includes:
 - a. Meningitis
 - b. Meningoencephalitis
 - c. Encephalitis
 - d. Polyradiculitis
 - e. Cerebral infarction (vasculopathy)
 - f. Cerebellar ataxia
 - g. Cranial neuropathy
 - h. Transverse myelitis

Neuropathology

1. There is direct CNS invasion and an autoimmune component
2. Demyelination
3. Perivenous inflammation
4. Possible arterial vasculopathy

Neuroimaging

1. MRI: Transverse myelitis

Laboratory Evaluation

1. RT-PCR in CSF

Lyme's Disease*General Characteristics*

1. Spirochete of the disease is *Borrelia Burgdorferi*; there are differences between the European and American diseases
2. Tick bite relapsing fever is also caused by *Borrelia*
3. Vascular damage occurs in many organs
4. Early meningeal invasion that is asymptomatic
5. Less acute than leptospirosis and less chronic than syphilis
6. Involves the skin, joints, heart as well as the CNS and PNS
7. Infections are acquired from May to July

Clinical Manifestations

1. Erythema chronicum migrans occurs in 60–80% of patients
2. Transverse myelitis accounts for 4–5% of neuroborreliosis patients
 - a. Acute catastrophic onset with back pain possibly has a poorer prognosis
3. Subacute progressive onset over several days to up to four weeks possibly better prognosis
4. Other neurologic manifestations include:
 - a. Aseptic meningitis

- b. Fluctuating meningoencephalitis
- c. Uni- or bilateral facial palsy
- d. Cardiac manifestations may occur concomitantly:
 - i. Myocarditis
 - ii. Pericarditis
 - iii. Atrioventricular block
- e. Rare neurologic features:
 - i. Seizures
 - ii. Chorea
 - iii. Cognitive decline
 - iv. Cerebellar ataxia
 - v. Myelitic syndrome with quadriparesis
 - vi. Optic nerve and VIth nerve palsy with meningitis
- f. Bannworth syndrome:
 - i. Cranial VII
 - ii. Meningoradiculitis
 - iii. More common in Europe

Neuropathology

1. Perivascular lymphocytic inflammation in the meninges
2. Subcortical and periventricular demyelination
3. Peripheral nerves show lymphocytic infiltration without vasculitis

Laboratory Evaluation

1. CSF lymphocytosis during meningitis with cells varying from 50–3000/mm³
2. Protein varies from 75–400 mg/dl
3. Glucose is normal
4. ELISA demonstrates + IgG; after several weeks patients have + IgM antibody response:
 - a. Western blot of CSF
 - b. PCR-RT

Neuroimaging

1. MRI:
 - a. Cerebral; multifocal and periventricular lesion on T2-weighted sequences
 - b. Spinal involvement:
 - i. Edematous cord
 - ii. Enhancement with gadolinium which may remain in patients with poor outcome

Mechanisms of Spinal Cord Injury from Parasites and Fungi Include

1. Epidural granuloma
2. Local meningitis
3. Meningomyelitis
4. Abscess

Sarcoid

General Characteristics

1. Spinal cord involvement usually occurs during the progression of systemic disease (lung, heart or kidney)

Clinical Manifestations

1. Remission and relapses
2. Paraparesis with bladder dysfunction

Neuropathology

1. Intramedullary granulomatous masses that may occur at multiple levels
2. Dural involvement

Neuroimaging

1. MRI:
 - a. Pituitary and posterior hypothalamic involvement
 - b. Focal T2-weighted gadolinium-enhancing brain lesions
 - c. Dural enhancement and thickening
 - d. Lesions in the spinal cord may enhance; may be longitudinally extensive

Laboratory Evaluation

1. CSF:
 - a. Lymphocytic pleocytosis
 - b. Moderately elevated protein
 - c. Glucose may be slightly depressed (3040 mg/dl)
2. Positive angiotensin converting enzyme

Differential Diagnosis of Granulomatous Spinal Cord Disease

Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss)

General Characteristics

1. Systemic small vessel vasculitis with asthma and eosinophilia
2. Mean age at diagnosis is approximately 50 years
3. Associated medical problems:
 - a. Ear, nose and throat involvement
 - b. Skin lesions
 - c. Lung infiltrates
 - d. Cardiomyopathy
 - e. Renal involvement

Clinical Manifestations

1. Mononeuritis multiplex
2. Ischemic optic neuropathy
3. Dural granulomas (spinal cord)

Neuropathology

1. Tissue eosinophilia
2. Necrotizing vasculitis
3. Eosinophilic granulomatous
4. Dural and spinal cord masses
5. Bright yellow mass
 - a. Lipid-laden macrophages combined with chronic and acute inflammatory cells
6. Fibrosis and giant cells

Neuroimaging

1. MRI:
 - a. Primary involvement is gall bladder, kidney
 - b. Paranasal sinus involvement
 - c. Intraparenchymal spinal cord lesions
 - d. Eosinophilia > 10% of a differential white blood cell count

Burcellosis*General Characteristics*

1. A zoonotic granulomatous disease
2. Endemic in Middle Eastern and Mediterranean countries
3. Contracted by consumption of unpasteurized milk or its products

Clinical Manifestations

1. The most frequent systemic symptoms are fever, myalgia, malaise, arthralgia, weight loss and night sweats. Lymphadenitis may be prominent
2. Neurologic complications occur in less than 5% of patients
3. Neurobrucellosis includes:
 - a. Chronic encephalitis
 - b. Meningitis
 - c. Radiculoneuritis (often at L5–S1)
 - d. Myelitis; extradural spinal mass
 - e. Behavioral alterations
 - f. Diabetes insipidus
 - g. TIA and stroke (rare)
 - h. Optic neuritis and papilledema have been reported in children
 - i. Pseudotumor cerebri
 - j. Cranial nerve VIII involvement
 - k. Guillain-Barré syndrome
 - l. Cerebral vein thrombosis

Neuropathology

1. Leptomeningeal involvement
2. Vascular inflammation with invasion of plasma cells, lymphocytes, and macrophages
3. Inflammation of the perineurium of nerve roots
4. Edema of the cortex; perivascular mononuclear cell infiltration

Neuroimaging

1. MRI:
 - a. T2-weighted hyperintensities of an infected disc and adjacent vertebral bone
 - b. Cold abscess
 - c. PET/CT detects spread of infection better than MRI

Laboratory Evaluation

1. CSF
 - a. Moderate leukocytosis
 - b. Increased protein
 - c. Slight hypoglycorrhachia
 - d. Increased lactate
2. Positive serologic titers

Meningomyelitis Caused by Fungi, Rare Organisms, and Major Parasites**Actinomycosis***General Characteristics*

1. Anaerobic gram-positive bacteria:
 - a. Colonizes the mouth, digestive and genital tracts
 - b. Cervicofacial infection following a dental focus; pelvic infection with intrauterine devices; pulmonary foci in smokers
 - c. Filamentous gram-positive bacilli
 - d. Spreads contiguously and progressively which mimics a malignancy

Clinical Manifestations

1. Brain abscess
2. Meningoencephalitis
3. Epidural abscess
 - a. Spreads to the spinal cord through vertebral foramen
4. Subdural empyema
5. CNS involvement from:
 - a. Hematogenous spread from the lung
 - b. Contiguously from cervicofacial focus

Neuropathology

1. Mandible is the most affected site which may spread to the CNS by direct extension
2. Multilocular abscesses with central necrotic inflammatory exudates
3. Colonies of branching organisms that form “sulfur granules” that are surrounded by granulation tissue
4. Giant cells are occasionally seen
5. Spinal epidural abscess
6. Actinomycetoma

Neuroimaging

1. Brain abscess
2. Epidural spinal abscesses
3. Cavernous sinus thrombosis
4. Actinomycotic cerebral abscesses are usually single
 - a. Predilection for temporal and frontal lobe
5. Restricted diffusion by DWI
 - a. Pus has a low apparent diffusion coefficient
6. MRI spectroscopic features
 - a. Elevated peaks for:
 - i. Amino acids
 - ii. Lactate
 - iii. Alanine
 - iv. Acetate
 - v. Pyruvate and succinate
 - b. Absent signals for:
 - i. N-acetyl aspartate (NAA)
 - ii. Creatine
 - iii. Choline
7. Osteolysis of affected bone

Laboratory Evaluation

1. Gram-positive branching hyphae
2. Culture
3. Actinomycotic granules have a positive reaction to periodic acids

Blastomycosis*General Characteristics*

1. Endemic to Mississippi and Ohio River Basins and upper Midwest and S.E. USA
2. Men have greater incidence than women
3. Airborne conidia are inhaled from the soil
4. Lung, skin, osseous, genitourinary and CNS infections occur
5. Blastomyces dermatitidis is the causal agent of blastomycosis that can become systemic

Clinical Manifestations

1. CNS infection occurs in 5–10% of disseminated disease and causes:
 - a. Diabetes insipidus
 - b. Pituitary involvement in conjunction with meningitis
 - c. Gains access to the lungs and spreads to the brain through the blood stream
 - d. Meningitis
 - e. Single or multiple abscesses
 - f. Pachymeningitis
 - i. Spinal cord and brain compressions
 - g. Osteomyelitis of bone with contiguous spread from the skull or a vertebra
 - h. Iritis and uveitis

Neuropathology

1. Abscess center contains caseous material, neutrophils, and lymphocytes
 - a. Surrounded by epithelial and giant cells
2. Fungus on H&E demonstrates a central basophilic body surrounded by a clear space

Neuroimaging

1. MRI: Typical brain abscess

Laboratory Evaluation

1. An assay for the detection of antigen is available
2. CSF
 - a. May demonstrate very high protein up to 1000 mg/dl

Coccidioidomycosis*General Characteristics*

1. Endemic mycosis caused by the fungal pathogen coccidioides immitis
 - a. Fungi is the soil of deserts in the western hemisphere
 - b. Infection is from airborne spores (arthroconidia)

Clinical Manifestations

1. Both pathogenic and the cause of opportunistic infections
2. Initially, a mild febrile illness occurs
3. Neurological involvement:
 - a. Occurs in 1/3 of patients
 - b. Meningitis (basal)
 - c. Secondary hydrocephalus
 - d. Osteomyelitis of vertebrae with extension to the spinal cord

Neuropathology

1. Granulomas with small abscesses and caseous necrosis within the brain and spinal cord
2. Disseminated CNS disease in AIDS patients

Neuroimaging

1. MRI:
 - a. Infection of bones and joints
 - b. Typical brain granulomatous lesions
 - c. Osteomyelitis of the patella and sacrum

Laboratory Evaluation

1. Complement fixation (IgG) titers
2. Grocott's methenamine silver staining demonstrates spherule

Cryptococcus*General Characteristics*

1. Cryptococcus neoformans:
 - a. Found in the soil and droppings of some birds
 - b. Southern USA; worldwide distribution
2. Greater than 85% of infections associated with immunocompromised patients

Clinical Manifestations

1. Meningitis; often localized at the base of the cerebellar hemispheres
2. Spinal arachnoiditis
3. Lumbosacral polyradiculopathy

Neuropathology

1. Brain changes are close to areas of meningeal involvement
2. Meningitic exudates have a minimal inflammatory cellular reaction
3. Meninges may demonstrate tubercles of 2–3 mm in diameter
4. Recent foci and in AIDS patients:
 - a. Organisms that produce a "gelatinous" pseudocystic dilatation of the Virchow-Robin spaces
 - b. Intramedullary granulomas

Neuroimaging

1. MRI:
 - a. Associated topographic strokes of the hemisphere
 - b. Thin-walled cysts (dilatation of the Virchow-Robin spaces) in the basal ganglia

Laboratory Evaluation

1. CSF:
 - a. Lymphocytic pleocytosis
 - b. Moderate elevation of protein 80–120 mg/dl
 - c. PCR-based diagnosis

Aspergillosis*General Characteristics*

1. Aspergillosis fumigates primarily infects the external ear, lungs or paranasal sinuses
2. Disseminated form occurs in patients with cancer, collagen vascular disease or immunosuppression (renal or liver transplants)
3. Spreads to the CNS directly from the paranasal sinuses, orbit or hematogenously from the lung or GI tract

Clinical Manifestations

1. Abscess or granuloma in the brain that may be single or multiple
2. Usual infection is in the cerebral hemispheres
3. Epi- and subdural locations in the thoracic cord
4. Sino-orbital infection
 - a. Focal bony erosion
 - b. Grows through blood vessel walls

Neuropathology

1. Branching septate hyphae
2. The degree of inflammatory reaction depends on the immune status of the patient
3. Granulomas occur in the course of a chronic infection
 - a. Aggregates of plasma cells, epithelioid cells, and collagen are seen in areas of necrosis
 - b. Multinucleated giant cells may be seen

Neuroimaging

1. Typical brain abscess found in immunocompetent patients; multiple abscesses in immunocompromised patients
2. Predilection for the sphenoid bone
3. Sino-orbital bone destruction
4. MRI demonstrates focal enhancement

Laboratory Evaluation

1. Culture (Broncho alveolar lavage)
2. Typical branching septate hyphae
3. Elevated (1-3)-B-D-glucan and Galactomannan
4. RT-PCR

Schistosomiasis*General Characteristics*

1. One of the world's most widespread parasitic diseases
2. Affects >200 million patients worldwide
3. Endemic areas for *Schistosoma mansoni* are South America, the Middle East, and sub-Saharan Africa
4. Humans are the definitive host

- a. Fresh water snail (*Biomphalaria*) is an intermediate host:
 - i. Cercaria, a larval form released from snails, penetrates the skin and enters the blood and lymphatic system
5. May infect the spinal cord through Batson's plexus

Clinical Manifestations

1. Acute infection causes:
 - a. Fever
 - b. Headache
 - c. Myalgia
 - d. Diarrhea
 - e. Abdominal pain
2. Spinal schistosomiasis:
 - a. Radicular pain
 - b. Myelopathy with flaccid paraplegia, dysesthesia or incontinence of bowel and bladder
 - c. Acute inflammatory myeloradiculopathy is the most common neurologic complication of *S. mansoni* infection; cord syndrome; transverse myelitis
 - d. Onset of myelopathy may be delayed for months or years

Neuropathology

1. Affects the conus medullaris and cauda equina
2. Granulomas are deposited on spinal roots
3. Deposition of eggs in the spinal cord (inflammation):
 - a. Cerebral hemorrhage is rare

Laboratory Evaluation

- a. Enzyme-linked immune-absorbent assay is sensitive for diagnosis; detects elevated titers of antibody against the schistosoma
- b. CSF:
 - i. Mononuclear and lymphocytic pleocytosis
 - ii. Increased protein
 - iii. Usually normal glucose
 - iv. Eosinophilia
 - v. Oligoclonal IgG bands

Differential Diagnosis of Granulomas in the Spinal Epidural Space

1. Actinomycosis
2. Blastomycosis
3. Coccidioidomycosis
4. Aspergillus
5. Cryptococcus (rare)
6. Echinococcosis (rare)

Syphilis**General Characteristics**

1. Recent shift in presentation from parenchymal involvement to chronic meningovascular disease

2. The number of reported cases has increased both in immunocompetent and in AIDS patients
3. The CNS is usually infected 3–15 months after the initial chancre
4. The initial CNS infection is meningitis which occurs in approximately 25% of patients and is most often asymptomatic or if symptomatic may cause:
 - a. Cranial nerve palsies
 - b. Seizures
 - c. Stroke
 - d. Increased intracranial pressure
5. Early clinical features:
 - a. Aseptic meningitis
 - b. After 1–2 years meningovascular syphilis
 - c. Tertiary syphilis may develop after several years which includes:
 - i. General paresis
 - ii. Tabes dorsalis
 - iii. Optic atrophy
 - iv. Subacute myelitis
 - d. All clinical syndromes derive from meningitis; there are overlapping syndromes

Clinical Manifestations

1. Spinal syphilis:
 - a. Tabes dorsalis:
 - i. Occurs approximately 15 to 20 years after the primary infection
 - ii. Lightning pains (dorsal roots) are involved
 - iii. Ataxia (dorsal column)
 - iv. Urinary incontinence (overflow)
 - v. Impaired vibration and position sense of the lower extremities is associated with a positive Romberg sign and absent knee and ankle reflexes. Argyll Robertson pupil is present in most patients
 - vi. Optic atrophy and ptosis
 - vii. Constipation and megacolon (rare)
 - viii. Charcot joints and tropic ulcers of the feet may be prominent
 - ix. Visual crisis causes severe spasm and pain of the affected organs
2. Syphilitic meningomyelitis:
 - a. Bilateral corticospinal involvement
 - b. Anterior spinal artery syndrome
3. Gummas are extremely rare except in AIDS patients
4. Hypertrophic pachymeningitis (rare)
 - a. Radicular pain
 - b. Amyotrophy of the hands
 - c. Long tract involvement of the legs
 - d. May be prominent at cervical levels

Neuropathology

1. Thinning of the affected nerve roots
2. Degeneration of the posterior columns and atrophy of the spinal cord

3. Inflammation of the posterior roots
4. In meningomyelitis
 - a. Subpial loss of myelinated fibers and gliosis
 - b. Fibrosing meningitis

Neuroimaging

1. Long segment T2-weighted sequence changes of the parenchyma
2. Contrast enhancement
3. Dorsal column involvement
4. Gummas in AIDS patients
5. Frontal lobe atrophy

Laboratory Evaluation

1. Positive VDRL (regain test) serum
2. Positive FTA/ABS in the serum
3. CSF:
 - a. Lymphocytic pleocytosis
 - b. Increased protein
 - c. Normal glucose
 - d. Increased IgG and oligoclonal bands
 - e. Dependent on the stage and type of:
 - i. RPR (rapid plasma reagin) tests may be negative in late syphilis
 - ii. FTA/ABS is directed against treponema antibodies and is needed for evaluation of possible false positive results or those with seronegative results

Autoimmune Spinal Cord Inflammation

Multiple Sclerosis

General Characteristics

1. Most often the brain and optic nerves are concomitantly affected
2. May be exacerbated by infection and heat (Uhthoff's phenomena)

Clinical Manifestations

1. Transverse myelitis:
 - a. Usually painless
 - b. No fever
 - c. Rapid onset over hours to a day
 - d. Level is often at T4–T6 but can be on the abdomen, or both arms may be affected
2. Inflammatory pseudotumor of the cord:
 - a. Similar to an intramedullary tumor (glioma)
 - i. Cervical and thoracic levels most often affected
3. Focal amyotrophy

Neuropathology

1. Inflammatory demyelination
2. Lymphocytic aggregation around venules
3. Loss of axons and anterior horn cells occurs to varying degrees

Neuroimaging

1. Focal intramedullary lesion:
 - a. MRI reveals edema and space occupying characteristics
 - b. "Open loop sign" the area of edema and T2-weighted sequence hyperintensity does not completely surround the lesion
2. Transverse myelitis
3. Cervical spinal cord maps of fractional anisotropy (FA) mean diffusivity, radial diffusivity (RD) reveal:
 - a. Lower FA
 - b. Higher radial diffusivity
4. Spinal cord gray matter radial diffusivity is associated with EDSS (loss of anterior horn cells)

Laboratory Evaluation

1. Lymphocytic pleocytosis
2. Slight protein elevation
3. Presence of oligoclonal bands
4. Increased IgG
5. Normal glucose

Neuromyelitis Optica (Devic's Disease)*General Characteristics*

1. An immune-mediated disorder that is relapsing and remitting
2. A hallmark autoantibody against aquaporin-4 water channel is characteristically found
 - a. A monophasic course associated with antibodies to myelin oligodendrocytes (MOG) may occur most often in children
3. Associated with organ specific and non-organ specific autoimmune disorders that include:
 - a. Myasthenia gravis
 - b. Antiphospholipid antibody syndrome
 - c. Sjögren's syndrome
 - d. SLE
 - e. Pernicious anemia
 - f. Paraneoplastic disorders
4. It is a spectrum disorder:
 - a. Optic nerves or spinal cord can be primarily involved

Clinical Manifestations

1. May have an explosive onset
2. Usually, the disease progresses in a stepwise fashion for months or years
3. Varying degrees of paraplegia, quadriplegia, sensory loss (often with spinal level), sphincter and sexual dysfunction
4. Optic neuritis may be bilateral concomitantly which is unusual for MS. The degree of visual loss and the extent of the optic nerve lesion as well as chiasmatic involvement distinguish the process from MS

Neuropathology

1. Antibodies are directed against aquaporin-4 receptors on astrocytic foot processes. They are IgG in type

2. The process affects capillaries of the brain stem and cerebellum as well as the optic nerves and chiasm as well as the spinal cord
3. Both gray and white matter of the spinal cord are involved
4. Necrotizing myelitis:
 - a. Inflammation and demyelination
 - b. Older lesions are cavitated
5. Complement-dependent cytotoxicity with granulocyte and macrophage infiltration

Neuroimaging

1. MRI:
 - a. Demonstrates a greater than 3 segment longitudinal involvement of the spinal cord
 - b. Double inversion recovery sequence (3D) is sensitive for spinal cord involvement
 - c. Fractional anisotropy is decreased in neuromyelitis optica (NMO) compared to MS in the spinal cord; axial diffusivity is higher in NMO than MS asymmetrically in anterior columns in normal appearing white matter

Laboratory Evaluation

1. CSF-restricted oligoclonal IgG bands are largely absent
2. Intrathecal IgG (rarely IgM synthesis is low and usually restricted to relapses)
3. Pleocytosis occurs in approximately 50% of patients and may include neutrophils, eosinophils, activated lymphocytes and plasma cells
4. Band T-cell subsets are involved in the modulations of inflammation within the CNS and systemically

Post-Infectious and Post-Vaccinal Myelitis*General Characteristics*

1. There is a temporal relationship following a viral infection or vaccination
2. Delayed development of neurologic signs and symptoms
3. Monophasic course
4. The most common organisms are the DNA viruses:
 - a. Epstein-Barr
 - b. CMV
5. Rarer infections:
 - a. Hepatitis B
 - b. Varicella
 - c. Enterovirus
 - d. Rhinoviruses
6. Mycoplasma
 - a. Bacterial trigger
7. Campylobacter jejune does not cause myelitis
8. At times, no antecedent infection can be documented

Clinical Manifestations

1. Progression of signs and symptoms is subacute
2. There is weakness and paresthesia of the lower extremities; this may also involve the upper extremities

3. Ascending sensory signs and symptoms
4. Sphincter alterations occur
5. Backache is frequently felt
6. May develop a sensory level
7. Babinski sign is a differential point that distinguishes the process from Guillain-Barré syndrome
8. Some patients demonstrate meningeal signs and symptoms
9. Typically there is asymmetric spinothalamic and corticospinal tract involvement
10. Latency from infection or vaccination to signs and symptoms is approximately two weeks

Clinical Variants

1. Relapsing myelitis that may be triggered by an infection
2. A pure paresthetic form with posterior column signs
3. Paraparesis and a truncal sensory level; no alteration of deep sensation
4. Dissociated sensory topography:
 - a. Leg or groin sensory loss that can be unilateral or bilateral
5. Saddle anesthesia and sphincter alteration
6. Brown-Séquard syndrome

The Recent Clinical Spectrum of Post-Vaccination

Inflammatory Demyelinating Syndromes

1. Between 1979–2013 there were 71 documented patients
2. The most common vaccinations:
 - a. Influenza
 - b. Human papillomavirus (HPV)
 - c. Hepatitis A or B
 - d. Rabies
 - e. Measles
 - f. Rubella
 - g. Yellow fever
 - h. Anthrax
 - i. Meningococcus
 - j. Tetanus
3. CNS signs and symptoms:
 - a. Usually occurred within two weeks following immunization
 - b. A few patients had a delayed presentation from three weeks to five months (approximately 1/3 of reported patients)
4. Clinical manifestations:
 - a. Optic neuritis occurred in greater than 75% of patients (following influenza and HPV vaccination)
 - b. Topography in a significant number of patients was optic neuritis and myelitis (with or without CNS manifestations of ADEM); similar to NMO spectrum disorder
5. Neuropathology:
 - a. Subpial or perivenular zones of demyelination
 - b. Perivascular and meningeal infiltration of lymphocytes and mononuclear cells
 - c. Pleomorphic histiocytes and microglia are seen

6. Neuroimaging (post-vaccination for H1N1)
 - a. High T2-weighted signal intensity in the cerebellum, sulcal hyperintensities in the frontal and parietal lobes
 - b. Spinal cord may demonstrate:
 - i. Slight enhancement and T2-weighted MRI sequence abnormalities over 2 to 3 spinal segments
 - ii. Swollen cord occurs in the affected segments
7. Laboratory evaluation:
 - a. CSF:
 - i. Lymphocytic pleocytosis (10–50/mm³)
 - ii. Slightly increased protein (no oligoclonal bands)

Myelitis with Connective Tissue Disorders

General Characteristics

1. Myelitis has been described in over 22 connective diseases. The most important and prevalent are SLE and Sjögren's
2. Autoimmune illnesses with primarily transverse myelitis include:
 - a. Myasthenia gravis
 - b. Celiac disease
 - c. Ulcerative colitis
 - d. Sclerosing cholangitis
 - e. SLE
 - f. Sjögren's syndrome
 - g. Thrombotic thrombocytopenic purpura
 - h. B12 deficiency
 - i. Pemphigus
 - j. Narcolepsy
 - k. CIDP
 - l. Autoimmune encephalitis
 - m. Paraneoplastic syndromes
 - n. Insulin dependent diabetes
 - o. Scleroderma
 - p. Mixed collagen vascular disease
 - q. Autoimmune thyroid disease
 - r. Dermatitis herpetiformis
 - s. Psoriasis
 - t. Alopecia areata
 - u. Polymyositis
 - v. Rheumatoid arthritis
 - w. Ankylosing spondylitis
 - x. Sarcoid

Clinical Manifestations

1. Rapidly progressive paraparesis and rarely quadriparesis
2. Usual level at T4–T6 (sensory)
3. Bowel, bladder, and sexual dysfunction

Neuropathology

1. Usually the inflammatory demyelination of transverse myelitis

Neuroimaging

1. MRI:

- b. T2-weighted sequence hyperintensity in less than three spinal cord segments; some entities demonstrate longitudinal involvement
- c. Affected cord segments are edematous, swollen and demonstrate gadolinium enhancement

Laboratory Evaluation

- 1. Systemic biomarkers are dependent on the disease process
- 2. Often there is inflammatory CSF with leukocytosis, moderately high protein and usually normal glucose (may be slightly depressed in some instances)

Systemic Lupus Erythematosus (SLE)

General Characteristics

- 1. Some SLE patients with transverse myelitis have circulating antiphospholipid antibody
- 2. Cardiovascular disease is the leading cause of SLE morbidity and mortality
- 3. Antiphospholipid antibodies are common in SLE:
 - a. Approximately 10% of SLE patients develop antiphospholipid syndrome
 - b. Lupus anticoagulant is associated with thrombotic events

Clinical Manifestations

- 1. SLE has two distinct clinical patterns:
 - a. Gray matter myelitis:
 - i. Prodrome of fever and urinary retention at presentation
- 2. Rapid deterioration (within six hours)
- 3. Paraplegia
- 4. No improvement
- 5. Gray matter disease occurred in the context of active systemic disease
- 6. Patients had more disability and responded poorly to treatment
- 7. White matter myelitis:
 - a. At the time of presentation, patients demonstrate spasticity and hyperreflexia
 - b. Less severe signs
 - c. Slower progression than gray matter disease
 - d. Absent prodromal features
 - e. Clinically similar or related to NMO spectrum disorder
 - f. Polyphasic course
 - g. SLE activity may be absent

Neuropathology

- 1. Widespread vasculopathy of small vessels:
 - a. Variable inflammation and myelitis
 - b. Vacuolar myelopathy

Neuroimaging

- 1. White matter myelopathy

- a. Longitudinal pattern of inflammation, spinal cord swelling and gadolinium enhancement
- 2. Gray matter myelopathy:
 - a. Greater swelling and enhancement with gadolinium on MRI
 - b. Longitudinal patterns of inflammation involving at least three segments occurs in greater than 95% of patients; a similar pattern occurs in >75% of patients with the white matter variant

Laboratory Evaluation

- 1. CSF of gray matter variant:
 - a. Striking inflammatory markers
 - b. Neutrophilic pleocytosis
 - c. Increased protein
 - d. Low CSF glucose
- 2. White matter myelitis:
 - a. NMO IgG autoantibody may be present
 - b. Associated with anti-RO antibodies antiphospholipid antibodies and lupus anticoagulant

Sjögren's Syndrome

General Characteristics

- 1. Chronic inflammation of exocrine glands (lacrimal and salivary glands) leading to sicca complex
- 2. Approximately 1/3 of patients present with extra-glandular neurological, pulmonary or gastrointestinal signs and symptoms
- 3. Neurological symptoms occur in approximately 20% of patients

Clinical Manifestations

- 1. Sensory ganglionopathy
- 2. Polyradiculopathy
- 3. Mononeuritis multiplex
- 4. Autonomic neuropathy
- 5. Cranial neuropathies (primarily II and V)
- 6. Transverse myelitis:
 - a. May occur independently
 - b. Associated with neuromyelitis optica
 - c. An association of anti-RO antibodies and recurrent transverse myelitis

Neuropathology

- 1. Direct invasion of the CNS by lymphocytes
- 2. Vascular injury due to anti-neuronal and anti-SSA antibodies
- 3. Ischemia from small vessel vasculitis

Neuroimaging

- 1. T2-weighted sequence hyperintensities diffusely in the cerebral hemispheres
- 2. Transverse myelitis
- 3. Long segment spinal cord inflammation

Laboratory Evaluation

1. +SSA/SSB antibodies in the serum
2. Lip biopsy

Differential Diagnosis of Spinal Cord Autoimmune Diseases Associated with Longitudinal Myelitis

1. SLE (white myelitis and gray variants)
2. Sjögren's syndrome (sicca complex)
3. Rheumatoid arthritis (small muscle involvement of the hands, C1–C2 spondylolisthesis with spinal cord compression)
4. Mixed connective tissue disease (elements of polymyositis, scleroderma, and SLE)
5. Regional enteritis (usually associated with stroke or cerebral sinus thrombosis due to loss of clotting inhibitors through the gut creating a prothrombotic state)

Stiff Person Syndrome*General Characteristics*

1. Antibodies to glutamic acid decarboxylase (GAD) are present in some patients
2. GABA-R associated (receptor), and gephyrin (intracellular proteins) antigens are also seen in some patients, but may not be pathogenic
3. Glycine- α 1-receptor antibodies have also been reported in a few patients with stiff person syndrome and may be pathogenic

Clinical Manifestations

1. Persistent and intense spasm of proximal and paraspinal musculature (often most severe in the quadriceps)
2. Insidious onset of spasms in middle-aged men and women which are intermittent early and then evolve to occur continuously
3. Spasms are painful
4. Severe patients have involvement of respiration, deglutition, and facial musculature
5. Eyes muscles are rarely involved
6. Noise or mechanical stimuli initiate spasms of all involved musculature
7. Axial spasms cause hyperlordosis
8. Involved muscles become hypertrophic
9. Tendon reflexes are depressed
10. "Stiff" limb syndrome is a variant:
 - a. Clinical features occur in one limb
 - b. Associated with GAD antibodies
 - c. May spread to both legs
11. Hyperekplexia occurs
12. Autonomic signs and symptoms

Neuropathology

1. Associated medical conditions:
 - a. Insulin dependent diabetes
 - b. Thyroiditis

- c. Pernicious anemia
- d. Vitiligo
- e. Celiac disease
2. Suggested central origin:
 - a. Disappearance during sleep
 - b. Absence with anesthesia
 - c. Proximal nerve block abolishes spasms
3. In stiff man syndrome associated with breast cancer:
 - a. Autoantibodies to amphiphysin and gephyrin (proteins associated with synaptic GABA receptors) are detected
 - b. GAD antibodies are detected in approximately 2/3 of patients
 - c. GLYR (glycine receptor) antibodies may be associated with GAD antibody expression

Neuropathology

1. Some autopsied patients showed to have no inflammation and minimal neuronal loss in the spinal cord
2. Positive spinal cord autopsies demonstrate:
 - a. Loss and degeneration of nerve cells with astrocytosis in medial motor nuclei of the anterior horn cells:
 - b. Lymphocytic perivascular infiltration of the brainstem, basal ganglia and spinal cord
 - c. Antibodies may be directed against conformational forms of GAD expressed in GABA-ergic neurons that cause:
 - i. Blockade of GABA synthesis
 - ii. Decreased function of the inhibitory motor network

Laboratory Evaluation

1. High titers of anti-GAD antibodies in the serum and CSF
 - a. Anti-GAD antibodies are seen in 1% of the normal population and 5% of patients with other neurologic disease
 - b. Anti-GAD antibodies occur in insulin dependent diabetes but at much lower titers
 - c. In Stiff Person syndrome (SPS):
 - i. Antibodies are too linear and denatured epitopes in the NH₂ terminal region of the GAD antigen
2. Anti-amphiphysin antibodies are not present in SPS without cancer

Neuroimaging

1. PET evidence of central GABA-ergic changes in stiff person syndrome

Progressive Encephalomyelitis with Rigidity and Myoclonus (PERM)*General Characteristics*

1. PERM is similar to stiff person syndrome
2. More severe, progressive and may be fatal

Clinical Manifestations

1. Additional features to those that are seen with SPS include:

- a. Eye movement abnormalities
- b. Speech and swallowing dysfunction
- c. Respiratory failure
- d. Seizures
- e. Auditory and vestibular dysfunction

Neuropathology

1. Inflammatory exudates are primarily perivascular and consist of both B-cells (CD20x) and T-cells (CD3)
2. Microglial nodules occur in the hippocampal formation and Purkinje cell layer of the cerebellum
3. Gray matter is more involved than white matter; relative sparing of the neocortex; no demyelination
4. Gray matter of the neocortex may be involved in those patients with cognitive impairment

Neuroimaging

1. MRI of the spine may be negative
2. MRI demonstrates (in some patients) T2-weighted sequence hyperintensities throughout the cervical cord and lower brainstem

Laboratory Evaluation

1. Glycine receptor alpha 1 antibodies in the serum and CSF
2. CSF may demonstrate:
 - a. Lymphocytic pleocytosis
 - b. Mildly elevated protein
 - c. Normal glucose
3. Anti-GAD and NMDA antibodies have been recorded in the syndrome

Propriospinal Myoclonus

General Characteristics

1. Propriospinal myoclonus definition:
 - a. Repetitive flexion or extension myoclonus of the torso that is initiated by stretching or movement
 - b. The exact generator is unknown
2. Irregular and segmental myoclonic jerks can occur with:
 - a. Zoster myelitis
 - b. Hyperosmotic states
 - c. Post-infectious transverse myelitis
 - d. Epidural cord compression
 - e. Multiple sclerosis
 - f. Cardiac pacemaker

Clinical Manifestations

1. Usually, the upper abdomen and lower thoracic muscles are involved
2. May be a sensory predominant illness
3. Positional exacerbation (usually supine)
4. A form very similar to SPS has been described

Neuropathology

1. Autopsy material in the form resembling SPS demonstrates:

- a. Primary involvement of the cervical cord
- b. Loss of interneurons with minimal involvement of motor neurons of the anterior horn
- c. Gliosis and microglial activation and proliferation
- d. Lymphocytic cuffing of small blood vessels
- e. Minimal meningeal inflammation

Neuroimaging

1. PET demonstration of GABA-ergic dysfunction (primarily in SPS)
2. T2 sequence hyperintensity of the spinal cord (all segments)

Laboratory Evaluation

1. Mild lymphocytic pleocytosis and protein elevation
2. Ulcerative colitis (most often associated with cerebrovascular accidents, cerebral sinus thrombosis, eye and joint involvement)
3. Relapsing polychondritis (most often associated with disc disease, optic neuritis, collapse of the trachea and larynx)
4. Any of the autoimmune diseases that have been associated with transverse myelitis

Differential Diagnosis of Arteritis Syndrome

1. Simulating autoimmune transverse myelitis:
 - a. Syphilitic proliferative endarteritis
 - b. Occlusion of the vertebral or anterior spinal arteries
 - c. Meningoencephalitis
 - d. In association with HIV (all stages occur simultaneously; "telescoped")
 - e. Pachymeningitis cervicitis
2. Antiphospholipid syndrome:
 - a. Primary
 - b. In association with SLE
3. Takayasu's disease:
 - a. Vertebral and anterior spinal artery occlusions
 - b. Anterior > medullary posterior spinal artery occlusions
4. Isolated angiitis of the spinal cord
 - a. No associated features or laboratory evidence of systemic arteritis
5. Giant cell arteritis:
 - a. Rarely can affect all arteries of the internal carotid system
 - b. A component of the aortic arch syndrome (both carotids and vertebral arteries may be slowly occluded)
6. Kohlmeier-Degos disease:
 - a. Characteristic atrophic skin lesions
 - b. Severe retinal artery spasm
 - c. Rare spinal cord infarction

Paraneoplastic Myelitis

General Characteristics

1. In general, these are subacute necrotic myelopathies

2. Various neurologic syndromes have been described with antibodies in association with specific malignancies that target intracellular antigens. These include:
 - a. Hu
 - b. Yo
 - c. Ri
 - d. Tr
 - e. CV2/CRMP5
3. Neuronal damage with intracellular antigen-antibody interaction is NK-cell mediated inflammatory response
4. Antibodies to cell surface antigens from malignancies:
 - a. Attack neuronal integral membrane proteins
 - b. Modulate the number or function of the specific target protein
 - c. Are probably pathogenic
5. The most common CNS cell surface directed antibodies associated with malignancies are:
 - a. NMDAR
 - b. LGH
 - c. CASPR2
 - d. GLYR
 - e. GABAB
 - f. AQP4
 - g. MOG

Clinical Manifestations

1. Slowly progressive and usually painless
2. Motor dysfunction prior to sensory loss
3. Sphincter alterations

Neuropathology

1. Necrotic lesions
2. Both gray and white matter are affected (white > gray)
3. Minimal mononuclear cuffing of blood vessels which are otherwise normal
4. Some autopsy material demonstrates that the posterior and lateral columns are primarily affected

Neuroimaging

1. T2-weighted sequence hyperintensity that may encompass as long segment
2. Slight gadolinium enhancement
3. Rarely the MRI of the spinal cord is negative

Laboratory Evaluation

1. CSF:
 - a. Slight mononuclear cell pleocytosis and elevation of protein
2. Cell surface antigens are identified with specific syndromes:
 - a. Stiff person syndrome with antiglycine receptor antibodies:
 - i. 5% of SPS is associated with malignancy
 - ii. May have seronegative SPS with malignancy
 - iii. Malignancies are described with SPS and include:
 1. Breast cancer
 2. Lung
 3. Thymoma
 4. Hodgkin's

3. Multiple malignancies have been described in association with subacute myelopathy without the detection of antibodies:
 - a. Hypereosinophilia
 - i. >1,500 eosinophils/mm³
 - b. Associated with:
 - i. Leukemia
 - ii. Stomach carcinoid
 - iii. Colon cancer

Vitamin Deficiencies with Spinal Cord Involvement

B12 Deficiency

General Characteristics

1. Vitamin B12 deficiency is more widespread than generally recognized. It is seen in older patients, pregnant women, vegans and in patients with renal and intestinal disease
 - a. Nitrous oxide depresses methionine synthase, a methylcobalamin-dependent enzyme:
 - i. Exposure to nitrous oxide in:
 1. Anesthesia personnel
 2. Dentists
 3. Drug abusers
 4. Elderly patients that are marginally B12 deficient that get nitrous oxide anesthesia
 - ii. Cause both the anemia and full combined spinal cord degeneration
 1. Usually, they have low levels of B12 but have methylmalonic acid levels

Clinical Manifestations

1. Weakness and extremity paresthesia which occur first in the hands
2. Unsteadiness of gait
3. Weakness and stiffness of the legs that evolves into an ataxic paraplegia
4. Severe loss of vibration sensibility (legs > hands); position is similarly involved
5. Increased reflexes, spasticity, and Babinski signs supervene
6. In general, the process is symmetrical and distal, sensory signs and symptoms precede motor involvement
7. Exclusionary signs for B12 deficiency include:
 - a. Motor signs prior to sensory
 - i. Asymmetry of signs and symptoms
 - ii. Truncal or facial involvement
 - b. Other associated neurological signs and symptoms:
 - i. Behavioral alterations

- ii. Optic neuropathy:
 - 1. Optic atrophy
 - 2. Centrocecal scotoma
- iii. Urinary sphincter and sexual dysfunction
- iv. Cerebellar ataxia

Neuropathology

1. A diffuse degeneration of white matter (demyelination) of the spinal cord and brain
2. Swelling of myelin sheaths by intramyelinic vacuoles with separation of myelin lamellae
3. Vacuolated myelopathy
4. Some axonal destruction
5. Late gliosis of affected areas
6. The process begins in the cervical and upper thoracic segments of the cord and then spreads
7. The optic nerves, chiasms, and central white matter are also affected
8. Posterior and lateral columns of the cord are particularly involved
9. Demyelinating peripheral neuropathy

Neuroimaging

1. MRI T2-weighted sequences demonstrate high-intensity signals in the posterior column and corticospinal tracts
2. May involve long cord segments
3. In acute and severely involved patients the spinal cord is swollen
4. Involvement of anterior columns has been reported
5. Restricted water diffusion in both posterior and lateral columns has been demonstrated on apparent diffusion coefficient maps (ADC maps)
6. Some enhancement with gadolinium due to spinal blood barrier disruption
7. Differential diagnosis of posterior and lateral column involvement on MRI:
 - a. Copper deficiency myelopathy
 - b. Infectious and post-infectious myelopathy
 - c. Multiple sclerosis
 - i. Brain involvement on MRI
 - 1. FLAIR and T2-weighted images
 - ii. High intensity signals in the periventricular white matter

Laboratory Evaluation

1. CSF:
 - a. Usually normal
 - b. Moderate increase in protein
2. Hypersegmented polymorphonucleocytes, macrocytic anemia, and decreased platelets
3. Radio isotope dilution assay for a serum cobalamin level:
 - a. Levels below 100 pg/ml are usually associated with neurologic symptoms
 - b. In 5–10% of patients, a level of 200–300 pg/ml may be pathogenic

4. Increased serum concentrations of methyl malonic acid (normal 73–271 mmol/L) and homocysteine are seen
5. Increased antibodies to intrinsic factor and parietal cells may be detected
6. EMG:
 - a. Slowing of distal sensory conduction
 - b. Some denervation
7. Somatosensory evoked potentials show slowing of central conduction

Vitamin E Deficiency

General Characteristics

1. Genetic form:
 - a. AR; mutations in the TTPA gene that maps to Chromosome 8q12.3
 - b. Encodes for alpha-TTP, a cytosolic liver protein
 - c. Pivotal for intracellular transport of alpha-tocopherol
2. Defect in intestinal absorption
3. Occurs with abetalipoproteinemia
4. Fat malabsorption
5. Cholesteric liver disease
6. Post-gastrectomy

Clinical Manifestations

1. Retinitis pigmentosa
2. Anemia
3. Proximal Myopathy
4. Deafness (rare)
5. Cerebellar and sensory ataxia
6. Cardiomyopathy (rare)
7. Resembles Friedreich's ataxia
8. Ataxia

Neuropathology

1. Degenerations of Clark's and the posterior columns of the spinal cord

Neuroimaging

1. T2-weighted MRI sequence hyperintensities of the posterior columns
2. Cerebellar atrophy

Laboratory Evaluation

1. Low vitamin E levels
 - a. Lipid soluble antioxidant

Spinal Cord Tumors

Overview

General Characteristics

1. Spinal-cord neoplasms may be divided anatomically:
 - a. Intramedullary

- i. Arise from the spinal cord parenchyma
 - 1. Primary
 - 2. Metastatic
- b. Extradural
 - i. Vertebral body origin
 - ii. From tissues or metastases in the epidural space
- 2. In hospitalized patients:
 - a. 5% of tumors are intramedullary
 - b. 40% are intradural and extradural
 - c. Approximately 35% are extradural

Epidural Tumors

General Characteristics

1. The overwhelming majority of tumors that are epidural are metastatic. Multiple myeloma and chordoma are the primary tumors (of the bone) that invade this space
2. Epidural spinal cord compression occurs in approximately 5% of cancer patients
3. 50% of all epidural metastatic lesions are from the lung or breast. Others include:
 - a. Prostate
 - b. Melanoma
 - c. Lymphoma
 - d. GI tract
4. Approximately 70% involve the thoracic cord. 10% the cervical cord and 20% the lumbosacral cord. Lung and breast metastasize to the thoracic spine; colon, prostate, and ovarian tumors to the lumbosacral spine and melanoma to the unusual areas of the spine (in addition to the heart surface, digits and intestinal wall). Metastases may go to any structure
5. Tumors reach the epidural space by:
 - a. Hematogenous spread
 - b. Through Batson's paravertebral plexus (prostate, ovarian, colon)
 - c. Through nerve root exit foramina

Clinical Manifestations

1. Symptoms are primarily related to cord compression:
 - a. Asymmetric spastic weakness
 - b. Sensory level on the trunk (diminished pain and temperature sensibility); posterior column deficits below the lesion (loss of vibration and proprioception)
 - c. Obstipation and ataxia often occur before weakness
 - d. Spastic bladder
 - e. The onset is usually gradual, and progression may be prolonged
 - f. Thoracic lesions often cause asymmetric weakness of the legs
 - g. Foramen magnum compressive lesions cause:
 - i. Pain and stiff neck
 - ii. Atrophy of the hands and posterior neck muscles
 - iii. Paralysis that may be cruciate (arm ipsilateral and leg contralateral) or progressive ipsilateral arm then

the ipsilateral leg, contralateral leg and finally contralateral arm. This depends on the differential involvement of pyramidal fibers at C1–C2. Intracranial spread causes lower cranial nerve and cerebellar dysfunction

- h. Lower thoracic and first lumbar lesions cause:
 - i. Cauda equina and spinal cord symptoms
 - ii. Babinski sign is present
- i. Cauda equina lesions:
 - i. Root pain (often in sciatic distribution (L4–S1))
 - ii. Asymmetric leg weakness
 - iii. Low back pain
 - iv. Involvement of sphincters
- j. Conus medullaris lesions:
 - i. Involve the lower sacral segments of the spinal cord
 - ii. Bowel and bladder sphincter dysfunction are early
 - iii. Back pain
 - iv. Hyperesthesia of sacral nerve roots (may have saddle anesthesia)
 - v. Sensory changes may precede motor involvement
 - vi. Impotence
 - vii. Loss of bulbocavernosus reflex and anal sphincter tone and reflexes
- k. Pain:
 - i. May be unremitting; mechanically sensitive and made worse with recumbency (as opposed to disc pain)
 - ii. Persists with bed rest (putatively related to venous congestion)
- l. Tumors of the thoracic and lumbar cord:
 - i. Induce a very high spinal cord protein
 - ii. Cause hydrocephalus

Laboratory Evaluation

1. CSF:
 - a. Malignant cell determination is directly related to the volume of fluid removed and studied (particularly with carcinomatosis)
 - b. Glucose 30–40 mg% (carcinomatosis)
 - c. Protein of 80–150 mg%
 - d. If the protein is 800 mg to 1000 mg/%, there is a spinal block (Freund's reaction)

Neuroimaging

1. Plain films (metastatic disease):
 - a. Pedicle involvement
 - b. Erosion of the end plates
 - c. Central vertebral body lesions
 - d. In general, bone involvement is cancer; disc involvement is infection
- e. MRI evaluation of metastatic disease of the vertebrae:
 - i. Multiple areas of T1-weighted sequences of low-density areas in the vertebrae
 - ii. Pathologic fractures

- iii. Osteoblastic bone changes:
 1. Rarely myeloma
 2. Prostate cancer
 3. Hodgkin's (marble vertebrae); extremely dense
 4. Rarely breast cancer
- iv. Cancer does not invade the disc space
- v. Increased density of the dura or enhancement in the CSF space between cerebellar folia suggests associated carcinomatosis of the meninges

Primary Tumors of the Vertebral Column with Secondary Epidural Compression

Multiple Myeloma

General Characteristics

- a. The skull and vertebral bodies are primarily involved
- b. Cranial lesions are primarily in the vault
- c. Predilection for the bones of the thoracic cage
- d. Plasma cell tumors, both plasmacytoma and plasmamyeloma, may be associated with HIV infection

Clinical Manifestations

- 1. Vertebral compression fractures with cord compression occur in 10% of patients
- 2. Rare necrotizing myelopathy

Neuropathology

- 1. Multiple myeloma is a tumor of monoclonal plasma cells
- 2. Expands primarily in the bone marrow
- 3. Produces a monoclonal antibody

Neuroimaging

- 1. MRI is standard for the evaluation of bone marrow infiltration
- 2. PET coupled with CT (PET/CT) demonstrates the extent of lesions throughout the body and is the best tool to distinguish active from the inactive disease

Laboratory Evaluation

- 1. 10% or more clonal plasma cells are demonstrated on bone marrow biopsy
- 2. Biopsy proven plasmacytoma plus evidence of associated end-organ damage
- 3. In the absence of end-organ damage, 60% or more of clonal, plasma cells in the marrow is diagnostic

Plasmacytoma

General Characteristics

- 1. May affect the CNS, the nasopharynx, upper respiratory tract, lymph nodes, gastrointestinal tract, testicles and soft tissue
- 2. Plasmacytomas are malignant proliferations of plasma cells that can occur with different plasma cell dyscrasia

Clinical Manifestations

- 1. May occur as solitary intracerebral lesions
- 2. Intraparenchymal spinal cord mass
- 3. The most common spinal cord lesion is involvement of the vertebral bodies with extradural compression

Neuropathology

- 1. Plasmacytomas may be associated with localized amyloid deposits
- 2. A mass of monoclonal neoplastic plasma cells
- 3. Associated histologically with follicle formation and fibrosis

Neuroimaging

- 1. MRI: Bulky soft tissue mass and isointense signal on T2-weighted images due to high cellularity

Laboratory Evaluation

- 1. Production of monoclonal immunoglobulins

Chordoma

General Characteristics

- 1. Constitute 2–4% of primary bone neoplasms
- 2. Intracranial chordomas are present at a younger age than those in the spine
- 3. Vertebral tumors occur between 40 to 50 years of age
- 4. Tumors occur where vestiges of the notochord remain. These encompass the sacrococcygeal, spheno-occipital and bones merge
- 5. Vertebral chordomas:
 - a. Noted anywhere along the spinal canal lumbar > cervical > thoracic spine
 - b. Rare reports of intradural extraosseous chordomas that are usually ventral
- 6. Slow aggressive local growth with a low and late tendency to metastasize
 - a. Approximately 40–60% metastasize over the course of the illness

Clinical Manifestations

- 1. Sacrococcygeal chordoma:
 - a. Pain
 - b. Sphincter incontinence
 - c. Mass over the coccyx
 - d. Radicular sciatic pain
- 2. Vertebral chordomas
 - a. Spinal cord compression with lower extremity weakness, pain (radicular) and bowel and bladder sphincter disturbance

Neuropathology

- 1. Hallmark is physaliphorous cells (bubble cytoplasm); other cells have a solid, eosinophilic cytoplasm
- 2. A lobular pattern from fibrous septae that extends through the tumor

3. MicroRNA-608 and 34a
 - a. Regulate chordoma malignancy in targeting EGFR, Bcl-XL and MET genes

Neuroimaging

1. Vertebrae are irregular (some remodeling)
2. MRI:
 - a. Hypo- or isointense on T1-weighted images; the lesions on T2-weighted sequences are hyperintense
 - b. May calcify and hemorrhage
 - c. Vertebral chordomas tend to extend posteriorly and compress the cord

Laboratory Evaluation

1. Biopsy of the tumor
2. PDGFR-B may be elaborated by the tumor
3. Chordomas usually stain positive for cytokeratin and epithelial membrane antigen

Intradural Extramedullary Tumors

Overview

Intradural extramedullary tumors are primarily neurofibromas and meningiomas. They comprise approximately 50% of all intraspinal tumors. Neurofibromas are primarily in the thoracic and lumbar segments of the spine while meningiomas occur over all segments. The differential diagnosis of extramedullary tumors include:

1. Neurofibroma
2. Sarcoma
3. Vascular tumors
4. Chordomas
5. Epidermoid
6. Teratomas
7. Dropped metastases from medulloblastoma and pinealoma
8. Meningioma
 - a. Extremely rare in the thoracic cord of men

Neurofibroma

General Characteristics

1. Spinal neurofibromatosis is a form of neurofibromatosis type I
2. It affects all spinal roots and may involve all major peripheral nerve branches with or without other systemic manifestations of NF1
3. Genetics:
 - a. NF1:
 - i. AD; associated with germline mutations in chromosome 17q 11.2 of the NF1 gene
 - ii. Encodes neurofibromin:
 1. Involved in the regulation of several cellular signaling pathways (RAS/MAPK)

2. RAS/mitogen-activated protein kinase (MAPK) pathway is pivotal in embryonic and postnatal development
3. NF2 genetics:
 - a. AD; chromosome 22
 - b. Encodes merlin
 - i. Merlin inhibits signaling by integrin and tyrosine receptor kinases (RTKs)

Clinical Manifestations

1. Diagnostic criteria include:
 - a. NF1:
 - i. Six or more café-au-lait spots; greater than two neurofibromas of any type
 - ii. Plexiform neurofibroma
 - iii. Freckling in the axillary or inguinal region
 - iv. Optic glioma
 - v. Sphenoid dysplasia, absence or thinning of long bone cortices with or without pseudoarthrosis
 - vi. First degree relative with NF1
 - b. Neurologic Manifestations of NF1:
 - i. Gliomas and astrocytomas (often midline)
 - ii. Low-grade optic nerve glioma
 - iii. Neurofibroma and plexiform neurofibroma involve peripheral nerves and nerve sheaths
 - iv. Plexiform neurofibromas:
 1. Cause radicular signs and symptoms
 2. Are more frequent in the lumbosacral plexus
 3. Neurofibrosarcoma may develop de novo or from sarcomatous degeneration of a pre-existing plexiform neuroma
 4. Oval shaped tumors that may extend into the spinal canal and compress the spinal cord

Neuropathology

1. The nerve tumors are a combination of fibroblasts and Schwann cells. The predominance of cell types determines whether the tumor is a neurofibroma or schwannoma
2. Both have palisading of nuclei and Verocay bodies
3. Rarely differentiated nerve cells are seen along spinal roots or sympathetic chains which form a ganglioneuroma
4. Malignant degeneration of the tumors occurs in 2–5% of cases:
 - a. Peripherally they are sarcomas
 - b. Centrally they are astrocytomas or glioblastomas

Neuroimaging

1. NF1:
 - a. Midline astrocytomas and gliomas
 - b. Unidentified bright objects (UBO's)
 - i. Non-tumor white matter lesions in the basal ganglia and posterior fossa
 - ii. Diminish with age
 - c. Hydrocephalus
 - d. Dural sac anomalies that may lead to meningoceles

- e. Neurofibroma and plexiform neurofibromas identified by MRI
- f. Osseous lesions include:
 - i. Thoracic scoliosis
 - ii. Posterior scalloping of vertebrae
 - iii. Absence of the sphenoid bone
 - iv. Bowing of the tibia that may cause pseudoarthrosis
 - v. Ribbon ribs
- g. Vasculopathy
- h. Heterogeneity of schwannoma is more than with neurofibroma on T2-weighted MRI sequences enhancement is often a sign of cystic degeneration

Laboratory Evaluation

1. MRI and CT (osseous abnormalities on CT and UBO's of basal ganglia, thalamus, hypothalamus, brainstem and cerebellum)
2. Slit-lamp examination of the irides
3. Visual and auditory evoked potentials (NF1 and NF2)
4. Severe hypertension (urine screen for epinephrine metabolite) to rule out pheochromocytoma

Meningiomas

General Characteristics

1. Genetics:
 - a. The most frequent genetic defects associated with meningiomas are truncating mutations in the neurofibromatosis 2 gene (merlin; chromosome 22q) that occur primarily in fibroblastic and transitional forms
2. Somatic deletions also occur in chromosome 1p, 6q, 9p, 10q, 14q and 18q
3. Epidermal growth factor receptor, P53 and VEGF are expressed by meningiomas
4. VEGF expression may be important in the vascularization of these tumors
5. Some meningiomas contain estrogen and progesterone receptors that may be associated with:
 - a. Increased incidence in women
 - b. Enlargement during pregnancy
 - c. Association with breast cancer (breast cancer metastases to meningiomas)
6. Germline SMARCE1 mutations predispose to both spinal and cranial clear cell meningiomas

Clinical Manifestations

1. Greater than 90% of spinal meningiomas are intradural
2. Rare in the thoracic cord of men
3. Peak incidences are between 40–70 years of age
4. Approximately 80% of spinal meningiomas are in women, and 80% of these are in the thoracic cord
5. Meningiomas (spinal) in men are in the cervical spine and may have an intradural extramedullary configuration
6. Pain in the back (usually central but may have a radicular component) followed by slowly progressive paraparesis

(rarely quadriplegia) sensory loss below the lesions and a neurogenic bladder are common signs and symptoms

7. Recurrence rate after surgery at ten years is less than 0.5%

Neuropathology

1. Origin of the tumor is controversial:
 - a. Arachnoid cap cell (meningothelial cells)
 - b. Dural fibroblasts
 - c. Rarely arise from arachnoidal cells within the choroid plexus that forms an intraventricular meningioma
2. Specific types:
 - a. Meningothelial
 - b. Fibrous (fibroblastic)
 - c. Transitional
 - d. Psammomatous
 - e. Angiomatous
 - f. Clear cell
 - g. Microcystic

Neuroimaging

1. Tendency to calcify and demonstrate extensive vascularity
2. Tumor blush on angiography
3. Homogeneous contrast enhancement on MRI
4. MR spectroscopy of atypical/anaplastic types:
 - a. Restricted diffusion
 - b. Higher Cho/Cr ratio
5. Isointense to spinal cord on T1-weighted and T2-weighted sequences

Laboratory Evaluation

1. Meningothelial cells (MFCo) are the cellular components of the meninges:
 - a. Forms the interface between neuronal tissue and the CSF
 - b. Also a component of the immune response:
 - i. Release proinflammatory cytokines during pathologic stress

Intramedullary Tumors of the Spinal Cord

General Characteristics

1. Ependymoma comprise approximately 60% of primary spinal cord neoplasms. Astrocytomas make up approximately 25%, and oligodendrogliomas are rare
2. The remaining 15% are non-gliomatous and include:
 - a. Lipomas
 - b. Epidermoids
 - c. Dermoids
 - d. Chordomas
 - e. Schwannomas
 - f. Hemangioblastomas
 - g. Hemangiomas
 - h. Meningiomas (rare)
3. There is an association of both gliomatous and non-gliomatous spinal cord tumors with syringomyelia
4. Intramedullary metastasis occurs and is primarily from bronchogenic carcinoma of the lung

Clinical Manifestations

1. Motor, sensory and sphincteric signs and symptoms are dependent on compression and destruction of specific tracts
2. Pain is common in almost all intramedullary tumors and is most common with tumors of the filum terminale
3. Ependymomas and astrocytomas often cause:
 - a. Asymmetric spastic paraparesis
 - b. Sensory level on the trunk primarily to pain and temperature
 - c. Sphincteric disturbance primarily of the bladder
 - d. If the central gray matter is involved, the patient may present with a syringomyelic pattern which exhibits:
 - i. Segmental or dissociated sensory loss; pain and temperature > vibration and position sense
 - ii. Amyotrophy of the involved segments
 - iii. Incontinence
 - iv. Late corticospinal tract involvement
 - v. Sacral sparing of sensation (sacral root representation lateral in the spinothalamic tract)
 - vi. Dissociation of pain and temperature from tactile modalities over several contiguous segments on the trunk
 - vii. Extramedullary tumors rarely give a similar clinical picture

Neuropathology

1. Dependent on the specific etiology

Neuroimaging

1. Enlargement of the involved spinal cord segment
2. Low signal on T1-weighted sequences with blurred tumor cord boundaries; high signal intensity on T2-weighted sequences
3. Peritumoral cysts are common with ependymomas and astrocytomas
4. Most tumors enhance although some astrocytomas do not
5. Ependymomas tend to be central in the cord while astrocytomas may be eccentric
6. Hemangioblastoma is associated with cord swelling and homogeneous contrast enhancement

Laboratory Evaluation

1. Froin's reaction in the CSF:
 - a. The CSF is blocked by swelling of the intramedullary tumor
 - b. The CSF under the blocks:
 - i. Xanthochromic
 - ii. Has an extremely high protein (500 to 1000 mg%)
 - iii. Clotting of the protein may occur

Spinal Ependymoma*General Characteristics*

1. Develop most often in children, adolescents, and young adults

2. Spinal cord ependymomas occur in an older age group (mean age of 40 years)
3. The frequency is equal between males and females
4. Ependymomas are the most common neuroepithelial tumor:
 - a. Most frequent sites are cervical and cervicothoracic segments, the lumbosacral area and the cauda equina
 - b. Ependymomas of the conus medullaris, cauda equina, and filum terminale are considered a separate entity
 - c. Ependymomas may be seen in extraneural areas that include soft tissue, ovary, and mediastinum. Mechanisms include:
 - i. Metastases
 - ii. Direct extension from a primary tumor
 - iii. Primary presacral, pelvic, thoracic or abdominal tumors
 - iv. Primary neoplasm of the sacrococcygeal region

Clinical Manifestations

1. Syringomyelic syndrome
2. Compressive and radicular syndromes
3. Cauda equina syndrome:
 - a. Back pain with L4–S3 root pain
 - b. Asymmetric motor and radicular sensory loss
 - c. Areflexia
 - d. Sphincter disturbances
4. Conus medullaris syndrome:
 - a. Early sphincter disturbance that is severe
 - b. Impotence
 - c. Minimal motor dysfunction
 - d. Symmetric sacral root sensory loss
 - e. Loss of anal and bulbocavernosus reflexes
5. Tumors of the thoracolumbar cord may be associated with hydrocephalus
6. Sensory symptoms may precede motor and reflex changes
7. Pseudotumor cerebri presentation has been reported (possibly due to the usually high protein that blocks CSF reabsorption by the Pacchionian granulations)

Neuropathology

1. The tumors arise from the ependymal lining of the central canal
2. Rosettes are seen in differentiated tumors
3. Perivascular pseudorosettes are not as diagnostic
4. Neoplastic ependymal cells may form tubules and canals or line irregular or slit-like cavities
5. The tumor demonstrates a glial fibrillary background
6. Histological variants include:
 - a. Papillary
 - b. Cellular
 - c. Clear cell

Neuroimaging

1. Spinal cord swelling
2. Contrast enhancement on MRI (homogenous)
3. Tumor is located in the center of the cord

4. Intracranial metastases are the most common site for myxopapillary ependymoma; metastases may be delayed

Laboratory Evaluation

1. Loss of DNA from 22q (NF2 gene)

Spinal Astrocytoma

General Characteristics

1. Peak incidence is in the 3rd to 5th decade
2. 30 years of age for high-grade astrocytomas and 40 years for lower grades. Approximately 75% are low grade
3. Malignant forms are more common in adults than children
4. Approximately 70% are thoracic

Clinical Manifestations

1. Localized back pain:
 - a. May be increased with recumbency; patients may sleep sitting up (tumor blocks venous drainage)
 - b. Malignant astrocytomas may have leptomeningeal spread
 - c. Asymmetric progressive weakness
 - d. Paresthesias > pain
2. C-scoliosis (asymmetric growth which destroys ipsilateral paraspinal muscles)
3. Relentlessly progressive course

Neuropathology

1. Consistent tendency for diffuse infiltration
2. No mitotic activity (low-grade tumors)
3. Occasional cysts (intratumoral)
4. Variants are determined by size, prominence and disposition of cell processes. The major types include:
 - i. Fibrillary
 - ii. Gemistocytic
 - iii. Protoplasmic

Neuroimaging

1. Enhancement patterns on MRI:
 - a. Focal nodular enhancement
 - b. Patchy enhancement
 - c. Inhomogeneous diffuse enhancement
 - d. 20–30% do not enhance
2. Diffuse cord swelling
3. Eccentric growth

Laboratory Evaluation

1. Anaplastic astrocytomas undergo p53 mutations
2. Duplication of 3pter and deletion of 21qter
3. Loss of 17p DNA

Pilocytic Astrocytoma

General Characteristics

1. May occur solo laterally and at different sites in the CNS (usually in association with NF1)

2. 75% manifest in patients < 20 years of age (8–13 years is peak incidence)
3. Spinal cord involvement manifests at a later age than optic nerve/chiasm or cerebellar disease
4. There is no progression to a malignant astrocytoma

Clinical Manifestations

1. Depends on the level of spinal cord involvement
2. Usually severe visual loss with the optic nerve and chiasmal variant

Neuropathology

1. Astrocytes with thin processes that are packed with intermediate filaments
2. Tumor tissue forms a radially oriented mass around blood vessels
3. Rosenthal fibers are present and are a morphological hallmark of the disease

Neuroimaging

1. MRI:
 - a. Lesions are hypo- or isointense on T1-weighted images and hyperintense on T2-weighted images
 - b. Fusiform enlargement of the optic nerve
 - c. Spinal cord lesions appear as a fusiform enlargement over several segments usually within the central cord
2. PET scans show increased glucose utilization

Laboratory Evaluation

1. Pilocytic astrocytomas are driven by the mitogen-activated protein kinase/extracellular signal-regulated kinase pathway
2. Tandem duplication of 7q34 encodes BRAF which produces KIAA1549-BRAF novel oncogenic fusions

Hemangioblastoma

General Characteristics

1. Spinal cord hemangioblastomas in Von Hippel-Lindau disease (VHL) are often multiple
2. Develop most commonly in the posterior fossa; approximately 3% are in the spinal cord
 - a. A rare site is dorsally at the cervicomedullary junction

Clinical Manifestations

1. May occur sporadically as well as with VHL syndrome
2. Usually, there are subtle long tract motor and sensory signs
3. Hemorrhage may cause hematomyelia with quadraparesis
4. An intrasyrinx hemorrhage with hemangioblastoma has been reported in one patient
5. May occur on nerve roots; bleeding causes cord compression

Neuropathology

1. Hemangioblastomas are well circumscribed but unencapsulated

2. They are cystic
3. The solid part of the tumor is composed of blood vessels lined by a single layer of endothelium
4. Stromal cells contain lipid droplets

Neuroimaging

1. In sporadic patients:
 - a. Cyst with a mural nodule
 - b. Some are purely solid
 - c. MRI:
 - i. Spinal cord swelling
 - ii. Homogeneous enhancement

Laboratory Evaluation

1. VHL gene on chromosome 3p25-26

Intramedullary Metastasis

General Characteristics

1. Accounts for approximately 5% of spinal tumors in cancer patients
2. Lung > breast > lymphoma > colorectal > head and neck > renal
3. Most are hematogenous; rarely growth is into the center of the cord from the meninges
4. Approximately 50% of spinal metastases are associated with brain metastasis
5. The conus medullaris is the most common site
6. Approximately 10% are multi-level
7. Occur in up to 8% of patients with non-Hodgkin's lymphoma; 70% of patients with leukemia
8. Risk factors for leptomeningeal spread of non-Hodgkin's lymphoma are:
 - a. Bone marrow and testicular involvement
 - b. Extranodal spread
 - c. Epidural metastasis
 - d. Lymphoblastic histology
9. General rule:
 - a. Primary lymphomas are parenchymal with leptomeningeal spread
 - b. Systemic lymphoma are meningeal with secondary parenchymal spread
10. Most common solid tumors causing infiltration of the arachnoid and pia mater with subsequent intramedullary invasion are:
 - a. Lung
 - b. Breast
 - c. Melanoma
 - d. Gastrointestinal tumors

Clinical Manifestations

1. Rapid progression of clinical signs
2. Weakness, ataxia, sensory level on the trunk (spinothalamic modalities)
3. Sphincter disturbance
4. Syringomyelic presentation (dissociated sensory loss)
5. Weakness is asymmetrical

Neuroimaging

1. MRI:
 - a. Intramedullary swelling of the affected segment
 - b. High-intensity signal on T2-weighted images
 - c. Contrast enhancement

Neuropathology

1. Dependent on tumor type

Laboratory Evaluation

1. Biopsy of systemic tumor
2. Cytology of CSF cells
3. CSF of associated carcinomatosis:
 - a. Flow cytometry
 - b. Histology of tumor cells
4. Protein 80–150 mg%
5. Glucose 30–40 mg%

Differential Diagnosis of Intramedullary Metastasis

1. Meningeal carcinomatosis
2. Paraneoplastic necrotizing myelopathy
3. Radiation myelopathy
4. Inflammatory demyelinating disease
5. Syringa

Differential Diagnosis of Extremely Rare Tumors of the Spinal Cord

1. Oligodendroglioma
 - a. Less than 3% of intracranial neoplasms
 - b. The majority of tumors in adults occur in adults between the 4th and 5th decade
 - c. Extremely rare in the spinal cord
2. Medulloblastoma
 - a. Approximately 20–25% occur after age 20; male > female, 1.6:1
 - b. Origin is most frequently the roof of the IVth ventricle (superior medullary velum)
 - c. Metastasize to the spinal cord via CSF pathways
3. Intravascular Malignant Lymphomatosis
 - a. A rare form of malignant lymphoma
 - b. Selective growth of lymphoma cells within the lumina of vessels without the involvement of adjacent parenchymal tissue
 - c. Predominantly B-cell lineage
 - d. A disease of middle age and elderly patients (61 years median age)
 - e. 34% of patients have myelopathy
 - f. Occludes and infarcts spinal vessels
4. Ganglioma
 - a. Most tumors develop in the temporal lobe
 - b. 20–50% arise in the spinal cord
 - i. Any site may be the origin including the conus medullaris
 - ii. Usual sites:

1. Cervicothoracic > thoracolumbar > multiple spinal cord segments
- c. May be associated with migration defects
5. Gangliocytoma:
 - a. Site of origin is the cerebrum and cervicothoracic spinal cord
 - b. Clinically symptomatic by age 30
 - c. Slowly evolving long tract signs
 - d. Increased number of abnormal neurons
6. Central neurocytoma:
 - a. A rare neuronal tumor; extraventricular neurocytomas putatively originate from bipotent progenitor cells, i.e., the potential for neuronal and glial differentiation
 - b. Large well-circumscribed lesions usually in the cerebral hemispheres (frontal and parietal lobes) but also occur in the spinal cord
 - c. There may be craniospinal dissemination
 - d. Tumors occur in the cervical spinal cord
7. Central Neuroblastoma
 - a. Ganglion cell differentiation occurs in 50% of patients
 - b. Age of onset is approximately 13 years (has been described into the 8th decade)
 - c. Rarely involves the spinal cord and cauda equina
8. Intramedullary Meningioma of the Spinal Cord
 - a. Differential diagnosis:
 - i. Atypical ependymoma
 - ii. Astrocytoma
9. Intradural extramedullary hemangiopericytoma
 - a. May arise from spinal pial capillaries
 - b. Radiographically mimics nerve sheath tumors
10. Diastematomyelia with embryogenic spinal cord
 - a. Diastematomyelia:
 - i. An occult spinal dysraphism characterized by clefting of the spinal cord by a fibrous band
 - ii. Associated with:
 1. Vertebral bony abnormalities
 2. Cutaneous lesions
 3. Myelomeningocele
 4. Hydrocephalus
 5. Hydromyelia
 6. Chiari malformation
 7. Kippel-Feil syndrome
 - iii. Association with dysembryogenic spinal cord tumors in adults is rare (approximately 20 reported patients)

Rare Benign Intramedullary Spinal Tumors

General Characteristics

1. These tumors comprise less than 1% of primary spinal tumors
2. They are usually found in the lumbar area associated with skeletal and skin stigmata which include:

- a. Spinal bifida
- b. Posterior dermal sinuses (primarily in children)
- c. Dimple in or off the midline
- d. Hypertrichosis (hair is thick)
- e. Cutaneous angioma
- f. Pigmented skin
3. Intraparenchymal associations:
 - a. Diastematomyelia
 - b. Syringomyelia
 - c. Tethered cord
 - d. Dermal sinus tract
 - e. Spinal dysraphism
4. Major tumors are:
 - a. Lipoma
 - b. Epidermoid
 - c. Dermoid
 - d. Teratoma

Clinical Manifestations

1. Due to the underlying associated features
2. Lipomas may degenerate into sarcoma and infiltrate the cauda equina

Neuropathology

1. Dependent on tumor type

Neuroimaging

1. Lipomas are high signal intensity on T1-weighted sequences and low signal intensity on T2-weighted images
2. Dermoids have mixed signal intensities
3. Epidermoids are bright on T1-weighted images

Laboratory Evaluation

1. Dependent on specific etiology

Differential Diagnosis of Benign Spinal Cord Tumors

Lipoma

General Characteristics

1. Non-dysraphic spinal intramedullary lipomas are extremely rare in adults
2. The majority of patients are children
3. Primarily occur in the dorsal cervical segments
4. Intramedullary lipomas are not associated with spina bifida or cutaneous stigmata

Clinical Manifestations

1. They may present in the 3rd and 4th decade
2. Non-specific dysesthesia
3. Dissociated sensory loss
4. Long tract motor signs occur later in the disease course
5. Not associated with spina bifida or cutaneous stigmata
6. Clinical features associated with extradural sites are:
 - a. Radicular pain and motor loss

- b. Congenital extradural lumbosacral lipomas present with tethered cord symptomatology
 - i. Conus medullaris is the primary site of involvement
- c. Tethered cord intradural lipoma:
 - i. Cervical to lumbar cord in location
 - ii. Dysesthesia pain (non-radicular)
 - iii. Mixed nerve root symptomatology

Neuropathology

1. Lipomas consist of normal mature fat
2. Greater than 50% have tissues that are derived from ectoderm, mesoderm or endoderm

Neuroimaging

1. No bone destruction
2. Lesions are hyperintense on T1-weighted sequences and less intense on T2-weighted images
3. The classic location of spinal lipomas is extradural; they may be intramedullary or a combination of both sites

Laboratory Evaluation

1. Normal CSF unless there is CSF blockage and a Froin's reaction

Dermoid Cyst

General Characteristics

1. Intramedullary dermoid cysts are rare tumors
2. Most are associated with spinal dysraphism and/or sinus tract
3. Intraspinal cysts are most often located in the lumbar and thoracic spinal segments
4. Most common sites of dermoid cysts:
 - a. Scalp; angle of the eye and the retromastoid region
 - b. Intradiploic skull bones
 - c. Suprasellar region or the posterior fossa
 - d. Intraspinal
5. Slow-growing benign lesion; rare malignant transformation to squamous cell cancer

Clinical Manifestations

1. If associated with a dural sinus tract (connects the skin through the dura) recurrent meningitis may occur:
 - a. Organisms reflect skin flora
2. There may be an associated midline skin dimple:
 - a. Below the inguinal crease they end blindly and do not extend intraspinally
 - b. Dimples above the inguinal fold may connect intradurally
 - c. Dermal sinuses are often associated with spinal cord tethering
3. Pes cavus is associated
4. Asymmetry of motor and sensory loss
5. Bladder dysfunction
6. Those that arise in the filum terminale cause symptoms primarily from the concomitant tethered cord

Neuropathology

1. Well demarcated, smooth, round or oval masses
2. Contain thick, cheesy yellowish material from secreted material of the sebaceous glands and desquamated epithelium; hair may be encountered
3. Connection of the dermoid cysts with dermal sinuses occur in the occipital and lumbar regions (route of recurrent bacterial infection)
4. Cholesterol crystals

Neuroimaging

1. MRI:
 - a. Hypointense on T1-weighted sequences; hyperintense on T2-weighted image
 - b. Rarely signals may be heterogeneous and demonstrate high T1-weighted signal intensity with peripheral rim enhancement
- c. DWI:
 - i. Restricted diffusion
 - ii. Arachnoid cysts which may appear similar on conventional MRI have no restricted diffusion

Laboratory Evaluation

1. Rupture into the CSF pathways may cause a severe meningeal reaction with foreign body giant cells

Epidermoid

General Characteristics

1. There is a low incidence of both epidermoid and dermoid cysts in the cervical spinal segments; related to the embryological process of neural tube closure
2. Usual sites of epidermoids:
 - a. Cerebellopontine angle
 - b. Parasellar
 - c. In the bone diploe of the skull
 - d. Rarely; the IVth ventricle, brain stem and the corpus callosum
3. Extremely rare in the spinal cord:
 - a. May extend into the cervical cord from the cerebellopontine angle

Clinical Manifestations

1. Sites:
 - a. Intramedullary
 - b. Intradural
2. Intradural extramedullary type:
 - a. May have bone or skin malformation that include:
 - i. Spina bifida
 - ii. Dermal sinus
 - b. Acquired from LP:
 - i. Epidermal cells are pushed in by the needle
 - c. Varied motor and sensory signs depending on the level of involvement
 - d. Congenital central site may have dissociated sensory loss; lumbar pain
 - e. Sphincter alterations
 - f. Thoracic epidermoid may cause paraplegia

Neuropathology

1. Well demarcated encapsulated mass of varying size
2. Lining of the cyst is composed of stratified squamous epithelium
3. Presence of keratin
4. Desquamation of keratin forms concentric lamellae which fill the interior of the cysts

Neuroimaging

1. Heterogeneity of signal in T1-weighted and T2-weighted sequences
2. Lack of contrast enhancement
3. Re-tethering of the cord after repair of lipomyelomeningocele

Laboratory Evaluation

1. Rupture of the cyst onto the dura or into CSF pathways causes a severe chemical meningitis

Teratoma**General Characteristics**

1. Teratomas are rare germ cell neoplasms composed of mixed parenchymal cells from one or more of the three germ cell layers (ectoderm, endoderm or mesoderm)
 - a. They are classified as immature or mature depending on the degree of maturation of their cellular components
2. They arise from pluripotent cells which can form skin, muscle bone, cartilage, fat, teeth and hair
3. Primary site of origin is the sacrococcygeal area:
 - a. May also occur in midline or paraxial locations
4. May affect any age group but are primarily seen in childhood
5. CNS teratomas are 0.1% of CNS tumors

Clinical Manifestations

1. Extradural teratomas:
 - a. Cord compression
 - b. May extend through the intervertebral foramina
 - c. Back pain
 - d. Radicular symptomatology
 - e. Cauda equina syndrome
2. Intradural extramedullary tumors:
 - a. Insidious onset
 - b. Localized or radicular pain
 - c. Deterioration of gait
 - d. Weakness
 - e. Paresthesias
 - f. Sphincter alteration
 - g. Scoliosis
3. Intramedullary tumor:
 - a. Weakness
 - b. Paresthesias
 - c. Spasticity
 - d. Autonomic dysfunction
 - e. Radiculopathy is rare

Neuropathology

1. Immature teratomas are the most common:
 - a. Contain cellular populations of an embryonic nature
 - b. Primitive neuroepithelial lineages
 - c. Immature cell lineages of one or more the primitive germ layers
2. Malignant teratomas are derived from the yolk sac or endodermal sinus

Neuroimaging

1. Associated:
 - a. Dystrophic states
 - b. Diastematomyelia
 - c. Lipomyelomeningocele
2. CT evaluation:
 - a. Vertebral body erosion
 - b. Displaced pedicles
 - c. Thinned laminae
 - d. Calcification
 - e. Diastematomyelia
3. MRI:
 - a. T2-weighted sequences
 - i. Inhomogeneous mass
 - ii. High signal intensity

Laboratory Evaluation

1. Alpha-fetoprotein is elevated in malignant teratomas
2. Chemical meningitis if contents are spilled into CSF pathways or on the dura with CSF:
 - a. Leukocytosis
 - b. Sterile on culture
 - c. Elevated protein

Metastatic Spinal Cord Tumors**Overview**

Spinal cord metastasis is the most common spinal tumor and can be divided into extramedullary and intramedullary types. Extradural metastases from carcinoma, lymphoma and myeloma are most common. They occur from the extension of a vertebral metastasis, are hematogenously deposited or invade through the intervertebral foramina. Intradural extramedullary metastasis arises primarily from carcinomatosis of the meninges, lymphomatosis or melanoma of the meninges. Characteristic of bony metastasis are:

1. Pedicle and posterior element involvement
2. Mid vertebral body destruction
3. Does not involve the disc space
4. Pathologic fracture

Clinical features of extradural metastasis are primarily compressive. Boring, mechanically sensitive back pain often prominent at night. Ataxia may occur prior to weakness which is usually overshadowed by the weakness. There is

early bladder involvement although obstipation may be noted prior to bladder symptoms. There is a dropped sensory level, particularly when the cervical spine is affected.

Parenchyma metastasis usually demonstrates asymmetric motor weakness and sensory loss (dissociative if central and spinothalamic fibers are involved), less bowel and bladder involvement and sacral sparing.

Specific Tumor Metastatic Patterns

1. Lung:
 - a. Multiple metabolic sites
 - b. Most common in men
 - c. Associated with hemorrhagic intramedullary necrosis
 - d. Direct extension from a sulcal apex lung tumor (Pancoast tumor)
 - e. Almost always concomitant cerebral metastasis
2. GI tract:
 - a. May destroy the sacrum
 - b. If associated with mucinous "signet cell type"
 - i. High incidence of non-bacterial thrombotic emboli (NBTE)
 - c. Often a concomitant dense cerebral lesion
3. Prostate:
 - a. Local lumbosacral nerve root and bone invasion
 - b. Spinal cord and radicular components (T10–L1–L3) roots are involved rather than L5–S1 roots which are involved in mechanical pathologies (spondylosis, disc and spondylolisthesis)
 - c. Slowly progressive
 - d. Petrous apex and posterior fossa involvement occurs by way of Batson's plexus
4. Renal cell:
 - a. Radicular component
 - b. Hemorrhagic cerebral metastasis that is often single
5. Leukemia:
 - a. Involvement of nerve roots and spinal cord compression
 - b. "Marble" vertebrae (dense on spine film; marrow change on MRI)
 - c. Approximately 70% have leptomeningeal spread
6. Lymphoma:
 - a. May infiltrate vertebral body (dense vertebrae)
 - b. Envelops the lumbosacral dura and cauda equina
 - c. Cord compression and nerve root involvement
 - d. Leptomeningeal spread
7. Drop metastasis:
 - a. Medulloblastoma
 - b. Ependymoma

Differential Diagnosis of Intrinsic Vertebral Body Bone Disease (with Spinal Cord Compression)

1. Paget's disease
2. Fibrous dysplasia
3. Brown bone cyst

4. Articular bone cyst
5. Osteosarcoma
6. Ewing's sarcoma
7. Chondrosarcoma
8. Osteosclerotic myeloma (POEM syndrome)
9. Multiple myeloma
10. Osteoid osteoma
11. Hemangioma of bone
12. Eosinophilic granuloma
13. Osteochondroma
14. Osteoporosis
15. Hyperparathyroidism
16. Ankylosing spondylitis
17. Vitamin deficiency (usually Vitamin D)
18. Osteomalacic syndromes
19. Prolonged IV heparin ("fish-mouth" vertebrae)
20. Chordoma

Paget's Disease

General Characteristics

1. Increased bone resorption followed by increased bone formation
2. Convex masses of partially calcified osteoid tissue project from the vertebral bodies to paravertebral regions
3. Weakened vertebrae may suddenly collapse:
 - a. Lumbar > thoracic levels
 - b. With spinal cord compression 3–5 vertebrae are involved

Clinical Manifestations

1. Usually a slow progression of disease over 6–12 months
2. Sensory loss and weakness occurs early; then spasticity and bowel and bladder involvement
3. Lumbar involvement may be of single vertebrae
4. Cervical involvement is rare
5. Sarcomatous transformation:
 - a. Occurs in skull or spine
 - b. Affects less than 1% of patients
 - c. Malignant degeneration of a vertebrae is rare
6. Associated features:
 - a. Benign giant cell tumor
 - b. Atlantoaxial fracture dislocation
 - c. Epidural calcification
 - d. Extramedullary hematopoiesis

Osteosarcoma

General Characteristics

1. Young patients
2. Long bones are the preferred sites; distal femur most commonly affected

Clinical Manifestations

1. Rare in vertebral bodies (15%)

Osteochondrosarcoma*General Characteristics*

1. Young patients

Clinical Manifestations

1. Painful
2. Rapid progression
3. Brainstem compression
4. Cervical vertebrae are affected
5. Petroclival suture

Neuroimaging

1. Cauliflower appearance (plain x-ray)

Multiple Myeloma*General Characteristics*

1. Multiple vertebrae are involved
2. Severe anemia

Clinical Manifestations

1. Multiple levels are involved
2. Osteoblastic bone lesions
3. Moth-eaten low density lesions on T1-weighted images

Osteoblastic Monostatic Myelomas*General Characteristics*

1. One vertebral body involved
2. May be any bone in the body or any vertebral level

Clinical Manifestations

1. Motor-sensory neuropathy
2. POEMS syndrome:
 - a. Polyneuropathy
 - b. Organomegaly
 - c. Endocrinopathy
 - d. Skin lesions

Eosinophilic Granuloma*General Characteristics*

1. Young patient (10–20 years of age)
2. Involvement of proximal humerus, skull and thoracic spine

Clinical Manifestations

1. Sudden vertebral collapse with spinal cord compression

Neuroimaging

1. Clean punched out oval lesions

Osteochondroma*General Characteristics*

1. Long bones are involved
2. Most often asymptomatic

Clinical Manifestations

1. Associated with syndromes that may affect the spinal cord
2. Bannayan-Zonana syndrome (AVM of the cord)
3. Gardner's syndrome

Giant Articular Bone Cyst*General Characteristics*

1. Often asymptomatic
2. Occur in thoracic vertebrae

Clinical Manifestations

1. Collapse of vertebrae with radicular symptoms
2. Rarely spinal cord compression

Hemangioma of Bone*General Characteristics*

1. Often multiple; uncommon in thoracic vertebral bodies
2. Extremely vascular tumors

Clinical Manifestations

1. Compresses the spinal cord by vertebral fracture and consequent hematoma
2. May become symptomatic with minor trauma

Neuroimaging

1. Reticulated pattern on CT
2. High intensity signal on T2-weighted sequences

Osteoid Osteoma*General Characteristics*

1. Most common in long bones; wrist is frequently involved

Clinical Manifestations

1. Locally painful
2. Affects the posterior vertebral body elements (pedicle and facets similar to metastatic disease)
3. Pain responds better to aspirin than narcotics
4. Frequent muscular atrophy that overlies the lesion:
 - a. Imaging evaluation:
 - i. Affects posterior elements of the vertebral body

Hyperparathyroidism*General Characteristics*

1. Prominent in renal failure (secondary forms)

Clinical Manifestations

1. Muscle symptoms-pain, aches and proximal weakness
2. Bone vertebral collapse
3. Diffuse involvement and weakening of the vertebral column

Ankylosing Spondylitis*General Characteristics*

1. Asymmetrical large joint arthritis

2. Plantar fasciitis
3. Sacroiliitis (often the first joint affected)

Clinical Manifestations

1. Worse in the morning
2. Anterior uveitis (associated)
3. Severe restriction of spinal movement
4. Falls (primarily neck extension) associated with quadriga- and paraparesis

Neuroimaging

1. Bamboo spine (posterior and anterior ligament calcification)
2. Dural ectasia
3. Cysts of lumbosacral nerve roots

Forester's Disease (Diffuse Idiopathic Hyperostosis)

General Characteristics

1. Bridging osteophytes between vertebrae
2. Osteoporotic vertebral bodies

Clinical Manifestations

1. Restriction of spinal movement
2. Spinal cord and root compression

Osteoporosis

General Characteristics

1. Decrease of the mineralized bone matrix without abnormality of bone cell populations or mineral metabolism
2. Vertebral compression fracture (anterior wedge) with minimal trauma
3. Fractures of proximal femur and distal radius

Clinical Manifestations

1. Vertebral compression fracture:
 - a. Local pain for 2–3 months
 - b. Thoracic spine anterior wedging causes dorsal kyphosis
 - c. Lumbar pain is induced from compensatory lumbar hyperlordosis
 - d. Neurologic deficits are rare (need to rule out underlying metastasis if present)
 - e. Back pain without radiographic evidence of fractures are possibly microfracture

Vitamin D Deficiency

General Characteristics

1. Occurs in a setting (in developed countries) of:
 - a. Kidney failure
 - b. Dilantin use
 - c. Dietary causes

Clinical Manifestations

1. Severe bone pain affecting the pelvic girdle

2. Associated proximal muscle weakness of the pelvic girdle > shoulder girdle

IV Heparin Therapy

General Characteristics

1. Thoracic vertebral deformity (fish mouth)

Clinical Manifestations

1. Local pain
2. Heparin use for longer than two weeks
3. Rare vertebral body collapse

Scoliosis

General Characteristics

1. Adult scoliosis:
 - a. A spinal deformity with a Cobb's angle on frontal plane equal or greater than 10° in an adult patient whose skeletal maturity is complete
2. Possibly effecting 1.4–12% of patients worldwide
3. Some neurologic deficit is related to herniated disc fragments
4. Treatment is required for less than 10% of those with curves greater than 10 degrees
5. Complication rate from surgery is high and approximate 25% of patients require a second operation
 - a. Especially for those patients undergoing posterior fusion with instrumentation

Clinical Manifestations

1. Pain (sciatic at the bottom of the curve)
2. Sagittal imbalance
3. Claudication upon standing or walking
4. Irritation of individual roots
5. Causa equina syndrome
6. Spasticity with paraparesis
7. Bladder tends to be spared

Neuropathology

1. Secondary degenerative scoliosis:
 - a. Trauma
 - b. Vertebral fracture
 - c. Osteoporosis
 - d. Metabolic bone disease
 - e. Iatrogenic causes
2. Due to asymmetric loading which causes segmental instability from:
 - a. Intervertebral disc and/or facet joint degeneration
 - b. Osteophyte formation at the facet joint (spondyloarthritis)
 - c. Eburnation at the endplate (spondylosis)
 - d. Hypertrophy and calcification of the ligamentous flavum
 - e. May cause spinal stenosis and facet hypertrophy
 - f. The curvature apex demonstrates synovitis and arthritis

Neuroimaging

1. Bone edema lies in the middle and inner part of the affected vertebrae (the scoliotic spine is C-shaped)
 - a. Due to trabecular microfractures
 - b. Bone remodeling due to excess loading of this component of the vertebrae

Thoracic Spine Kyphoscoliosis*General Characteristics*

1. In the past tuberculosis and poliomyelitis were major causes
2. Associated anomalies:
 - a. Hemivertebrae
 - b. Absence of ribs
 - c. Diastematomyelia
 - d. Myelomeningocele
 - e. Klippel-Feil deformity
 - f. Sprengel's deformity (occurs with Klippel-Feil)
 - g. Arnold-Chiari malformation
3. Kyphoscoliosis occurs in patients with hydrocephalus that is unrelated to congenital spine defects

Clinical Manifestations

1. Similar to those of scoliosis
2. Complications following surgery:
 - a. Halo-femoral or halo-pelvic traction
 - i. Cranial nerve palsies involving VI, IX, X, XI (cervical kyphoscoliosis)
3. Brachial plexus traction injury
4. Horner's syndrome
5. Myelopathy with motor and sensory deficits
6. Instrumentation:
 - a. Paraplegia
 - b. Anterior spinal cord syndromes
 - c. Urinary dysfunction

Neuropathology

1. Acquired kyphoscoliosis of the thoracic spine is from:
 - a. Infection of the vertebral body, lamina or pedicles
 - b. After laminectomy for tumor
 - c. Syringomyelia

Neuroimaging

1. Similar to that of scoliosis

Laboratory Evaluation

1. Awareness and follow-up of complications following surgery (principally that with instrumentation):
 - a. Pedicle screw impinging on a nerve root
 - b. Infection (sed rate and CRP are elevated)
 - c. Lack of fusion with hyperinstability and spondylolisthesis

Extramedullary Hematopoiesis*General Characteristics*

1. Ectopic extramedullary hematopoiesis is the formation of blood cells outside of the bone marrow

2. Associated with:
 - a. Thalassemia
 - b. Polycythemia Vera
 - c. Myelofibrosis
 - d. Hemolytic anemia
 - e. Hemoglobinopathies

3. Can involve the liver, spleen thorax and lymph nodes
4. Involves paraspinal tissues with extension and involvement of the spinal canal

Clinical Manifestations

1. Compressive signs and symptoms:
 - a. Paraparesis, sensory impairment and sphincter dysfunction
 - b. Paraplegia and quadriplegia

Neuropathology

1. Compensatory mechanisms to sustain erythropoiesis
2. Hematopoietic precursor cells in the local extradural space which proliferate with the stress of chronic anemia
3. Spread of activated precursor cells into the epidural space from a paravertebral mass

Neuroimaging

1. The signal characteristics of the lesion on MRI depend on the presence of blood products (iron in ferrous/ferric states)
2. The signal intensity on T1 and T2 changes depending on the presence of deoxyhemoglobin, methemoglobin, hemosiderin or a combination of these elements
3. MRI
 - a. Isointense lobulated mass on both T1-weighted and T2-weighted sequences

Laboratory Evaluation

1. Investigation of the cause for the usual chronic anemia

Epidural Lipomatosis*General Characteristics*

1. Spinal epidural lipomatosis is an abnormal accumulation of unencapsulated epidural fat
2. It can be divided into idiopathic and secondary and genetic forms
3. It can be a component of mutations in the phosphatidylinositol/AKT/mTOR pathway that includes:
 - a. Fibroadipose overgrowth
 - b. Hemihyperplasia-multiple lipomatosis (HHML)
 - c. Congenital lipomatous overgrowth
 - d. These fat overgrowth syndromes overlap with:
 - i. Vascular malformations
 - ii. Epidermal nevi
 - iii. Scoliosis/skeletal and spinal (CLOVES) syndrome
 - iv. Macrodactyly
 - v. Megalencephaly syndrome

- vi. All of the above syndromes have adipose dysregulation
- 4. Secondary forms include:
 - a. Prolonged administration of steroids
 - b. Endocrinopathies
 - c. Cushing's syndrome
 - d. Obesity

Clinical Manifestations

1. Occurs primarily epidurally in the thoracic and lumbar cord
2. Back pain
3. Radicular and slowly compressive myelopathy
4. Male predominance
5. Cauda equina syndrome

Neuropathology

1. Accumulation of normal unencapsulated epidural fat
2. Spontaneous regression has been reported

Neuroimaging

1. Epidural mass lesion of thoracic and lumbar spine
2. High-intensity signal on T1-weighted sequences; much-diminished signal on T2-weighted sequences

Laboratory Evaluation

1. Medical evaluation for underlying endocrinopathy
2. Awareness of the PIK3CA overgrowth spectrum

Differential Diagnosis of Intrinsic Disc Disease with Spinal Cord Involvement

1. Extruded disc fragment (though the posterior longitudinal ligament)
2. Free fragment disc (may migrate)
3. Relapsing polychondritis (autoimmune disc destruction)
4. Ochronosis (homogentisic aciduria)
5. Collagen gene defects (COL A 1–5)
6. Ehlers-Danlos (type IV) syndrome
7. Marfan's syndrome
8. Tuberculosis
9. SBE (staph aureus; acute post-operative infection)
10. Charcot joint (disc destruction):
 - a. Syphilis
 - b. Diabetes mellitus
 - c. Amyloid
 - d. Syringomyelia
11. Gram-negative infections (usually occurs late following surgery)
12. Trauma (exacerbates the existing disc dysfunction; does not cause degenerative disc disease)
13. Fungal infection:
 - a. Nocardia
 - b. Cryptococcus
 - c. Blastomycosis
 - d. Coccidioidomycosis (from contiguous sacroiliac infection)

Disc Disease

General Characteristics

1. Central disc protrusion may compress the spinal cord acutely or chronically at cervical, thoracic and lumbar levels
2. Most dangerous area is the thoracic cord due to the small diameter of the spinal canal at this level
3. A disc fragment may erode through the posterior longitudinal ligament and compress the cord; it may migrate rostrally and caudally
4. Radicular symptoms are most often noted ipsilaterally; rarely contralaterally from loss of bilateral foraminal integrity; this may occur with or without cord compression
5. Initial thoracic disc protrusion signs and symptoms:
 - a. Patients legs collapse during heavy lifting
 - b. Severe thoracic radicular pain
6. Central cervical disc rupture is most common at C5–6 and C6–C7 (greatest flexion and extension movement segments)

Clinical Manifestations

1. Incomplete spinal cord injury
2. Brown-Séquard syndrome
3. Anterior spinal artery syndrome
4. May cause pseudo-peripheral sensory loss (cervical disc protrusion usually) in the lower extremities due to spinal cord sensory laminations (ascending leg numbness)
5. Conus medullaris and cauda equina syndromes

Relapsing Polychondritis

General Characteristics

1. Autoimmune disease of cartilage
2. Associated cartilage involvement of the trachea, pinna, and nose
3. Cause of relapsing meningitis

Clinical Manifestations

1. May affect a disc at any level
2. Rare cord compression

Ochronosis

General Characteristics

1. Defect of homogentisic acid metabolism
 - a. AR; Chromosome 18
 - b. Deficiency of Homogentisate 1,2-dioxygenase (HGD) activity that results in the accumulation of homogentisic acid (HGA)
 - c. Oxidation products polymerize and deposit as a melanin-like pigment primarily in cartilage and connective tissue

Clinical Manifestations

1. A progressive disease

2. Darkening of the urine at birth
3. Ochronosis (dark pigmentation of connective tissue) at around 30 years of age (ear and eye)
4. Severe ochronotic arthropathy at approximately 50 years of age
5. Cardiovascular and renal complications
6. Weight bearing joints and the thoracolumbar spine are most often affected
7. Calcification of thoracic disc ("rugger Jersey")
8. Rare neurologic signs

Charcot Joints and Disc – Destruction of the Thoracic Spine

General Characteristics

1. Also known as spinal neuropathic or neurogenic arthropathy
2. Affects the intervertebral disc and the adjacent vertebral bodies
3. Loss of pain and proprioceptive input to the joint
4. Occurs with:
 - a. Spinal cord injury
 - b. Diabetes mellitus
 - c. Amyloidosis
 - d. Syphilis
 - e. Thoracic or cervical syrinx

Clinical Manifestations

1. Proprioceptive pain and temperature loss at affected levels
2. Back pain
3. Progressive thoracic scoliosis
4. Cord compression with quadriparesis or paraparesis, radicular pain, and segmental sensory loss
5. Collagen defects all may have disc capsule defects with extrusion of the nucleus pulposus:
 - a. Marfan's disease
 - b. COL A 1–5 gene defects
 - c. Ehlers-Danlos (type IV)
 - d. Osteogenesis imperfect

Infections of the Disc Space

Overview

General Characteristics

1. Exquisite pain with movement or vibrating the patients' bed
2. Frequent radicular pain
3. High sedimentation rate
4. Local pain at the level of involvement
5. Involvement of the pre- and postvertebral fascia is common; may extend over several segments
6. Usually, only one disc level is involved; arteries that supply the disc are end arteries
7. Paravertebral muscle involvement:
 - a. Common in the iliopsoas (cold abscess) at L1–L3 levels in American patients with tuberculosis

- b. Asian patients with tuberculosis tend to have cervical involvement
8. SBE with septic emboli:
 - a. Tend to deposit at T4 level (watershed)
9. Post-surgical procedures

Clinical Characteristics of Specific Infections of the Disc Space

1. *Staphylococcus aureus*:
 - a. Common with IV drug abuse and in HIV-infected patients and with acute surgical procedures
 - b. Rapid spinal cord symptomatology
 - c. Can occur at any spinal level but most often at thoracic levels (T4–T6)
 - d. Concomitant with SBE
2. Gram-negative infections:
 - a. Post disc surgery
 - b. *Pseudomonas*, *E coli*, *enterococcus* are the most common organisms
 - c. Signs and symptoms may have a delayed onset; 2–3 weeks after a surgical procedure; rarely 6–8 weeks after surgery
3. *Nocardia*:
 - a. Noted in patients with lung abscess
 - b. May have cervical spinal cord predilection
 - c. Associated with immunosuppressed patients
4. *Cryptococcus*:
 - a. Low cervical and thoracic disc spaces are most commonly involved
 - b. Lung is the origin of the infection
 - c. HIV and immunocompromised patients
 - d. Associated meningitis and cranial nerve II involvement
5. *Coccidioidomycosis*
 - a. The lumbosacral disc spaces are infected from contiguous sacral osteomyelitis:
 - i. Associated arteritis (cerebral)
 - ii. S.W. USA (San Joaquin Valley fever)
6. *Actinomyces*:
 - a. Thoracic and low cervical discs are involved
 - b. Contiguous from a lung infection
 - c. Draining soft tissue sinuses with sulfur granules

Spondylitic Myelopathy

General Characteristics

1. Spondylitic myelopathy is a combination of degenerative disc disease (a biochemical change in the nucleus pulposus; "hard disc") and osteophytic remodeling of bone
2. Hypertrophy of the ligamentum flavum
3. Facet joint arthropathy
4. A progressive slowly developing process
5. The most common cause of compressive myelopathy; may be more severe in patients with a congenital spinal stenosis

Clinical Manifestations

1. The disease process is most severe at the motion segments of the spinal cord (C5–C6 and L5 S1)

2. The patients demonstrate a stiff forward flexed neck with the limitation of movement to all planes. This is invariant in cervical myelopathy. Lumbar spondylosis is frequently associated with positive straight leg raising test but not to the same degree as patients with spinal stenosis (often concomitant processes)
3. Pain is a deep ache noted in the C5–C6 distribution of the upper arms and shoulders. Rare for radiations into the fingers unless an osteophyte compromises a foraminal exit canal. In the lower extremity the pain is often midline. If there is concomitant radicular pain, it is in the L4–S1 dermatomal distributions. S1 frequently radiates into the groin and L5 to the top of the thigh. As a good general, rule-high lumbar root and spinal cord involvement is a medical problem while L5–S1 root disease is mechanical
4. Paresthesias and numbness of the hands (all fingers concomitantly)
5. Asymmetric weakness and atrophy of C5–C6 muscle groups, particular the supraspinatus and deltoids. In the lower extremity the medial gastrocnemius, anterior tibialis, and extensor digitorum brevis are involved. The gluteus maximus is often atrophic. Fasciculation may be seen in affected weak and atrophic muscles
6. There is often an inverted radial reflex due to a combination of cord compression above or at C4 combined with osteophytic occlusion of the C5–C6 intravertebral exit foramina. Ankle jerks are frequently depressed while knee jerks are exaggerated (cord compression at cervical levels combined with L5–S1 radiculopathy)
7. Poor tandem gait (compression of the dorsal and ventral spinocerebellar pathways in the lateral spinal cord). The proprioceptive fibers for the upper extremities traverse the cuneocerebellar tract C1–C4 which is much less involved
8. Babinski sign and clonus are prominent with cervical cord compression. Easily elicitable (1/2 of the outer aspect of the foot). Spasticity of the lower extremities is common
9. Lhermitte's sign (paresthesias of the upper extremities or upper spinal column with neck flexion)
10. A Romberg sign and posterior column dysfunction may be predominant in a subset of patients
11. Mirror hand movements have been reported in severe cervical myelopathy
12. Quadriparesis or paraparesis may occur with moderate flexion or extension of the neck
4. Demyelination or focal necrosis at attachment points of the dentate ligament
5. Loss of myelin occurs in the posterior and lateral columns
6. Loss of anterior horn cell neurons occurs at affected levels
7. Spondylitic symptomatic canals are usually 7–12 mm in the AP diameter (normal is 17–18 mm). There is a great deal of movement of the cervical cord with flexion and extension of the neck that may cause trauma in the setting of stenosis
8. Both arterial compromise and progressive venous outflow obstruction may also play a role in cord pathology

Neuroimaging

1. MRI:
 - a. Demonstrates cord compression. It is not nearly as accurate in estimating bony changes. It demonstrates high-intensity signal within the cord on T1-weighted sequences which portends myelomalacia
 - b. In complicated patients with a combination of root involvement and spinal cord compression, a CT-myelogram is warranted. The contrast outlines the nerve roots while the CT is excellent for detailing the bone compression on the root. The technique also gives an excellent appraisal of facet anatomy and the lateral recesses of root exit canals. Tropism of a degenerative facet (rotation into the foraminal exit canal causing stenosis) is often not appreciated

Laboratory Evaluation

1. There are no laboratory signs of systemic disease
2. EMG:
 - a. Determines the most involved radicular segments
 - b. Nerve conduction velocities help to rule out concomitant peripheral neuropathy as a cause of sensory loss and gait ataxia

Lumbar Stenosis (LSS)

General Characteristics

1. Classified as primary due to a congenital abnormality or a disorder of postnatal development
2. Secondary due to degenerative changes, local infection, trauma or surgery
3. By far the most common cause is a slowly degenerative process of the lower lumbar segments
4. Degenerative lumbar stenosis involves:
 - a. The central canal
 - b. Lateral recess
 - c. Foraminal exit canals

Clinical Manifestations

1. Degenerative lumbar stenosis is uncommon in patients less than 50 years
2. Radicular symptoms are usually referable to L4–S1 roots
3. Back pain with buttock and sciatic radiations that is elicited by sitting, standing and walking. Usually relieved by rest

Neuropathology

1. A spondylitic bar occurs from degenerative changes of the annulus fibrosis. There is frequent disc bulging at several levels
2. The dura is often thickened and adherent to the posterior longitudinal ligament
3. Bone remodeling causes osteophytes in the intervertebral canals that compress the dural sleeves of the nerve roots

4. Neurogenic cramps in the gastrocnemius are frequent. This is usually a dull pain whereas that from vascular claudication tends to be burning
5. Neurogenic claudication:
 - a. A gradual onset of numbness or weakness of the legs that is associated with asymmetric L4–S1 root involvement
 - b. Patient obtains relief with rest and in severe disease utilizes flexion of the hips and knees for pain relief
 - c. The asymmetric leg numbness ascends when the patient walks
 - d. Bladder and sexual function are relatively spared
 - e. Degenerative spondylolisthesis is a frequent concomitant, the symptoms of which include:
 - i. Severe pain with flexion or extension of the spine and with severe loading of the spine at L5. This is usually from sitting for periods of greater than 30 minutes
 - ii. Radiation of pain is usually to the lateral thigh (L5) with radiations into the groin (S1) and top of the thigh (dural projection of L5)
 - iii. A slippage of L5 (forward) over S1 (spondyloptosis)
 1. Protrusion of the lower abdomen
 2. Radicular symptoms at L4–S1
 3. Rarely bladder involvement

Clinical Signs of Lumbar Spinal Stenosis

1. Forward flexed posture
2. Paraspinal muscle spasm
3. Very positive straight leg raising test
4. Preserved muscle strength and bulk
5. Hyperactive reflexes in both upper and lower extremities (due to concomitant cervical stenosis or compressive myelopathy)
6. Concomitant spondylolisthesis:
 - a. Pelvic shelf atrophy of the gluteus maximus, medius and minimus
 - b. Severe pain on extension > flexion of the axial spine
 - c. Radicular signs with mild atrophy of L4–S1 roots
 - d. Rare continuous moving toe syndrome (sinuous toe movements). Continuous moving fingers has been described from cervical stenosis and myelopathy
 - e. Rare to have degenerative lumbar arthropathy without a similar process occurring in the cervical spine

Neuropathology

1. Claudication of the cauda equina is caused by compression of the nerve roots by:
 - a. Hypertrophied facet joints
 - b. Thickened posterior longitudinal, dentate and ligamentum flavum ligaments
 - c. Loss of vertebral height from disc desiccation and bulging of the annulus fibrosis

- d. Osteophytic overgrowth both posteriorly from the vertebral body and in the foraminal exit foramina
2. There may also be a vascular compromise of the arterial supply from branches of the great radicular artery of Adamkiewicz or the vasa vasorum
3. Inflammatory cytokine elevation IL-1B but not of IL-6 or tumor necrosis factor-alpha have been demonstrated in cartilage and synovial membranes of zygapophyseal joints

Neuroimaging

1. Asymptomatic patients may have radiologic features of lumbar spinal stenosis
2. Verbiest suggested that an AP diameter of 10–12 mm was relative stenosis whereas absolute stenosis is present if the diameter is less than 10 mm
3. A trefoil shape of the canal and ligament, facet, hypertrophy, osteophytes from the vertebral body and hard disc bulges all contribute to spinal stenosis
4. Shortened pedicles and a shallow tight canal are components of congenital stenosis

Laboratory Evaluation

1. EMG evaluation:
 - a. Determines the specific root involvement
 - b. Nerve conduction velocities define concomitant neuropathies that need medical evaluation (diabetes mellitus, B12 deficiency, Vitamin E deficiency (rare))

Spinal Cord Compression from Pathology of Ligaments, Arachnoid Cysts, and Pial Processes

Differential Diagnosis

1. Posterior longitudinal ligament calcification
2. Ankylosing spondylitis
3. Acromegaly
4. Mucopolysaccharidosis (Schie's disease)
5. Syphilitic cervical pachymeningitis
6. Familial amyloid polyneuropathy (type-1 with meningeal involvement)
7. Sarcoid infiltration
8. Lipomatous dural thickening
9. Tuberculous meningitis
10. Rheumatoid dural proliferation
11. Ligamentous laxity syndromes
 - a. Mongolism (C1–C2 subluxation)
 - b. Ehlers-Danlos type IV
 - c. Marfan's disease
 - d. Rheumatoid arthritis (pannus formation destruction and erosion of the atlantoaxial ligaments at C1–C2)
12. Spinal arachnoid cysts
13. Hirayama's disease

Ankylosing Spondylitis

General Characteristics

1. Inflammation occurs at the ligamentous insertion into bone with calcification

2. The sacroiliac joint and the lumbar spine are often most severely affected, but all levels are involved; the entire spine becomes fused and rigid
3. Primarily affects young men
4. HLA-B24 is elevated
 - a. Non-major histocompatibility gene complex susceptibility loci include ERAP and IL23R are associated
5. Absence of rheumatoid factor

Clinical Manifestations

1. Modified New York criteria:
 - a. Limited motion of the lumbar spine
 - b. Persistent lower back pain
 - c. Decreased chest expansion
 - d. Radiologic evidence of stenosis
2. Neurological manifestations:
 - a. Spinal stenosis
 - b. Cauda equina syndrome
 - c. Dilatation of the caudal dural sac (possible defect in CSF reabsorption)
 - d. Arachnoidal diverticula on posterior root sleeves
 - e. Thoracic and cervical myelopathy
 - f. Fracture of the vertebral column with minimal trauma; consequent spinal cord compression

Rheumatoid Arthritis of the Spine

1. Ligamentous degeneration of the atlantoaxial junction is affected
2. Pannus formation at this level (C1–C2)
3. Intermittent or permanent quadriparesis
 - a. Sudden death may occur with minimal trauma

Ossification of the Posterior Longitudinal Ligament

General Characteristics

1. Occurs primarily in the cervical spine in Japanese patients
2. Males > females; in patients greater than 40 years of age
3. May extend for only two segments or over the entire spine

Clinical Manifestations

1. Myelopathy > radiculopathy; both may occur concomitantly
2. Posterior cervical pain may be an isolated complaint
3. Usually a slowly progressive myelopathy
4. Trauma may precipitate acute cord compression
5. Most frequently involved segments are C7, C8, T1
6. Partial Brown-Séquard syndrome rarely occurs

Neuroimaging

1. MRI and CT evaluation:
 - a. Cancellous bone formation may occur along a segment of the posterior longitudinal ligament

Hirayama Disease

General Characteristics

1. Muscles innervated by C7, C8 T1 are primarily affected
2. Disease primarily of young men

Clinical Manifestations

1. Asymmetric involvement of the lower cervical roots
2. No fasciculation
3. No sensory changes
4. Painless process

Neuroimaging

1. CT/MRI demonstrate:
 - a. Atrophy and signal changes (MRI) in the ventral cord
2. Buckling of the dorsal dural sac with intermittent anterior displacement and ligamentous compression of involved segments with neck flexion

Paget's Disease of Bone

General Characteristics

1. Enlargement of the vertebral bodies, pedicles, and lamina

Clinical Manifestations

1. Spinal cord compression
2. Elevated alkaline phosphatase
3. Areas of bone growth and lysis

Acromegaly

General Characteristics

1. Major complications include:
 - a. Hypertension
 - b. Hyperglycemia
 - c. Diabetes mellitus
 - d. Cardiomyopathy
 - e. Sleep apnea

Clinical Manifestations

1. Carpal and tarsal tunnel syndromes are often presenting complaint
2. Spinal cord compression with myelopathy (all levels)
3. Elevated growth hormone and insulin-like growth factor 1 levels (IGF-1)

Mucopolysaccharidosis Type IV (MPS IV, also Known as Morquio Syndrome)

General Characteristics

1. AR; deficiency of the enzyme N-acetylgalactosamine-6-sulfatase (GALNS)
 - a. Catalyzes a step in the catabolism of glycosaminoglycan keratan sulfate and chondroitin 6-sulfate
 - b. Accumulation of the KS and C6S in the bone and cornea

Clinical Manifestations

1. Variable age of onset and rate of progression
2. Short stature, pectus carinatum, kyphoscoliosis, genu valgus, cavity of joints and corneal clouding
3. Normal intelligence
4. Congenital absence or hypoplasia of the odontoid bone in conjunction with lax ligaments leads to atlantoaxial subluxation that causes:

- a. Cervical spinal cord compression
- b. Children develop spastic quadriparesis
- c. Delayed walking
- 5. Other mucopolysaccharidoses:
 - a. Severe pachymeningitis of the dura with spinal cord compression

Idiopathic Hypertrophic Pachymeningitis

General Characteristics

- 1. IgG4-related pachymeningitis (IgG4-RHP) is a manifestation of IgG4-related disease
- 2. It is a fibro-inflammatory condition
- 3. Oligoclonal restricted IgG4-positive plasma cells within inflammatory meningeal niches

Neuropathology

- 1. Lymphoplasmacytic infiltration of IgG-4-positive plasma cells, fibrosis, and obliterative fibrosis

Clinical Manifestations

- 1. Cranial nerve palsies
- 2. Compressive myelopathy

Neuroimaging

- 1. MRI:
 - a. Meningeal thickening with gadolinium enhancement

Differential Diagnosis

- 1. Sarcoid
- 2. Lymphoma
- 3. Rheumatoid arthritis
- 4. Syphilis (pachymeningitis cervical)
- 5. Deep fungal meningitis

Ligamentous Laxity Syndrome

General Characteristics

- 1. Atlantoaxial hypermobility
- 2. Odontoid and axis should separate no more than 3 mm on neck flexion in an adult
- 3. The cruciate ligament (behind the odontoid) is the major ligament of the odontoid process; lateral ligaments attach the odontoid to the lateral masses of C1
- 4. Atlantoaxial subluxation > subaxial subluxation

Clinical Manifestations

- 1. Paresthesias of the hands
- 2. Minimal trauma may cause quadriparesis (most common in the spondylolisthesis of rheumatoid arthritis)
- 3. Neck flexion may cause drop attacks with increased reflexes

Arachnoid Cysts

General Characteristics

- 1. Arachnoid cysts occur both intradurally and in the extradural space

- 2. They may occur dorsally and ventrally to the spinal cord
- 3. Etiology is incompletely understood but defined causes include:
 - a. Trauma
 - b. Hemorrhage
 - c. Infection
 - d. In children
 - i. Association with neural defects
 - e. In adults they may be associated with:
 - i. Spinal deformities
- 4. Majority of cases occur in the thoracic and cervical areas

Clinical Manifestations

- 1. Paraparesis (may be intermittent when the cyst fills with CSF)
- 2. Neuropathic pain (radicular)
- 3. Gait ataxia (cervical location)
- 4. Sphincter disturbance

Neuropathology

- 1. Intradural arachnoid cysts are most often dorsal to the spinal cord
- 2. Craniocaudal extension is approximately 3.7 vertebral bodies
- 3. Arachnoid webs occur concomitantly
- 4. Splitting of the arachnoid membrane which is reinforced by a layer of collagen (by EM)
 - a. Normal trabecular arachnoid cells
- 5. Dorsal cysts could arise from diverticula of the septum posticum

Neuroimaging

- 1. MRI:
 - a. High-intensity signal on T2-weighted images
 - b. Occasionally CT myelogram is necessary for long cysts with multiple septae

Laboratory Evaluation

- 1. Evaluation in adult patients for associated congenital defects

Differential Diagnosis

- 1. Intradural:
 - a. Cystic neoplastic lesions
 - b. Acquired arachnoid cysts
 - c. Inflammation following meningitis
 - d. Parasitic lesions

Other Cerebrospinal Fluid Containing Cysts

- 1. Arachnoid diverticulum
- 2. Extradural arachnoid cysts
- 3. Extradural pseudo meningocele

Idiopathic Spinal Cord Herniation

General Characteristics

- 1. Primarily affects the thoracic spinal cord

2. Ventral displacement of the spinal cord through a dural defect
3. Neurologic deficits putatively caused by adhesion and vascular compromise
4. Spontaneous displacement of the spinal cord through an anterior dural defect
5. Theories of pathogenesis include:
 - a. Congenital dural insufficiency
 - b. Trauma
 - c. Pressure erosion of the dura
 - d. Duplication of the ventral dura
 - e. T3–T7 are most frequently affected

Clinical Manifestations

1. Dependent on the site of spinal cord herniation
2. Longstanding prior to diagnosis
3. Affects middle-aged women
4. Progressive partial Brown-Séquard syndrome is most common presentation
5. Paraparesis
6. Sensory disturbances
7. Sphincter dysfunction
8. Chest pain

Neuroimaging

1. MRI:
 - a. Enlargement of the dorsal subarachnoid space
 - b. Ventral displacement and an anterior C- or S-shaped kind of thoracic spinal cord
 - c. The cord is attached to the anterior dural mater with no intervening CSF
 - d. May or may not have cord atrophy; no T2-weighted sequence hyperintensity in the cord
 - e. Nerve roots transverse the dorsal subarachnoid space whereas, with dorsal subarachnoid cysts, the roots are at the periphery of the cyst

Neuropathology

1. Atrophy of the cord in some patients
2. Congenital duplication of dural membranes

Laboratory Evaluation

1. No associated systemic features

Differential Diagnosis (Misdiagnosis)

1. Dorsal arachnoid cyst
2. Thoracic disc herniation
3. Transverse myelitis
4. Arachnoiditis
5. Intradural mass
6. Extradural compressive lesion

Spinal Arachnoiditis

General Characteristics

1. In lumbar arachnoiditis, the arachnoid membrane is thickened or opaque near the cauda equina

2. The term may also apply to thickened arachnoid sheaths around nerve roots
3. In the past, the problem occurred from the use of lipid soluble contrast agents often associated with a mixture of blood
4. Also associated with ruptured discs, operative procedures, and infections. Rarely epidural anesthesia is implicated

Clinical Manifestations

1. Intractable low back pain with radicular signs and symptoms
2. Maybe a delayed onset of signs and symptoms (months to years)
3. Associated progressive syringomyelia or myelomalacia due to spinal cord tethering

Neuropathology

1. The exposed cord and roots are encircled by leptomeningeal fibrous tissue often containing lobulated cysts
2. Spinal cord kinking from focal adhesive arachnoiditis

Neuroimaging

1. MRI:
 - a. Clumping and adhesion of nerve roots on T2-weighted sequences; thickened meninges in the spinal canal
2. Myelographic imaging utilizing true fast imaging with steady-state precession (TrueFISP) sequences

Laboratory Evaluation

1. Signs of aseptic meningitis following a causative procedure (acute CSF sample)

Hypertrophic Nerve Roots

General Characteristics

1. Hereditary sensory neuropathies I, III, and V and chronic inflammatory demyelinating neuropathy are the most common neuropathies to compress the spinal cord

Clinical Manifestations

1. Clinical signs of congenital neuropathy
2. Cauda equina compression
3. Radiculopathy
4. Associated with nerve root cysts
 - a. Rupture of these perineural cysts are associated with low pressure headache
5. Spinal cord compression

Differential Diagnosis of Dural Ectasia

1. Neurofibromatosis type I
2. Marfan's syndrome
3. Ehlers-Danlos type IV
4. Collagen gene defects (I–V)
5. Ankylosing spondylitis
6. Spinal cord dural herniation
7. Meningomyelocele
8. Osteogenesis imperfect

Further Reading

Further Reading on Spinal Cord

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Chapter 5

Radiculopathy

Overview of Pain

Pain problems are a major component of consultative neurology. The perception of pain is complex and is composed of a discriminative component (location, quality, intensity), and an affective component (unpleasantness) and a motivational and emotional component (anxiety, depression, coping maneuvers). Each component has its unique circuitry.

Pain itself may be characterized as:

1. Nociceptive, the physiologic alerting mechanism that guides the organism from further harm
2. Inflammatory pain that ceases when the inciting injury heals
3. Neuropathic pain which is caused by injury to the somatosensory system which often continues after the injury has healed and is destructive to the organism

Specific modalities of pain are expressed in pain state. Hyperalgesia is defined as heightened sensitivity to a painful stimulus. Allodynia is pain that is elicited from a non-painful stimulus. In neuropathic pain conditions mechanical and heat allodynia are cardinal features. Dynamic mechanical allodynia refers to pain elicited by a moving cutaneous stimulus (a wisp of cotton stroked across the skin) whereas static allodynia refers to pain elicited by pressure at ordinarily non-painful thresholds. Mechano-allodynia is carried by A-beta fibers (myelinated 8–12 μ fibers). Thermal hyperalgesia is associated with A-delta fibers that convey cold and polymodal C-fibers that respond to heat, tissue destruction, and chemical stimuli. Mechanical and thermal hyperalgesia (particularly cold) are major modalities of peripheral neuropathic pain that is caused by radiculopathy. Radicular conditions (disc disease, spinal stenosis, trauma to nerves) are primary causes of peripheral neuropathic pain. Pain is a very dynamic and plastic process in that chronic pain afferences actually change the response characteristic of pain transmission neurons (PTNs). In general, they become more responsive. Pain is a very sensitive modality in that only one C-fiber when stimulated during microneurography can convey location quality and intensity of a stimulus. It is now clear that immune mechanisms are important at many levels of pain production and maintenance.

As a general chain of events, a tissue-modifying stimulus triggers the firing of transient receptor potential (TRPV1, TRPV8, and TRPA1) receptors on primary pain afferents. In turn, they initiate action potentials in C-fibers and A-delta fiber nociceptive neurons (cell bodies are in the dorsal root ganglia) that synapse in different components of the dorsal horn. These second order neurons give rise to spinothalamic and other afferents that activate the pain matrix. Specific aspects of inputs into PTNs induce both central and peripheral sensitization of the pain matrix, which modifies anatomic, physiologic, and genetic components of the pain matrix at all levels.

Some Aspects of the Anatomy of Pain

The skin is a complex sensory organ that also serves homeostatic and immunologic barrier functions. It is a neuroimmune cutaneous system that signals the sensory modalities of touch, pressure, temperature, and pain. As noted earlier, these primary modalities are modified in pain states (hyperalgesia, allodynia, and hyperpathia). All chronic pain conditions induce plasticity in pain transmission neurons. It is poorly recognized that there is a descending facilitating and inhibitory pain control system, the diffuse nociceptive inhibitory control system (DNIC) that modifies the transmission and physiology of pain transmission after a painful stimulus. This is a dynamic system at both central and peripheral levels that adjusts its sensitivity (thresholds) by complex mechanisms of central and peripheral sensitization. Sensory transduction occurs following activation of primary intraepidermal nerve terminal C and A-delta nociceptive afferents. Activation of these primary intraepidermal nerve terminal C and A-delta nociceptive afferents is dependent on neuronal and non-neuronal skin cells of the neuroimmune cutaneous system (NICS). The epidermis is primarily composed of keratinocytes, melanocytes, Langerhans and Merkel cells. These cells express sensor proteins and neuropeptides (substance P and calcitonin gene-related peptide) that are pivotal in nociception and neurogenic inflammation (vasodilation, plasma extravasation, and hypersensitivity). Keratinocytes comprise approximately 85% of dermal cells and form a tight junction with primary nociceptive nerve fibers. They express transient receptor potential vanilloid 1 (TRPV1) and transient receptor potential ankyrin (TRPA1) receptors. These channels are members of the transient receptor (TRP) superfamily of nonselective cation channels. TRPV1 channels are noxious heat-gated cation channels that are expressed on nociceptive primary afferents and respond to protons, endogenous lipid ligands that include endocannabinoids, lipoxygenase metabolites, lysophosphatidic and linoleic acid metabolites in the microenvironment following injury. These receptors (TRPV1 and TRPA) that are activated following injury or inflammation depolarize nociceptive primary afferents in the dorsal root ganglia whose central terminals project to the dorsal horn (DH) of the spinal cord. The dorsal root ganglia are composed of large diameter neurons that mediate mechanical modalities, small diameter neurons that mediate pain and temperature, as well as satellite cells that are similar to glial cells in the CNS. There are also blood vessels innervated by unmyelinated autonomic fibers. Following injury, there is upregulation of various receptors on the neuronal elements of the DRG and under specific conditions sprouting of sympathetic fibers from the blood vessels. These fibers may form basket-like terminals around nociceptive and large mechanosensitive neurons. The spinal blood-nerve barrier is not as tight as the blood-brain barrier. This is important in the pathophysiology of neuropathy caused by chemotherapy (direct toxic injury from cisplatin and paclitaxel) as well as from au-

to immune attack from activated lymphocytes and other cellular agents. In the skin, keratinocytes, macrophages, TRPV1-expressing nociceptors release nerve growth factor (NGF), prostaglandins (particularly E2), proinflammatory cytokines (IL-1, IL-6), and transforming growth factor beta 1 (TGFB1) as well as chemokines which sensitize (lower the threshold to fire) primary afferent nociceptors. In many instances, after the nociceptors are exposed to the above noted “inflammatory soup” and they fire spontaneously which is the origin of spontaneous pain in many chronic neuropathic pain syndromes.

Nociceptive afferents are principally unmyelinated ($1\ \mu$) C-fibers and thinly myelinated ($1\text{--}4\ \mu$) A-delta fibers. The A-delta fibers signal location, intensity, cold and the lancinating quality of pain (epicritic qualities or fast pain). C-fibers are slowly conducting, transmit a burning quality of pain, and are poorly localizing (second pain).

A dermatome consists of the primary neurons of the DRG, their peripheral and central afferents that include cutaneous and visceral endings. Each dermatome is segregated as it enters the spinal cord: the medial fibers that are primarily myelinated and are mechanosensitive, and the lateral pain and temperature fibers (segregation of the spinal roots at the dorsal root entry zone (DREZ)). Each dermatome maintains a specific topography throughout its projections in the CNS (brainstem, thalamus, and cortex).

A sclerotome refers to pain projection pathways from bones, ligaments, and fascia that project slightly differently from the dermatomal pattern. After traversing the dorsal root entry zone, C-fibers innervate the specific spinal segment, but also approximately two spinal segments rostrally and caudally by means of Lissauer’s tract. There is thus overlap of sensory pain dermatomal innervations. There is a small contralateral segmental DH innervation through the anterior commissures.

The dorsal horn is cytoarchitecturally organized in Rexed layers (laminae). A-delta fiber afferents synapse in lamina I and the outermost lamina II cells. There are also important synapses from A-delta fibers in lateral lamina V. Large mechanosensitive (heavily myelinated) fibers synapse in layers III and IV. The primary synaptic connections of C-fibers is in the substantia gelatinosa (Rexed layer II). C-fiber collaterals project to the intermediolateral column (ILC) and the motor neurons of Rexed layers IX. Cells in lamina VII (primarily motor interneurons) and lamina VIII (autonomic neurons) also respond to painful stimuli. These neurons receive projections from the DNIC (descending pain-modulating system; principally from the rostral ventral medullary neurons). Rexed layer VII motor interneurons also synapse segmentally with C-fibers. Reflex connections from C-fiber afferents to motor neurons in IX and autonomic neurons of the ILC are activated in pain states. There are sympathetic chemical connections at the site of injury, where released norepinephrine may excite upregulated sympathetic alpha receptors on nociceptive afferents, as well as plastic sympathetic upregulations within the DRG. In addition to the secondary neurons (pain

projecting neurons PTN) of Rexed layers I and II (the primary neurons are in the DRG), the neurons of lateral Rexed layers V and VI are pivotal for many of the secondary modalities of pain sensation seen in neuropathic pain states. Neurons in these layers are widely dynamic in range: they receive low threshold mechanoreceptive input (LTM; A-beta myelinated afferents), sympathetic, temperature (C-fiber; heat; A-delta cold fiber afferents) and nociceptive specific CNS projections. Integration of these afferent inputs determines if these neurons will depolarize.

Ascending Pain Pathways

The secondary axons of Rexed layers I, II (inner/outer layers), lateral V and VI form the major components of the lateral spinothalamic tract. The spinal thalamic tract (STT) decussates in the anterior spinal commissure and ascends contralaterally as the spinothalamic tract that synapses at brainstem and thalamic levels. Pain and temperature fibers decussate approximately at two segmental levels rostral to their level of entry. Therefore, there is a drop of pain and temperature sensations on the trunk of approximately two levels with spinal cord injury (often slightly higher posteriorly). Sacral fibers are outermost in the tract while those carrying cervical and arm pain are most medial. There is also segregation by modality.

The modalities may be segregated superiorly to inferiorly:

1. Temperature
2. Pain
3. Touch
4. Deep pressure

Medially placed anterolateral fascicular fibers comprise the spinoreticular thalamic pathway. It projects to the reticular core of the medulla and midbrain and synapses in the medial (DM) and intralaminar nuclei of the thalamus (centralis medialis, lateralis, and zona reticularis). This paleospinothalamic system synapses with the nucleus gigantocellularis, parabrachial nucleus, midbrain reticular formation, periaqueductal gray (PAG) and hypothalamic nuclei. Other fasciculi of the medial anterolateral pathway synapse with the brainstem reticular core by a series of short interneuronal projections. There is also a direct spinohypothalamic pathway.

The medial fasciculi of the spinothalamic pathway conduct pain from the gastrointestinal tract, periosteum, and peritoneum. There is some evidence that deep visceral pain may also be carried in a deep pathway in the posterior columns. It has been proposed that this primarily medial pathway (slowly conducting with widespread diffuse core and limbic projections) is for the affective components of pain. The direct fast conducting spinothalamic pathway projects to the ventroposterolateral (VPL) and ventroposteromedial (VPM) of the thalamic ventrobasilar complex (VB). This system projects primarily to SI of the primary sensory cortex. This pathway mediates the discriminate aspects of pain (quality, localization, and intensity): it is generally referred to as the lateral pathway.

Visceral pain from the esophagus, stomach, small bowel and proximal colon project via the vagus nerve to the nucleus tractus solitaries (NTS).

The direct spinothalamic tract separates into two major divisions before synapsing in the thalamus (as noted above, it gives off collaterals to many nuclei in the brainstem as it ascends): the lateral division synapses in the VPL and some posterior nuclei, while the medial division synapses in the intralaminar complex and submedial nucleus. As noted above, the spinoreticulorhinal pathway synapse with the parafascicular and centrolateral thalamic nuclei. Thus they overlap medial spinothalamic projections. The laminar fiber projections also overlap with direct spinothalamic projections.

Projections from the dorsal horn are widespread and overlapping. The lateral system, the discriminative pain pathway, is primarily composed of dorsal horn projections to the VB complex (VPM and VPL) of the thalamus and consequently to the primary sensory cortex. The affectual pain circuits comprise components of the reticular formation, the parabrachial nucleus, the amygdala insular cortex, anterior cingulate gyrus, and SII. Both of these circuitries are commonly referred to as the pain matrix that encodes the discriminative and motivational components of the perception of pain.

The primary excitatory neurotransmitter in pain transmission neurons (PTNs) is glutamate. There is a contribution from aspartate and kainate. Na(V)1.7 sodium channels are pivotal for initiation of the action potential while a variety of potassium and HCN (hyperpolarization-activated cyclic nucleotide gated) channels return the membrane to its resting potential. HCN channels are activated with membrane hyperpolarization and conduct an inward excitatory current. Dorsal horn inhibitory interneurons utilize GABA-B and glycine, as their inhibitory neurotransmitters. The potassium chloride co-transporter is essential for inhibition in the DH. It functions under physiologic conditions to decrease intracellular chloride in pain transmission neurons. Thus if it is defective, afferents from inhibitory neurons that release GABA-B onto PTNs would depolarize (excite) PTNs as chloride would follow its electrochemical gradient (leave the cell) and the membrane potential would fall to threshold levels. The NMDA receptor (N-methyl-D-aspartate) is extremely important for plastic changes in the DH which occur in chronic pain states. These are a class of ionotropic glutamate receptors that are essential for the plasticity that occurs in chronic pain states. NMDARs have slow deactivation kinetics, are highly Ca^{2+} permeable, and require partial depolarization to relieve their external Mg^{2+} channel block. C-fibers coexpress substance P and calcitonin G-related peptide in addition to glutamate. Thus, a continual C-fiber input to NMDA receptors depolarizes these receptors due to the release of the neuromodulator SP, which depolarizes the receptor enough to release its Mg^{2+} channel block and allow sodium and calcium influx. Additionally, under conditions of a continuous C-fiber input

lateral synaptic NMDA receptors move to the synapse and acquire more AMPA channels. The increased calcium concentration in the PTN activates calcium calmodulin II which in turn activates mitogen-activated kinase (MAPK) and extracellular regulated kinase (ERK) 1/2 to effect gene expression through cyclic AMP response element (CREB transcription factor). The phosphorylation and dephosphorylation of intracellular enzymatic cascades determine PTN excitability. The induction of new protein synthesis by activation of CaMKII and ultimately the CREB transcription factor is a major cause of neuronal plasticity in chronic pain states.

Radicular trauma from disc and degenerative osteoarthritic conditions, as well as autoimmune disease, are major causes of chronic neuropathic pain. In the area of injury, the microenvironment that includes protons, bradykinin, leukocytes, serotonin, prostaglandin (i.e. an "inflammatory soup") induces peripheral nociceptive afferent terminal sensitization. C-fiber activation (from the inflammatory milieu) induces phosphorylation of ERK in small DRG neurons (PTN). C-fiber stimulation also induces phosphorylation in MAPKs and extracellular signal-regulated kinases (ERKs) in neurons with myelinated fibers. These intracellular enzymatic cascades lower the firing threshold of the C-fiber and A-delta fiber nociceptors. Prolonged nociceptive afferent input from C-fibers (primarily the mechanical insensitive ones) induces central sensitization in the DH and other components of the pain matrix. Central sensitization refers to the increased synaptic efficacy in PTNs (pain transmission neurons at all levels of the pain matrix) that follows intense peripheral noxious stimuli from tissue injury or nerve damage.

Central sensitization is manifested by:

1. Reduction in pain thresholds
2. Enlarged peripheral receptive fields of PTNs
3. Amplification of pain
4. Decreased pain inhibition
5. After sensations (PTN firing is not stimulus bound)

This physiological state is similar in many physiologic parameters to long-term potentiation (LTP) and depression (LTD) that are important for memory and learning.

In parallel with the molecular changes in pain transmission neurons is activation of segmental microglia. Chemokines released from activated neurons (fractalkine) as well as extracellular neuropeptides play pivotal roles in the physiology of PTNs and microglia which express several subtypes of P2XR (purine receptors) which contribute to pain signaling in the spinal cord under pathologic conditions such as neuropathic pain. Activated microglia secrete inflammatory cytokines which both induce and maintain neuropathic pain and contribute to central sensitization.

Nerve roots exit and enter the spinal cord through the neural foramina. These are bony canals of varying length depending on the spinal segment. The contents of the neural foramina (canals) are the spinal nerve roots, recurrent meningeal nerves, and radicular blood vessels. The anatomical boundaries are the pedicles inferiorly and superiorly, anteriorly

the intervertebral disc and vertebral body and posteriorly the facet joint. The superior and inferior facets are lined by synovium. The dorsal root ganglia (DRG) are in the foraminal canals.

The blood supply to a spinal nerve root derives from the corresponding radicular artery. At the root entry zone, blood vessels lie on the surface of rootlets and in inter-radicular spaces. Capillary density is high in the ventral root entry zone. In osteoarthritic degenerative conditions, facet joints are frequently remodeled by hypertrophic bone expansion. Tropism occurs whereby the facet rotates into the foraminal exit canals and the lateral recess. This process impinges on the exiting nerve root at its level. The facet joints are innervated by branches of the posterior primary ramus of the spinal nerve root. The clinical effect of degeneration of the annulus pulposus and the posterior longitudinal ligament are not well categorized. Both structures receive nociceptive innervations. Extruded disc material induces an inflammatory response around the nerve root eliciting the expression of IL-1, IL-6 and tumor necrosis factor- α which directly depolarize nociceptive C-fiber and A-delta afferents. Dorsal root ganglia have a less permeable blood-nerve barrier than the blood-brain barrier. This is important in the context of chemotherapy-induced radiculopathy and autoimmune processes such as Sjögren's syndrome or paraneoplastic processes. The cell bodies for PTNs may thus be directly affected in the course of these disorders.

Radicular pain is caused by depolarization of A-delta and C-fiber nociceptive afferents. A-delta primary nociceptive afferents (1–4 μ) cause lancinating well-localized pain in the expected dermatome. With root irritation, the lancinating pain is frequently followed by a deep aching pain that has a burning quality. This second pain is mediated by 1 μ unmyelinated slowly conducting C-fibers. Sympathetic discharge elicited by somatic sympathetic reflexes may amplify and drive this pain in chronic conditions. The usual radicular pain radiates within its specific dermatomes. However, it may be appreciated in only part of the anatomical confines of the dermatome. Thus, an L5 root injury may be felt just or predominately in the lateral thigh or great toe and not the lower back.

The pain is usually increased by mechanical maneuvers that increase intraspinal pressure or stretch the nerve root. The nervi nervorum that innervate the nerve sheath are sensitized so that a mechanical stimulus rather than a tissue destructive one will depolarize then (basis for the straight leg raising test and other provocative stretch maneuvers).

Dorsal Root Entry Zone

There is segregation of spinal root afferents at the dorsal root entry zone (DREZ). Medial dorsal root fibers carry proprioception, vibration, and light touch. Lateral dorsal root fibers (closest to the area dorsolaterally where discs extrude) carry lancinating pain (A-delta fiber mediated), cold (A-delta fiber), temperature and burning pain (C-fiber). Lesions that affect

the dorsal root entry zone are, in general, painful. Lesions peripheral to the DRG in the neuronal exit canals cause numbness. Lesions of the medial branch of the posterior primary division of the dorsal root are associated with numbness and paresthesias (1½ inches laterally from the spinous process). Meningeal afferents from the dorsal root innervate the dura at each spinal segmental level. These are the recurrent branches of Spurling. The L5 branch is particularly relevant as its referred pain is to the top of the thigh when it is stimulated (often mistaken for L1, L2, L3 root pain).

Ventral Root Lesions

Ventral root lesions cause segmental weakness. If these axons are injured, there will be associated atrophy and fasciculation along with weakness of the innervated muscles. Early with compressive or irritative lesions, reflexes may be enhanced. This has been posited to result from the differential susceptibility of inhibitory afferents in the ventral root. In the lower extremity (if reflexes are increased), the examiner must always be aware of compressive or intrinsic spinal cord lesions that may injure the corticospinal tract and disinhibit neurons below the lesion level.

The Structural Bone and Ligamentous Anatomy of the Spine

The vertebral bodies are connected by intervening discs and partially supported by the anterior and posterior longitudinal ligaments. The posterior elements from the vertebral bodies are composed of the pedicles, laminae, and dorsal spine. The transverse dorsal spinous processes are the origin and insertions of the paraspinal musculature. The ligamentum flavum is on the ventral surface of the laminae, and the posterior longitudinal ligament runs dorsally on the vertebral body. The dentate ligament connects the spinal cord to the dura. The interspinous ligaments connect the spinous processes and facet joints. The facet and sacroiliac joints have a synovial lining. Spine stability depends on the integrity of its skeletal and ligamentous components as well as active muscular support from the paraspinal musculature. The L5 vertebral body is the load segment for the lower spine (subject to the weight of the upper body). The skeletal and ligamentous structures are most vulnerable at movement segments (C5–C6 cervically and L5–S1 in the lumbar spine). If a segment is fused, the next uppermost spinal segment becomes the movement segment. Stress on bone activates osteoblasts and molecular mechanisms that remodel bone. This is evidenced by endplate increased bone density (Modic's sclerosis). Transforming growth factor beta-1, osteoblast and osteoclast activation, as well as complicated bone metabolism, are all important in this process. Voluntary and reflex activity of the paraspinal, sacrospinalis, abdominal, gluteus maximus and hamstring musculature not only support the spinal column but adjust their activity following pathologic processes. These adjustments change gait and posture, which in turn modify load and stress points in the vertebral column.

After the exit of the lumbar spinal roots from the cord, they course downward in the subarachnoid space prior to entering the exit foramina. The area on the inner surface of the pedicle (area prior to their entrance of the foramina) is known as the lateral recess. This area may be compromised by congenitally shortened pedicles (common in achondroplasias and other congenital bony dysostosis) or extruded disc fragments.

Far lateral disc protrusions may just entrap the exiting nerve root affecting one spinal segment. A more medial extrusion may compress the exiting nerve root and the next lower root as it descends prior to its exit. Degenerative changes in the nucleus pulposus (alterations of its glycosaminoglycans) contribute to its water loss and shrinkage with age. This distortion may compromise the exit of nerve roots contralaterally as well as ipsilaterally.

General Features of Radicular Pain

All parts of the body are innervated by a nerve root and a peripheral nerve and have a specific pattern of referred pain. Thus, sensory complaints may be overlapping such that a particular pain distribution may be composed of a root, nerve, or plexus distribution as well as its referred pattern. The sensory patterns may be difficult to discern in the face and extremities. Further complicating sensory patterns are the radiations of sclerotomes and those of the posterior rami of the lower back. Each body part receives some overlapping root rostral and caudal innervations, and there is further overlap in the dorsal horn as noted above from Lissauer's tract.

Face

The V1–V3 divisions of the facial nerve are well demarcated. The C2–C3 roots comprise the pre-auricular nerve that innervates the side of the face overlapping V2 and V3. C2 innervates alone innervates an area just anterior to the ear. C2–C3 comprises the lesser occipital nerve which innervates the back of the head. C3–C4 comprises the post-auricular nerve that innervates the ear and portions of the parietal skull. C3 primarily innervates the neck and C4 the trapezius ridge. C5 innervates the top of the shoulder. C6 innervates the thumb and index finger, C7 primarily the third and 4th finger and C8 the little finger. T1 innervates the lower forearm and T2 the inner humerus. T4 innervates the nipples, T10 the umbilicus and L1 the groin. L2 and L3 innervate the anterior thigh while L5 innervates it laterally. The cap of the knee is L3, the inner knee L4 and the outside of the knee is innervated by L5. A strip of the inner lower leg is innervated by L4. The outside of the lower leg and foot is innervated by S1. L5 innervates the great toe and top of the foot. The bottom of the foot medially is L5 and laterally it is S1. The medial posterior thigh is L3 and more laterally S3. The anus is usually presented as being innervated by S5 roots. Saddle areas are primarily S2–S4. A sclerotome is derived from an enlarged somite. During

development, the somite develops into a variety of different structures. These include disks, cartilage, joint capsules and ligaments which refer pain to the body surface in specific patterns. In general, when a portion of a sclerotome is irritated by a mechanical or chemical stimulus (rupture of a disc, facet and ligament irritation from disc material) pain may be experienced as originating from the dermatome innervated by a nerve although it originated from the facet. Sclerotogenous pain is often reported as a dull ache and is diffuse.

Referred Pain

A primary mechanism of referred pain is somatic and visceral convergence. The skin surface and a specific internal organ are innervated by the same DRG. In the instance of referred pain, the spine may be projected to the visceral or other structure in the territory innervated by lumbar and upper sacral roots. Pelvic and abdominal viscera may refer pain to the spine. Sclerotomal pain radiations from the upper part of the lumbar spine may be referred to the medial flank, groin, hip and anterior thigh. This occurs most often (my experience) from discogenic disease at L5–S1. The literature supports irritation of the superior cluneal nerves (that are derived from the posterior divisions of the first three spinal nerves) which innervate the upper buttocks as a source of referred pain. It has been proposed that pain radiations into the lower buttocks and posterior thigh originate from lower lumbar and upper sacral roots. As a general rule referred pain: 1. has the same intensity as local pain; 2. stretch maneuvers that increase local pain similarly exacerbate referred pain.

Pain referred to the spine from visceral processes may be posturally related but are not influenced by back movement. A common functional relationship of root irritation and visceral activity is micturition and defecation initiated by L5–S1 root irritation.

Local Pain

Local pain in the spine is caused by pathological processes of the facet joint, ligaments, periosteum, capsule of apophyseal joints and the annulus fibrosis. If there is pain from annulus fibrosis stretch or tear is debated. It is innervated by nociceptive fibers and disc contents initiate an immune response that may induce the release of inflammatory cytokine (IL-1, IL-6, and TNF-alpha among others) that theoretically could irritate nociceptive afferents.

Pain from these spinal structures is:

1. Steady and aching
2. Not well circumscribed and may be intermittent and sharp
3. Is appreciated at the site of pathology
4. May be referred in a sclerotomal distribution

Radicular Pain

Radicular pain, in general, is:

1. Intense

2. Lancinating or sharp (A-delta fiber)
3. Confined to a specific dermatome
4. Usually exacerbated by stretching, irritation or compression
5. May be superimposed on the dull ache of referred pain
6. Often radiates from a paracentral spinal area to a component of its root territory
7. Often is increased by valsalva maneuvers

Examination reveals:

1. Paresthesia or sensory loss in components of the involved dermatome
 2. Mechanically evoked pain (pressure) in innervated muscles
 3. Weakness, atrophy, and fasciculation of involved muscles
- In general, referred pain from lumbar bony, articular or ligamentous structures does not project below the knee. It is not associated with clear neurologic deficits.

In general, involvement of upper lumbar roots suggests a medical problem such as metastasis, retroperitoneal bleeding, autoimmune disease, and infection. Lower L4–L5–S1 involvement suggests spondylosis, disc disease, spinal stenosis, spondylolisthesis, facet hypertrophy, and spondylolysis. The history, age, relieving and exacerbation factors, as well as the examination, should determine etiology in the vast majority of patients.

Diagnostic Points of the Low Back Examination

1. Inspection determines:
 - a. Scoliosis, kyphosis and a pelvic tilt (Trendelenburg sign) and gibbus:
 - i. An S-shaped (scoliotic) curve is compensatory
 - ii. C-shaped scoliotic curve suggests asymmetric loss of paraspinal musculature from a spinal tumor
 - iii. A gibbus (severe kyphotic angulation) suggests a fracture
 - b. Atrophy of the gluteus maximus with a dropped gluteal fold (primarily an S1 root). Bilateral gluteal atrophy and weakness suggest spondylolisthesis in young patients
 - c. L5–S1 radiculopathy causes a flexed leg (relieves pressure on the sciatic nerve). If there is posterolateral disc extrusion (impingement on the lateral dorsal root entry zone), the patient may be unable to lie down and straighten the spine
 - d. Severe paraspinal muscle spasm suggests local disease and possible posterior ramus syndrome
2. Gait
 - a. As a general rule patients with radiculopathy do not limp. This is much more common in patients with lower extremity joint degeneration
 - b. An antalgic gait suggests that any weight bearing increases pain
 - c. A forward flexed posture with minimal or no gastrocnemius atrophy suggests spinal stenosis. The patient usually has a shortened swing phase of the gait

- d. Patients that are more comfortable standing than sitting suggest L5–S1 disc disease or spondylolisthesis

3. Positional Testing:

- a. Decreased forward flexion when standing suggests mobility at the decreased lumbosacral segment and includes:
 - i. Disc disease ($L5-S1 > L4-L5$)
 - ii. Spinal stenosis ($L4-L5 > L5-S1$)
 - iii. Spondylolisthesis and spondylolysis ($L4-L5$ or $L5-S1$)
 - iv. Posterior ligament, articular facet or rarely sacrospinalis
 - v. Extension of the spine following flexion is difficult with lumbar disc disease
 - vi. Lateral bending:
 1. Ligament pathology or muscle strain:
 - a. Painful bending to the opposite side
 - b. Disc disease:
 - i. Bending to the opposite side is painful
 - vii. Straight leg raising:
 1. Positive with disc disease
 2. In spinal stenosis, there is often restriction but the maneuver is much less painful
 3. Very positive with all forms of spondylolisthesis
 - viii. Extension of the leg (patient lying on the stomach) is painful with:
 1. Fracture of the vertebral body or posterior elements
 2. Inflammatory processes
 3. Most helpful with upper lumbar root pathology
 - ix. Lateral decubitus position:
 1. Abduction against resistance of the upside leg causes sacroiliac joint pain
 2. Internal and external rotation induces intrinsic hip joint pain (easier to elicit with patient supine)
4. Palpation:
 - a. Percussion of the spine (to detect mechanical hypersensitivity)
 - i. Positive for any disc infection and metastatic disease of the vertebrae
 - ii. Less positive for inflammatory processes or infection
 - b. Tenderness over the interspinous ligament at L5–S1 suggests disc disease
 - i. Sacroiliac joint tenderness may be an early sign of ankylosing spondylitis
 - c. Pressure in the sciatic notch and posterior popliteal fossa suggests sensitization of the sciatic and posterior tibial nerve respectively. Tenderness of the gastrocnemius muscle often accompanies and is strong evidence of S1 root disease
 - d. Costovertebral angle tenderness occurs with genitourinary and adrenal disease as well as with fractures of the transverse processes of L1 and L2

- e. Examination of strength, atrophy, sensory loss and reflexes (including Babinski sign) completes the lower back examination

Almost all older patients have some combination of degenerative osteoarthritic changes in addition to nerve root and sclerotomal pain radiations.

Differential Diagnosis of Lumbar Radicular Pain

Congenital Lesions

1. Most congenital defects themselves do not cause compression of roots. However, bone metabolism is a dynamic molecularly driven process such that changes in loading forces on vertebrae or inflammatory conditions cause remodeling of bone by activation of osteoblasts, osteoclasts, the immune system and tissue transforming factor beta 1

Congenital Defects of the Lumbar Spine

1. Sacralization of L5
 - a. A fusion of the fifth lumbar vertebral body to the sacrum or separation of the first sacral segment (6 rather than 5 lumbar segments). There are no clinical consequences (other than rare localization difficulties on MRI for radiculopathies)
2. Spina bifida
 - a. Lack of fusion of the laminae of one or several lumbar or sacral vertebrae
 - i. Associated rarely with a subcutaneous mass, cutaneous hyperpigmentation or hypertrichosis over the defect
 - ii. Rare association with facet joint or pedicle anomalies
3. Asymmetric facet joints, narrow lateral recesses, and short pedicles may cause radicular involvement
4. Spondylolysis:
 - a. A congenital bony defect in the pars interarticularis (the junction is the pedicle and the lamina; often bound by cartilage)
 - b. Predisposition to fracture or disjunction with slight trauma such as stepping off a curb or jumping
 - c. Young patients may have aching in lumbar areas exacerbated by extension
 - d. Bilateral spondylolysis predisposes to spondylolisthesis. In this instance, the vertebral body, pedicles and superior facets slip forward. The degree of slippage is usually graded by the percentage of displacement relative to the lower vertebra
- e. Spondylolisthesis:
 - i. A common and severe problem that requires surgical intervention often with instrumentation when symptomatic
 - ii. Slippage in non-severe traumatic cases is L4 over L5 or L5 anteriorly to S1

- iii. Flexion and extension of the back are painful as in bending
- iv. Radicular pain is prominent primarily in L3–4 and root distributions
- v. Weakness of the gluteus maximus, anterior tibialis, and/or extensor hallucis longus is most prominent
- vi. Rare bladder involvement
- vii. Atrophy of the gluteus maximus is often prominent
- viii. Decreased ankle reflexes
- ix. Degenerative osteoarthritis (primarily spondylosis is causative in older patients)

Lumbosacral Trauma

1. Acute sprain and strain:
 - a. When there is severe pain and accompanying paraspinal muscle spasm, the segmental nerve roots have been stretched or otherwise injured
 - b. Trauma does not cause degenerative disc or bony structural disease but may exacerbate pain by compression of nerve roots against osteophytes in exit foraminal canals, increasing the bulge of an annulus fibrosus or mechanically stimulating the nervi nervorum of the nerve sheath and root sleeves or A-delta and C-fibers within the nerve root itself
 - c. Spasm of involved musculature localized low back pain and unusual splinting postures usually abate in less than a week:
 - i. Sacroiliac joint and ligamentous injury:
 1. Pain may radiate to the buttock and thigh; there is pain directly over the sacroiliac joint (an example of sclerotomal pain; injury to a component of an embryologic somite may radiate to dermatomes derived from the involved somite)
 2. Abduction of the thigh against resistance may cause pain radiation into the groin and symphysis pubis (sclerotomal radiation)

Recurrent Low Back Pain from Bony and Ligamentous Structures

1. Recurrent aching pain in lumbar areas. Some radiation into the buttocks and posterior thigh (never below the knee)
2. No weakness, sensory loss or reflex changes
3. Complaint of stiffness and aggravated by specific movements
4. CT and MRI frequently demonstrate mild disc desiccations and degenerative bony changes, but may be normal

Vertebral Fractures

1. Fractures of lumbar vertebra:
 - a. Result of flexion injuries
 - b. If patient falls and lands on his feet calcaneal and hip fractures may be associated

2. Specific fractures from severe injury (MVA, falls, skiing):
 - a. "Burst" fracture of a vertebral body (one or several)
 - b. Pedicle, lamina or spinous process (most often asymmetrical)
 - c. Loss of height of a vertebral body (wedge or compression; anterior border is most often involved with osteoporosis)

Differential Diagnosis of Pathologic Fractures

1. May occur spontaneously or with minimum trauma
2. Osteoporosis (women; thoracic anterior compression fracture)
3. Hyperparathyroidism (kidney disease)
4. Metastasis:
 - a. Pedicle involvement
 - b. Disc body
5. Corticosteroids
6. Myeloma (often multiple vertebrae)
7. Hemangioma (often with hemorrhage)
8. Various bone cysts
9. Prolonged heparin use (fish mouth endplate)

Clinical Features of Pathologic Fractures (Lumbar)

1. Immediate localized pain
 - a. Rare delayed onset of pain
2. Lower paraspinal muscle spasm:
 - a. Limitation of lumbar spine movement
 - b. Mechanical sensitivity

Clinical Features of a Transverse Process Fracture

1. Setting is almost always a high impact rotary injury of the spine
2. Associated paraspinal muscle injury with hematoma
 - a. If bleeding is retroperitoneal (or extends to this space from sacrospinalis or paraspinal muscle hemorrhage):
 - i. Severe pain, a local hematoma at the injury site
 - ii. A quiet patient whose position of comfort may be lying on a side with flexed legs
3. Groin pain
4. Proximal > distal leg weakness
5. Loss of the knee jerk on the affected side
6. After seven to ten days – Grey Turner's sign of blood breakdown products in the skin and subcutaneous tissue of the affected flank

Disc Disease (Lumbar)

1. L5–S1 herniations is the most common level of herniation followed by L4–L5 > L3–L4 > L1–L2 (rare)
2. L5–S1 is the primary motion segment of the lumbosacral spine while L5 is the primary load segment. If there is fu-

sion of L5–S1, then L4–L5 becomes the primary motion segment

3. Primary causes of disc herniation are not clear:
 - a. Degeneration of the annulus and the nucleus pulposus, as well as the posterior longitudinal ligament, has been posited. Rarely acute flexion injuries seem a likely cause of annulus pulposus tear
4. Nucleus pulposus fragments generally extend through degenerated areas of the annulus most often dorsolaterally and asymmetrically. Central and medial protrusions may involve descending nerve roots prior to entering the exit foramina. A far lateral protrusion compresses a single root at that level. Thus, a lateral protrusion at the interspace between L4–L5 will involve the L5 root. The L4 is spared as it exits above the protrusion. A medial protrusion at L4–L5 may involve the L5 root as well as sacral roots S1–S2 prior to their exit
5. The affected interspace may be mechanically sensitive to pressure. There may be a slight decrease of sensation 1½ inch laterally from the corresponding spinous process. The dorsal rami syndrome (discussed below) may be prominent
6. Mechanical stretch maneuvers are positive and exacerbated by Lasegue's maneuvers. This involves extension of the ankle with the leg extended
7. Tinel's signs are positive over the nerve that carries the affected roots. Tinel's sign (mechanical pressure on the nerve elicits pain) is positive in the sciatic notch and posterior popliteal fossa with L5–S1 root involvement
8. There is muscle tenderness of those muscles that are innervated by the sensitized roots (usually elicited by moderate squeezing). The root compression by the extruded disc material sensitizes the deep polymodal C-fiber and A-delta fiber afferent nociceptors such that mechanical pressure rather than tissue-destructive stimuli will depolarize them
9. Pain radiations are consistent but most often consist of a combination of dermatome and sclerotome patterns. The latter (pain from structures of the embryonic somite-vertebrae, facet joints and their capsules, periosteum, ligaments) often activates structures not often thought of as emanating from the affected roots
10. Bilateral symptoms and sphincter (overwhelmingly bladder) dysfunction most often occur with large midline disc extrusion that compresses the cauda equina

L2–L3 Disc Space

1. L3 root affected
2. Pain:
 - a. Anterior thigh
 - b. Top of the knee
3. Weakness of thigh adductors, quadriceps and iliopsoas muscles
4. Decreased knee jerk

L3–L4 Disc Space

1. L4 root affected
2. Pain:
 - a. Anterolateral thigh
 - b. Medial leg below the knee
3. Weakness of the anterior tibialis
4. Knee jerk decreased

L4–L5 Disc Space

1. L5 root affected
2. Pain
 - a. Posterolateral gluteal area, lateral thigh, lateral leg below the knee, dorsal foot to the lateral malleolus, great toe and 2nd and 3rd toes

Additional Radiations of L5 (Sclerotomal)

1. Hip
2. Top of the thigh:
 - a. Somatic referred pain possibly from the innervations of the annulus fibrosis (controversial mechanism but the radiation is helpful)
3. Dural innervations at L5; the innervations of the recurrent nerve of Spurling at this level
4. Scrotum
5. Rarely the anterior lower abdominal wall
6. Weakness of the extensor hallucis longus, extensor digitorum brevis, and anterior tibialis that cause partial foot drop. There is also weakness of invertors of the foot which does not occur in the foot drop of peroneal palsy
7. Ankle jerk is unaffected
8. Straight leg raising test and its variants are positive. Irritation of nociceptive afferents in the affected root or its sleeve synapse with Rexed layer VII interneurons that then depolarize Rexed layer IX flexor motor neurons that elicit hamstring muscle contraction which halts the further extension of the leg. This comprises a nocifensive reflex
9. Chronic disc disease causes atrophy of the anterior tibialis and the extensor digitorum brevis
10. Tenderness with compression over the fourth lumbar lateral process and between the fourth and fifth spinous space, the ligaments and laterally in the sciatic notch

L5–S1 Disc Space

1. The S1 root is affected
2. Classic pain radiations:
 - a. Mid gluteus maximus pain
 - b. Tenderness in the sciatic notch, posterior thigh, posterolateral leg, lateral foot, heel and lateral toes
 - c. Especially helpful is the radiation to the little toe
 - d. Low calf dull pain to the heel
3. Unusual pain radiations of S1 (components of the sclerotomal innervations):
 - a. Groin

- b. Tip of the penis
- c. Ipsilateral vagina
- d. Anus (controversial as there is evidence that this is an S5 root territory)
4. Weakness of plantar flexors, hamstring muscles, and the toes; abductor digiti (Vth metatarsal)
5. Depressed or absent ankle jerk
6. Positive straight leg raising test; tenderness of the sciatic notch, posterior popliteal fossa, and pain elicited by squeezing the gastrocnemius muscle; tenderness over the L5–S1 interspace; increased pain with walking on the heels but more difficulty walking on the toes due to plantar flexor muscle weakness

Visceral Association with L4, L5 and S1 Root Disease

1. Increased frequency of micturition
2. Slight decrease of bladder emptying (30cc residual urine) with S1 disease
3. Increased pain during menstruation (sciatic radiations). Convergent innervations from the uterus, fallopian tubes and ovary to L5, S1 DRG (somatic-visceral convergence) cause pain in these distributions

Exacerbating Factors for L4–S1 Radicular Pain

1. Flexion and extension posture; sitting; driving a car
2. Valsalva maneuvers
3. Sleep (veins that overlie the root compress the sensitized root; patients awaken with back pain at 4–5 AM. Inability to lie down suggests intraparenchymal spinal cord tumor (patients sleep upright in a chair). Awakening slightly earlier at night (3–4 AM) suggests a subarachnoid cyst that compresses the spinal cord)
4. The leg feels as if it will suddenly “give way” and will not support the patient’s body weight

Relieving Factors for L5–S1 Disc Disease

1. Rest; supine position with flexed knees (pillow behind the knees)
2. Heat over the affected interspace
3. Some patients improve with exercise (heat may decrease conduction in sensitized nerve roots)

Extreme Lateral Disc Protrusion

1. Unrelenting radicular pain without concomitant back pain (proximal portion of the intervertebral exit canal)
2. Pain is increased with extension and torsion toward the side of the extrusion
3. Intradural disc rupture with a free fragment may not cause sciatic pain as it may not impinge upon the cauda equina roots

Lower Sacral Radiculopathy

1. Usually, S2–S5 roots are involved concomitantly often from a large central disc herniation

2. Pain and sensory loss may be prominent in the perineal area
 - a. Usually asymmetrically
 - b. "Sudden anesthesia"
 - c. Prominent pain and numbness may also occur over the gluteus maximus, posterior thigh and if S1 is involved the calf and heel
3. Urinary incontinence and retention; rarely fecal incontinence
4. Loss of ankle jerks
5. Varying degrees of paraparesis
6. Severe back pain
7. Reduced or absent anal sphincter tone; decreased bulbocavernosus and anal wink reflexes with S1–S5 lesions

High Lumbar Root Disease

In general, the L1–L3 roots are not affected by disc disease as they are not motion segments.

They are involved by:

1. Diabetic plexopathy
2. Ilioinguinal
3. Genitofemoral nerve injury from:
 - a. Surgical procedures (hernia, catheterization of the femoral artery) and intra-abdominal surgical procedures
 - b. Lymphoma
 - c. Retroperitoneal hematoma
 - d. Autoimmune processes
4. Rarely the roots are involved in high impact injuries (MVA accidents, falls, and skiing injuries)

L1 root:

1. Pain and paresthesias of the inguinal area
2. Slight iliopsoas weakness

L2 root:

1. Pain referred to the lateral hip and anterolateral thigh pain
2. Weakness of the iliopsoas muscle
3. Differential diagnosis includes high lumbar plexopathy, meralgia paresthetica, or femoral neuropathy
4. In general, femoral neuropathy is associated with severe quadriceps weakness and a decreased or absent knee jerk

L3 radiculopathy:

1. Pain is in the anterior thigh to the kneecap
2. Iliopsoas and quadriceps weakness
3. A plexus lesion usually involves the hip adductor muscles and the obturator nerve
4. The knee jerk is depressed
5. The sensory loss overlaps the projected pain from the recurrent nerve of Spurling at L5 (the dural radiation from this level)
6. Diabetic amyotrophy frequently involves this root as a component of its plexopathy

L5 weakness:

1. Causes extensor hallucis longus and extensor digitorum brevis weakness along with mild weakness of the anterior tibialis and slight foot drop

2. Inversion of the foot is involved
3. There is no inversion weakness with a perineal neuropathy
4. Weakness of the gluteus minimus and medius localizes a lesion proximal to the formation of the sciatic nerve
5. L5 involvement could also be a component of a lumbosacral plexopathy

S1 weakness:

1. Primarily causes weakness of the gastrocnemius and soleus muscles > hamstring and glutes
2. Gluteus maximus weakness localizes a lesion prior to the formation of the sciatic nerve
3. Differential diagnosis includes:
 - a. Lumbosacral plexopathy and medical causes of radiculopathy:
 - i. Metastasis
 - ii. Autoimmune disorders
 - iii. Metabolic disorders (diabetes mellitus)
 - iv. Infectious diseases (HIV, CMV, and brucellosis)

Posterior Rami Syndrome

1. Also known as Maigne's syndrome or the dorsal ramus syndrome
2. Is due to activation or irritation of the primary division of a posterior ramus of a spinal nerve
3. Referred pain occurs in a tri-branched pattern:
 - a. Innervation of the groin or pubic region
 - b. Innervation of the lower back and upper gluteal region
 - c. Anterolateral thigh or trochanteric area
 - d. The affected posterior ramus ends cutaneously and may cause trophic skin changes:
 - i. Thickening or nodularity of the skin
 - ii. Hair loss
 - iii. Neurogenic edema
 - e. These are sclerotomal radiations and thus can originate from several levels. Patients should have facet and spinous processes palpated over a wide area

Differential Diagnosis of Low Back Pain

1. Spinal canal stenosis
 - a. Bone, joint and ligamentous changes that narrow the spinal canal and neural foramina:
 - i. The spinal roots are compressed by:
 1. The vertebral body anteriorly
 2. The facet joints laterally
 3. The ligamentum flavum posteriorly
2. Coccydynia:
 - a. The coccyx is composed of 3 to 5 vertebrae some of which may be fused
 - b. The coccyx attaches to the sacrum from two dorsal grooves being either a symphysis or as a true synovial joint
 - i. It also has attachments to the gluteus maximus muscle, the coccygeal muscle, and the anococcygeal ligament

- c. The mechanisms that cause coccydynia are:
 - i. Sudden impact due to a fall
 - ii. Childbirth pressure
 - iii. Partial dislocation of the sacrococcygeal synchondrosis
- d. Clinical manifestations
 - i. Pain at the end of the spine exacerbated by mechanical stimuli
3. Spondylolisthesis:
 - a. A prominent cause of L4–S1 radiculopathy in young patients
 - i. A pelvic tilt, atrophy of gluteal musculature and pain with extension and flexion
 - b. Older patients have degenerative spondylolisthesis, often forward slippage of L4 anteriorly over the L5 vertebra and L5 over S1 (spondyloptosis)
4. Vascular claudication:
 - a. Atherosclerosis of large and medium-sized blood vessels
 - i. Exercise-induced (intermittent) or ischemic rest pain
 - b. Thigh and calf muscles are predominantly involved
 - c. Leriche syndrome:
 - i. Distal aorta and iliac arteries are involved
 - ii. Hip and buttock claudication with walking
 - iii. Impotence
 - d. Burning and squeezing quality to the pain
 - e. Ischemic rest pain:
 - i. Primarily in the foot and toe
 - ii. Buerger's disease affects the medial foot
 - iii. Worse at night
 - iv. Relieved by dependency
 - v. Severe peripheral vascular disease
5. Facet syndrome:
 - a. Degenerative changes of the facet joint with tropism
 - i. The inferior or superior facet rotates into and compresses the nerve root in the canal
 - b. Not relieved by position
 - c. Back and radicular pain that is most often unilateral
6. Adhesive arachnoiditis:
 - a. The arachnoid is thickened over the cauda equina and its nerve roots
 - b. Clumping and adhesion of nerve roots
 - c. Burning pain and paresthesias predominate over motor weakness in the legs
 - d. Rare at present due to new water soluble myelography agents
7. Ankylosing Spondylitis:
 - a. HLA-B27 positive
 - b. Pain in the low back with radiation to the thighs
 - c. Limitation of spine movement is progressive and severe
 - d. Severe morning stiffness
 - e. Progressive flexion of the hips and flexion spine deformity
 - f. Severe late stages may cause cauda equina syndrome
 - g. Failure of chest expansion
 - h. Involvement of the hips may exacerbate gait difficulties and back pain
8. Metastatic disease:
 - a. Pain is often constant, dull, unrelieved by rest
 - b. Mechanically sensitive
 - c. Worse at night
 - d. Radicular pain with lateral extension or pedicle involvement
 - e. Osteoid osteoma may also involve the pedicle
9. Gynecologic processes with referred pain to the back
 - a. Uterosacral ligaments:
 - i. Pathologies include endometriosis or metastasis from uterine or cervical cancer
 - ii. Sacral radiations
 - iii. Endometrial tissue may deposit on lumbosacral roots that cause pain with menstruation
 - iv. Fibroid tumors may cause traction on uterosacral ligaments
10. Metastatic infiltration of pelvic nerve plexuses
 - a. Radiates to low back usually diffusely but may be in a dermatomal distribution
11. Iliopsoas region tumors:
 - a. Unilateral lumbar spine dull ache
 - b. Radiates to the groin, labia, and testicle
 - c. Involvement is frequently of the upper lumbar roots
12. Aneurysm of the abdominal aorta:
 - a. Pain at the segmental level
 - b. T10–L1 vertebral involvement
 - c. Erosion of the segmental vertebrae
13. Retroperitoneal bleed:
 - a. Severe back pain
 - b. Usual lumbar root involvement at times with a dermatomal radiation
 - c. A quiet patient lying in bed with flexed legs
14. Colon neoplasm:
 - a. Pain in the lower abdomen and mid lumbar areas
 - b. Belt-like radiation
 - c. Transverse colon or descending colon:
 - i. Central or left-sided abdominal pain
 - ii. Refers to second or third lumbar vertebrae
15. Inflammatory Processes Affecting the Cauda Equina
 - a. May produce back pain and bilateral L5–S1 pain radiations:
 - i. CMV in the HIV-infected patients
 - ii. Lyme's disease
 - iii. Herpetic infections
 - iv. Carcinomatosis of the meninges
 - v. Guillain-Barré syndrome
 - vi. Lumbosacral plexitis
16. Stenosis of the Lateral Recess:
 - a. A congenital cause of radiculopathy
 - b. Acquired from osteophytes

- c. Clear dermatomal pattern of sensory loss and weakness
- 17. Synovial cysts of the facet joint
 - a. Usually in association with severe degenerative spine and disc disease. Occurs in the proximal portions of the foraminal canal
 - b. Effects the exiting nerve root
- 18. Tarlov cysts
 - a. Dilatation of the perineural sheath; most often asymptomatic
 - b. Usually, sacral roots are involved
- 19. Piriformis syndrome
 - a. Peroneal trunk of the sciatic nerve; local and sciatic pain
 - b. Pain induced by flexion, adduction and internal rotation of the hip and compression
 - c. Etiologies include subarachnoid, subdural, epidural bleeding
 - d. Trauma, coagulopathy (usually warfarin), various arterial venous malformations and mechanical compression by sitting are the primary etiologies
- 20. Visceral Referred Pain Radiations to the Spine
 - a. Posterior gastric wall ulcer:
 - i. Pain radiates to the central thoracic spine
 - b. Pancreatic pain:
 - i. Straight through to the back; to the right of the spine if the head is involved and left of the spine if the body and tail are the source of pathology
- 21. Retroperitoneal neoplasms:
 - a. Thoracic pain or lumbar pain
 - b. Schwannoma
 - c. Radiates to lower abdomen, groin, anterior thigh or flank
 - d. Lymphoma, renal cell, sarcoma are characteristic neoplasm
- 22. Osteomyelitis of Vertebrae:
 - a. Involvement of the vertebral body and the disc. Cancer does not breach the disc space
 - b. Paravertebral mass
 - c. Tuberculosis of the spine is common in developing countries with areas of spinal involvement differing by ethnicity. Pott's disease and drainage sites may be prominent
 - i. Back pain without MRI evidence occurs with SBE
- 23. Epidural Abscess:
 - a. Most often caused by staphylococcal aureus infection
 - b. Hematogenous spread or surgical procedures are etiologic
 - c. Localized severe spine pain with leukocytosis and low-grade fever; may have a radicular component
 - d. May quickly affect the spinal cord with paralysis, sensory loss and sphincter dysfunction
- 24. Intraspinal Hemorrhage
 - a. Sudden onset of severe midline back pain with rapidly evolving signs of spinal cord

Cervical Disc Disease

1. General considerations:
 - a. A bulging disc extends beyond the margin of the endplate of the vertebral body, but the annulus fibrosis is intact
 - b. A disc extrusion is an extension of the nucleus pulposus through the annulus; usually, it remains anterior to the posterior longitudinal ligament (rarely it extrudes through the posterior longitudinal ligament)
2. Cervical spine roots exit horizontally from the spinal cord to the neural exit foraminal and entrap the root corresponding to the vertebral body directly below it
3. The ventral and dorsal roots join just distal to the DRG (which is in the vertebral foraminal exit canal) and form a spinal nerve
 - a. The dorsal ramus supplies the paraspinal muscles (its origin is just distal to the DRG) as well as the cutaneous innervations of 1½ to 2 inches lateral to the spinous process
4. Posterolateral disc herniation compresses the root that will exit one level below
5. Disc disease occurs at motion segments (C6–C7 > C5–C6)

Inspection and Palpation of Cervical Disc Disease

1. Limitation of neck movement due to pain is common with disc disease. Spurling's maneuver (extending and rotating the neck to the side of the lesion and then gently pressing the shoulder down) may irritate the involved root. Neck extension induces posterior disc bulging and lateral flexion and rotation narrows the ipsilateral neural foramina. A position of comfort for a patient with an acute cervical disc is to place the arm over the head, which decompresses the nerve root at its exit foramina. All patients with cervical spondylosis have limitation of neck movement to all planes. Extension may be most limited. Spondylolisthesis, rotary subluxation and jumped facets have specific clinical features. As spondylosis progresses, there are clear degenerative changes at segments C5–C7 which are similar to those that occur in the lumbar spine. These, in general, are most severe at C5–C6 and C6–C7
2. The neck is forward flexed with cervical spondylosis. Almost always, this is associated with some atrophy of the deltoid caps and spasm of the trapezius ridge
3. The head is splinted and often tilted to the side of an extruded disc
4. Spondylolisthesis patients are also splinted, and the neck is usually forward flexed
5. Subluxation at C2–C3 or C3–C4 is most often seen with severe rheumatoid arthritis. The intrinsic muscles of the hand are often concomitantly atrophic. There is ulnar deviation of the hand
6. Dystonic postures from movement disorders (cervical dystonia) have hypertrophy of the sternocleidomastoid muscles and may affect the ulnar nerve with pain and sensory

- loss of the lateral half of the fourth finger and the entire fifth finger. The ulnar nerve innervates a small ventral area (triangular) above the wrist
7. The upper trunk of the brachial plexus radiates pain clearly across the trapezius ridge and straight down the medial scapular border
 8. The lateral cord of the brachial plexus radiates pain to the thumb, index, and the radial part of the third finger. The medial cord encompasses the ulnar side of the third finger and the fourth and fifth finger as well as the medial forearm
 - a. Bilateral hand (rather than finger numbness) is common; occasionally the sensory loss is in the legs and feet (due to lamination of the dorsal columns and spinothalamic tract)
 - b. There may be a thoracic sensory level, usually several segments below the compression
 - c. Reflexes in the lower extremities may be enhanced, and a subtle Babinski sign may be elicitable

Intervertebral Disc Clinical Manifestations

Vertebral Disc C1–C2

1. There is no disc between C1–C2
2. Ligaments and joint capsules resist excessive motion at this level

Intervertebral Disc Space at C2–C3

1. Rarely trauma induces C2–C3 disc extrusion
2. Clinical manifestations include:
 - a. Non-specific neck and shoulder pain
 - b. Perioral hypesthesia
 - c. Radicular pain to pre-auricular areas and the lateral neck
 - d. A retro-odontoid disc may result from an upwardly migrating disc fragment
 - e. Concomitant cord injury may cause motor and sensory symptoms below the disc level

Intervertebral Disc Space at C3–C4

1. Disc herniations at this level are rare
2. May present with no or mild pain
3. A myelopathy may be caused
4. Hand numbness may be a prominent symptom

Clinical Manifestations of Cervical Disc Herniation

Intervertebral Disc Space at C4–C5

1. C5 root is affected
2. Pain is felt across the trapezius ridge to the shoulder
3. Weakness of the supra- and infraspinatus muscles, deltoid, and biceps muscle (slight)
4. Depressed biceps reflex

Intervertebral Disc Space at C5–C6

1. C6 root is affected
2. Pain across the trapezius ridge to the shoulder. Anterior and upper arm, thumb and index finger

3. A sequestered fragment is completely separated from the nucleus pulposus. This segment may migrate rostrally or caudally down the spinal canal
4. Weakness in the biceps, brachioradialis, extensor carpi radialis
5. Reflexes – diminished biceps and supinator jerk
6. Tenderness over the spine or scapula as well as the suprascapular area; paresthesias of the thumb and index finger

Intervertebral Disc Space at C6–C7

1. The affected root is C7
2. Pain in the shoulder, posterolateral arm, elbow and the middle finger and rarely the axilla
3. Weakness of triceps and wrist extensors
4. Diminished or absent triceps reflex
5. Tenderness down the medial scapular border and in the supraclavicular fossa; rarely the triceps; rarely patients complain of paresthesias of all fingers

Intervertebral Disc Space at C7–T1

1. C8 root is affected
2. Pain radiates to the medial forearm
3. There is weakness of the intrinsic hand muscles
4. Slight or no decrease in the triceps reflex
5. May be misdiagnosed as an ulnar palsy

Cervical Stenosis

General Characteristics

1. The confines of the cervical spinal canal are:
 - a. Laminae and ligamentum flavum posterolaterally
 - b. Pedicles anterolaterally
 - c. Discs and vertebral bodies anteriorly
 - d. The dimensions of the cervical spinal canal at:
 1. C1–C3 normally are (16–30 mm)
 2. C4–C7 (14–23 mm)
 - e. Extension of the neck reduces the canal 2–3 mm

Pathology of Cervical Canal Stenosis

1. Congenitally small canal
2. Disc herniation with concomitant facet and uncovertebral joint osteoarthritic overgrowth of bone
3. Hypertrophy and calcification of the posterior longitudinal ligament (more common in Asian patients) are rare; this is primarily a motor illness
4. Most often, there are depressed biceps and brachioradialis reflexes. The inverted radial reflex is often present (decreased biceps reflex with increased triceps and associated finger flexion)
5. Poor tandem gait; compression of the dorsal and ventral spinocerebellar tracts that are lateral in the spinal cord and carry cerebellar afferents from the legs. This occurs late in the course of the disease
6. Neurogenic bladder

Cervical Spondylolisthesis

- Occurs most frequently following trauma and may be associated with “jumped” lamina or rotator facet joint subluxation
- Extreme guarding with restriction of neck flexion and extension neck movements
- Bilateral enhanced reflexes at the appropriate level due to severe pain:
 - If the roots are compromised and there are arthritic changes in the neural exit foraminal canals, reflexes may be depressed
 - Brachial plexus lesions
 - Lesions of the shoulder joints and muscles (innervated by cervical nerve roots)

Cervical Spondylosis*General Characteristics*

- Mechanical signs:
 - Forward flexed neck (spondylitic posture) with restricted movement to all planes
 - Proximal > distal weakness in the upper extremities; this is a C5–C6, C6–C7 disease
 - Weakness and atrophy of the deltoid, supra- and infraspinatus muscles, the rhomboids are slightly weaker than the biceps and triceps
 - Trapezius ridge is often in spasm and tender; C8–T1 muscles are generally spared (almost always affected in motor neuron disease and peripheral neuropathy)
 - Prominent sensory loss at C5, C6, C7 from the spinal nerve
- Spinal segmental muscle weakness
- Atrophy of involved muscles
- Fasciculations of involved muscles may be evoked by gentle pressure or tapping
- Absent or depressed segmental reflexes:
 - Acutely with compressive or irritated lesion, the reflexes may be slightly enhanced; they are then decreased or lost
 - In the lower extremities, the knee and ankle jerks may be enhanced (although there is lumbar segmental pathology) because the spinal cord is disinhibited (higher compressive lesions, B12 deficiency, and spinal stenosis). There are putative inhibitory fibers in the ventral root that may be affected first with compressive root lesions

Differential Diagnosis of Cervical Root Disc Disease

- The major entities that comprise disease of the cervical roots are:
 - Disc degeneration
 - Immune processes
 - Traction injuries
- Clinically:
 - Lesions affecting the dorsal root entry zone (DREZ) are painful
 - Lesions peripheral to the DRG cause numbness

- Lesions of the posterior ramus (origin is prior to the DRG):
 - Have both medial and lateral branches
 - Cause numbness, paresthesias and pain approximately 1.5 inches from the spinal process laterally
 - These lesions may also cause segmental paraspinal atrophy, sclerotomal sensory alterations, and cutaneous lesions
- Meningeal branches (dural innervations of the meninges):
 - Recurrent nerves of Spurling occur at each level
 - Particularly relevant at the L4–L5 root level (interspace) affecting the L5 root as its referral pattern is to the top of the thigh
- Ventral Root Lesions (a component of the anterior rami) give rise to motor fibers prior to joining the sensory fibers that form the spinal nerve
- Dorsal Root Entry Zone Lesions of the Cervical Spine
 - Medial dorsal root afferent fibers are thickly myelinated and carry proprioception, vibration, light touch and mechanosensation
 - Lateral dorsal root fibers carry lancinating pain (A-delta thinly myelinated) fibers and cold; C-fibers carry heat and second pain (burning quality). Gentle pressure over the exit foramina is helpful in eliciting pain in sensitive roots, C5–C6 and C6–C7 are most easily accessible in the lateral neck. Pain in the supraclavicular fossa is most often severe with upper trunk brachial plexus lesions and with C5 and C6 root lesions. Pain in the infraclavicular fossa is most often from medial cord involvement. It may be associated with evoked pain in the distribution of the intercostobrachial nerve distribution. This pain is felt in the axilla and radiates down the lateral chest wall, under the breast to the midline
 - Muscle weakness and dermatomal sensory loss at disc levels (as noted above)
 - The inverted radial reflex is extremely helpful for C5–C6 lesions
 - Rotary subluxations of the facet joints are difficult to evaluate by neuroimaging but almost always are accompanied by a head tilt
- Klippel-Feil Anomaly
 - Congenital fusion of C4–C5 > C5–C6 (C8–C4 occurs but is rare)
 - Pain at the level of the affected root
 - Spinal stenosis may be concordant at the fused level or one segment rostral
 - Associated with Sprengel’s deformity:
 - Metameric abnormalities at the level of the fusion
 - Shoulder muscles and the scapular are poorly developed; the shoulder is elevated
- Syringomyelia is common in association with high cervical and skull base anomalies:
 - Atrophy of the muscles innervated by the involved roots

- b. Associated with Arnold-Chiari Type II malformations
- 9. Congenital Root disease
 - a. C1–C3 roots
 - b. Abnormal ossification of the odontoid process or the lateral masses of the atlas
 - c. Traction on C2 and C3; there is no somatic surface sensory representation of C1 (motor only)
- 10. Platybasia of the skull:
 - a. The angle formed by the intersection of the plane of the clivus and the plane of the anterior fossa is greater than 135 degrees; traction on C2 and C3
- 11. Basilar invagination:
 - a. An upward bulging of the occipital condyles above the plane of the foramen magnum
 - b. C2–C3 impingement or nerve traction
 - i. Arnold-Chiari malformation with traction on the posterior roots of C2 and C3 that causes pain; specifically cough or valsalva maneuvers may cause severe C2 lancinating pain and/or traction

Thoracic Disc Disease

General Characteristics

- 1. Rare approximately 0.5% of herniated discs
- 2. Affect primarily T8–T11
- 3. Falls on the heels and buttocks as well as lifting very heavy objects are etiologic
- 4. These are dangerous protrusions due to a small canal at these levels that favors spinal cord compression

Clinical Manifestations

- 1. Deep boring spine pain with a lancinating radicular component that may radiate to the thorax or abdomen
- 2. Valsalva maneuvers and downward pressure on the shoulders (increase disc extrusion with further pressure on the spinal cord) exacerbate radicular pain and myelopathy
- 3. Early leg weakness with sphincter involvement occurs if the cord is compressed
- 4. Bilateral Babinski signs with cord compression are concomitant with weakness, atrophy and loss of the specific segmental reflex
- 5. Ability to hop on the toes (without the heel touching the ground) is an excellent method of uncovering leg weakness
- 6. Lateral protrusion causes intercostal or radicular pain
- 7. C8–T1 discs may affect the ipsilateral sympathetic chain to cause a Horner's syndrome

Medical Causes of Thoracic Discs

- 1. Diabetes mellitus
- 2. Syphilis (denervated disc capsule and contiguous structures; a Charcot's joint)
- 3. Amyloid (painless joint; associated with small fiber neuropathy)
- 4. Ochronosis (homogentisic aciduria; pigmented discs; "Rugger Jersey" discs by x-ray)
- 5. Relapsing polychondritis
- 6. High impact trauma

Thoracic Outlet Syndrome

- 1. The major components of the thoracic outlet:
 - a. Sterno-costovertebral space:
 - i. Most proximal part of the thoracic outlet tunnel
 - ii. Anatomy:
 - 1. Anteriorly (sternum)
 - 2. Posteriorly (spine)
 - 3. Laterally (first rib)
 - iii. The subclavian artery and vein as well as the C4–T1 roots of the plexus transverse the space
 - iv. Nerve roots have exited the spine but have not formed trunks
 - v. Associated structures:
 - 1. Apex of the lung and pleura
 - 2. Sympathetic trunk
 - 3. Jugular vein
 - 4. Lymphatics of the neck
 - vi. Rarely, the space is congenitally narrowed
 - vii. The usual pathology in the sternocostovertebral space:
 - 1. Thyroid mass
 - 2. Enlarged thymus gland
 - 3. Parathyroid mass
 - 4. Lymph nodes
 - 5. Pancoast tumor (squamous or adenoma – carcinoma of the lung)

Scalene Triangle

- 1. Anatomy:
 - a. Anterior scalene muscle anteriorly
 - b. Middle scalene muscle posteriorly
 - c. The first rib forms the base
- 2. Anterior scalene muscle:
 - a. Origins are the transverse processes of C3–C6
 - b. Insertion on the scalene tubercle of the first rib varies; tubercle insertion is between the subclavian artery and vein and pleural dome
 - c. Variants of insertion:
 - i. Behind the artery
 - ii. Between the artery and the brachial plexus
 - iii. Entire base of the scalene triangle (traps the neurovascular bundle)
 - iv. Anterior insertion may merge with insertion of the middle scalene muscle (20% of patients)
 - v. The C5 and C6 roots may traverse the anterior scalene muscle rather than descend between the anterior and middle scalene muscles
- 3. Middle scalene muscles:
 - a. Origin is the transverse processes of C2–C7
 - b. Insertion is Chassaignac's retroarterial tubercle of the first rib
 - c. May insert on the fibrous septum of the pleural dome; lateral fibers insert on the second rib
 - d. The C8–T1 roots (individually or together is the lower trunk of the brachial plexus) are compressed by a more

anterior or forward insertion of the middle scalene muscle (its sharp anterior edge)

4. First rib:
 - a. Forms the floor of the scalene triangle
 - b. T1 is closest to the rib
 - c. Congenital rib anomalies, bony ridge, hypoplasia and inward curvature may compress the neurovascular bundle
5. Scalene triangle congenital variations:
 - a. The base of the triangle is 0.77 cm in men and 0.67 cm in women
 - b. C5, C6, and C7 roots emerge from the apex of the triangle; the fibers of the middle and anterior scalene muscles also merge at the apex. Patients with C5, C6, and C7 root involvement have a greater incidence of roots that emerge from the apex:
 - i. Interdigitation of anterior and middle scalene muscles occurs in 70% of symptomatic patients
 - ii. Adherence of C5 and C6 roots to the middle scalene muscle may occur and places these roots under traction when the arm is moved
6. Costoclavicular space (compresses the brachial plexus)
7. Pectoralis minor space (compresses the lateral and medial cords of the brachial plexus)

Cervical Ribs That Compress Cervical Roots

1. 0.17% to 0.74% (average 0.3%) of the general population (female > males, 2:1) have cervical ribs
2. Approximately 10% of patients with cervical ribs are symptomatic
3. Symptomatic patients often have suffered arm trauma or are in professions that require repetitive overhead arm movement
4. Aneurysmal dilatation or subclavian artery stenosis is most often associated with a rudimentary thoracic rib or a cervical rib
5. Neurological symptoms from cervical ribs are caused by nerve compression primarily of the lower trunk (composed of the C8, T1 roots)

Rib-Band Syndrome of Gilliat

1. A Roos type II band
2. Compression of the C8, T1 roots
3. Paresthesia of the 4th, 5th finger, medial forearm to the medial humerus
4. There is atrophy and wasting of intrinsic hand muscles

Other Structural Congenital Anomalies Affecting Cervical Roots

1. Hypoglossal duct cyst (involvement of C3, C4 roots)
2. Brachial cleft cysts (involvement of C2–C5 roots)
3. Short pedicle and block vertebral bodies:
 - a. Entrapment of the root under the pedicle and in the neural foramina exit canal
 - b. Achondroplasia (at all cervical levels); there are block vertebrae and often a foramen magnum stenosis

Trauma of Cervical Nerve Roots

1. Flexion-extension injury of the neck (whiplash)
 - a. Nerve traction injury (neuropraxis) rather than soft tissue, ligament, disc or joint injury is etiologic
 - b. C8–T1 is most often involved due to congenital anatomical predisposition
 - c. C5, C6 roots are injured either prior to or after having formed the upper trunk
 - d. The dorsal root of C2, C3, and C4 are frequently injured with whiplash trauma
 - e. There is immediate pain that worsens over time and may spread extrateritorially (peripheral and central sensitization)
 - f. Autonomic dysregulation occurs (usually adrenergic sympathetic over activity) particularly with C8, T1, T2 injury. The former carry sympathetic innervations to the face, and the T2 ganglion is the primary innervation of the arm
2. Damage to cervical roots occurs during transaxillary first rib resection:
 - a. C8, T1 is most frequently involved
 - b. C5, C6 roots are most often damaged with scalenectomy and neurolysis procedures (supraclavicular approach)
 - c. Flexion-extension injury may damage the ansa hypoglossi:
 - i. Causes slight weakness of the sternocleidomastoid muscle as most of its innervations are derived from the spinal component of cranial nerve XI. Spasm of the muscle may be severe
 - ii. Hyoid and omohyoid muscles may be involved
 - iii. Scalene and trapezius muscles may be slightly weak
3. Pain radiations:
 - a. Pre-auricular nerve territory (C2, C3 roots). The radiation overlaps with V2 and V3 radiations of the trigeminal nerve for which it is confused
 - b. Post auricular nerve territory (C3, C4 roots). This territory covers the ear, overlaps with C2 at the angle of the jaw and radiates to the parietal and occipital areas of the skull
 - c. Specific radiations of C2 in isolation are to the base of the occiput, angle of the jaw, parietal scalp and to the brow. The brow radiations are common with cough or valsalva maneuvers in the face of Chiari malformations and with severe cervical spondylosis
 - d. Greater and lesser occipital nerve distributions (C2, C3, C4) posterior roots. Primarily innervate the basiocciput and occipital areas of the scalp
4. Surgical trauma:
 - a. C5, C6, C7 roots are most often affected
 - b. Instrumentation that requires plates and pedicle screws
 - c. Arachnoiditis of the nerve sleeves or direct injury or irritation of the affected roots

- d. High impact trauma (MVA, falls, contact athletics)
 - i. Spondylolisthesis of cervical vertebrae
 - ii. Avulsion of nerve roots (a common motor cycle injury)
 - iii. Jumped laminae
 - iv. Rotary subluxation of a facet joint presents with:
 1. Pain at the segmental level in the neck with radiation into the affected segmental distribution
 2. Torticollis (to the affected side)
 3. Segmental weakness
 - v. Injury by epidural catheterization with bupivacaine >0.25% or trauma by the catheter itself

Complex Regional Pain Syndrome I and II (CRPS)

1. CRPS occurs most frequently after injury of small nociceptive afferents in soft tissue (Type I) or of a specific injured nerve (Type II)
2. Clinically it is manifested by:
 - a. Hyperalgesia and thermal and mechanical allodynia
 - b. Autonomic dysregulation:
 - i. Temperature change
 - ii. Hyper- or hypohidrosis
 - c. A movement disorder associated with atrophic changes in the affected areas
 - d. Severe spreading pain that involves multiple roots and hence is regional

Red Ear Syndrome

1. The C3 root is involved
2. Usually, one ear is involved but the process may be bilateral
3. The ear is beet red, slightly edematous and non-painful
4. The underlying pathology is thought to represent neurogenic edema. The irritated small fibers that innervate blood vessels of the ear and release vasoactive neuropeptides (principally substance P and calcitonin gene-related peptide). These peptides cause vasodilatation of the capillaries in the ear (CGRP) and leakage of the plasma through the endothelium (substance P)

Lax Ligament Syndrome (That Attach the Odontoid Process to the Atlas)

1. Four ligaments are involved:
 - a. A cruciate posterior ligament that attaches the odontoid process to the axis
 - b. Lateral ligaments that attach the odontoid process to the lateral mass of C1
 - c. The alar ligament from the tip of the odontoid process to the rim of the foramen magnum
2. Normal posterior odontoid displacement with neck flexion is:
 - a. 3–5 mm in children
 - b. 1–2 mm in adults
3. In abnormal displacement the C2 root is primarily involved with concomitant spinal cord compression

Differential Diagnosis of Cervical Ligament Disorders

1. Rheumatoid arthritis:
 - a. Frequently there is tingling of all fingers, the arms and the hands, most likely from cervical spinal cord compression
 - b. Subluxation at high cervical levels with spinal cord compression
 - c. The rheumatoid pannus erodes the cruciate ligament
2. Trisomy 21
3. Ehlers-Danlos syndrome (Type IV)
4. Marfan's syndrome
5. Trauma (flexion/extension) injury of the neck

Ligament Hypertrophy with Cervical Root Impingement

Differential Diagnosis

1. Acromegaly
2. Mucopolysaccharidosis:
 - a. Morquio's syndrome has concomitant absence or hypoplasia of the odontoid process
3. Posterior ligament ossification syndrome
4. IgG-4 syndrome – a form of pachymeningitis
5. Hirayama syndrome (ligament laxity at lower cervical levels with spinal cord compression)

Pachymeningitis with Cervical Root Compression

1. Syphilis
 - a. Dense fibrous dural thickening surrounding the roots and cervical cord
2. Sarcoid
3. Tuberculosis
4. IgG-4 syndrome and idiopathic pachymeningitis
5. Subarachnoid hemorrhage with consequent arachnoiditis
6. Hodgkin's and non-Hodgkin's lymphoma

Tumors of the Cervical Nerve Roots

1. Schwannoma:
 - a. Associated with neurofibromatosis (NFT) type I mutations on chromosome 17; Type II causes bilateral Schwannoma on the VIIIth nerve (the mutation is in chromosome 22)
 - b. May affect multiple nerve roots concomitantly
 - c. Root and plexiform involvement > in lumbosacral than brachial distributions
 - d. A dumbbell tumor; characteristically it involves the nerve which enlarges the nerve exit foramen and occupies the intradural extramedullary space with slowly progressive cord compression
2. Neurofibroma
3. Meningioma
 - a. Intradural extramedullary growth; concomitant nerve root compression
 - b. Plexiform (en-plaque growth)
4. Lymphoma (infiltration of nerve roots)
5. Leukemia:

- a. Hemorrhage into a nerve root (acute presentation)
- b. Infiltration of nerve roots (insidious presentation)
6. Carcinomatosis of the meninges:
 - a. Primary tumors are lung, breast, GI tract and prostate
 - b. Mental status alteration
 - c. Asymmetric cranial nerve and radicular presentation
 - d. Weakness, atrophy, sensory alterations, loss of reflexes in a segmental distribution
7. Chordoma:
 - a. Most common in the clivus and sacral vertebrae; rarely occur in the thoracic and cervical vertebrae (10%)
8. Osteogenic sarcoma is rare
9. Fibrosarcoma (degeneration of a neurofibroma)
10. Chondrosarcoma (rare)
11. Ewing's sarcoma
 - a. Greater than 5% occur in the axial vertebrae
12. Pancoast tumor:
 - a. Occur at the apex of the lung (adenoma or squamous carcinomas)
 - b. Involvement is primarily of lower nerve roots (C8–T1) in the sternocostovertebral space
 - c. Pain (usually burning in quality) along the medial forearm and into the 4th and 5th fingers
 - d. Horner's syndrome (involvement of the sympathetics at C8–T1)
13. Lymphomatous B-cells
 - a. Diffuse radiculopathies
14. Post x-ray treatment sarcoma:
 - a. Follows x-RT for breast cancer most frequently
 - b. Involves roots of the brachial plexus C8, T1 > C5, C6
 - c. May be delayed in onset from the last treatment by years
 - d. Associated with myokymia in the irradiated arm
 - e. Associated with skin changes that include hyperpigmentation, telangiectasia and proliferative endarteritis
 - f. MRI reveals hypertrophy and swelling of the trunks and cords of the plexus that enhance with contrast
15. Neuromyotonia with Hodgkin's disease
 - a. Rippling fasciculation in the innervated muscles of the affected nerve roots
 - b. Anti-TA antibodies may be detected in the serum
16. Mixed salivary gland tumors:
 - a. Infiltrate C1–C4 roots
 - b. "Sugar coated" roots
17. Parotid gland tumors:
 - a. VIIth nerve most frequently involved
 - b. Cervical C2–C4 roots are involved less frequently
 - c. Swollen parotid glands noted in diabetes mellitus, mumps, HIV, tumors, and uremia
18. Salivary gland cylindroma:
 - a. Cervical C1–C4 roots are infiltrated
 - b. May have concomitant cranial nerve involvement

Infection Involving Cervical Nerve Roots

Herpes Zoster

1. C5, C6 > C4, C5 > C8, T1 are the most commonly involved roots (cervical)
2. Clinical symptomatology:
 - a. Grouped vesicular eruption in a dermatomal distribution
 - b. Sensory loss in a dermatomal pattern to all modalities; severe pain in the affected dermatome
 - c. Atrophy, weakness much less than sensory alterations (subtle)
 - d. May have dermatomal sensory alterations for weeks to (occasionally) months prior to the vesicular eruption:
 - i. Sometimes there may not be an eruption (herpes sine herpetica)
 - ii. There is often burning pain in the affected dermatome

Post-Herpetic Neuralgia

1. Spontaneous lancinating pain
2. Deep continuous ache with lancinating exacerbations in the involved dermatome
3. Decreased sensory threshold to pinprick, touch or temperature of the dermatome
4. Allodynia to both static and dynamic mechano and thermal stimuli of the neighboring dermatomes but at times of the affected dermatome
5. Hyperalgesia of the involved dermatome
6. Neuroma in continuity along the root of the affected dermatome as well as central sensitization may be the mechanisms
7. Immune suppression is often concomitant

Herpes Simplex

1. A single or grouped vesicular eruption
2. Painful erythematous base
3. May be dermatomal but can be regional (several roots involved) pain

Brucella Mellitensis

1. Hyperhidrosis with fever
2. Non-pasteurized milk may be the source
3. Rare cervical root involvement (L5 is particularly involved)

Lyme's Disease

1. Unilateral or bilateral VIIth nerve palsy
2. C5, C6 cervical roots most often affected
3. Often arthralgia or erythema migrans is noted prior to neurologic symptoms

Staphylococcus Aureus

1. Contiguous spread from site of infection
2. Usually seen with IV drug abuse or following surgical procedures; hematogenous spread with SBE
3. Disc space involvement first; the nerves are compromised in the foraminal exit areas or laterally

Viral Infections

1. Parsonage Turner syndrome
 - a. The sudden onset of severe lancinating, burning, and deep pain
 - b. C5, C6 dermatomes are most often affected
 - c. A cause of neuralgic amyotrophy
 - d. May affect individual nerves (phrenic)
2. EBV
3. Hepatitis C (associated cryoglobulinemic neuropathy)
4. Poliomyelitis acute:
 - a. Usually groups of anterior horn cells are affected
 - b. Pain and deep ache in affected muscles
 - c. Isolated muscles affected (including fingers); asymmetric involvement; non-dermatomal distribution
 - d. Fasciculation and atrophy are prominent long after the infection
 - e. Post-polio syndrome follows in a significant percentage of patients and is characterized by:
 - i. Pain in affected muscles
 - ii. Weakness returns in formerly weak muscles; increased weakness may occur
 - iii. Enterovirus (polio-like syndrome) primarily motor
 - iv. Adenovirus
 - v. Coxsackie particularly 6 and 9 strains

Systemic Diseases Affecting Cervical Nerve Roots*Diabetes Mellitus*

1. Diabetic amyotrophy is much more common in L2–L4 roots
2. Putative involvement of the vasa vasorum in addition to axonopathy and demyelinating features of the polyneuropathy
3. May be bilateral; the second event occurs 6–8 weeks following the first

Acute Intermittent Porphyria

1. C5, C6 roots are most commonly involved
2. Overwhelmingly there is a motor neuropathy with severe atrophy and wasting of the involved muscles
3. Sensory symptoms more often than signs may be patchy; often out of a dermatomal distribution

Variegate Porphyria

1. Rare root involvement
2. May have associated skin rash

Post-X-RT Therapy

1. C5, C6 roots primarily are involved following cervical cord treatment
2. Myokymia may be prominent

*IgG4 Pachymeningitis**Sicca Complex*

1. Autoimmune

2. May have patchy anhidrosis and sensory loss out of a dermatomal distribution
3. Probable dorsal root ganglionopathy
4. May involve definable cervical roots

Amyloidosis

1. Familial amyloid
2. FOLMA (familial oculoleptomeningeal amyloidosis)
 - a. Meningeal involvement with nerve root compression

Isolated Angiitis of the CNS/PNS

1. Arteritis of the vasa vasorum that supply cervical nerve roots

Inflammatory Spondyloarthritis with Radiculopathy

1. Rheumatoid arthritis
2. Psoriasis
3. Ankylosing spondylitis
4. Crohn's disease
5. Ulcerative colitis
6. Behçet's disease

Vascular Disease of Cervical Nerve Roots*Arteriovenous Malformation*

1. Nerve root (on the root itself)
2. Dural AVM with accompanying compression of the nerve root

Dilated Vein Compressing the Nerve Root

1. Venous congestion from severe cervical spondylosis or an extruded disc
2. Concomitant venous congestion of the spinal cord (myelomalacia) and the nerve root
 - a. Postulated that veins over the nerve root cause mechanical pressure on the sensitized root that awakens patients with disc disease in the early morning

Foix-Alajouanine Syndrome

1. Arteriovenous malformation involving the anterior spinal artery
2. Cervical nerve roots and the spinal cord may be compressed

Weber-Klippel-Trenaunay Syndrome

1. Arteriovenous malformation of an extremity
2. Enlargement of the bone and soft tissue components of the extremity
3. Enlarged epidural veins and their tributaries may compress segmental nerve roots

Superficial Siderosis

1. Hemosiderin deposits on nerve roots
 - a. Radiculopathy
 - b. Cranial nerves I and VIII may be concomitantly involved

- c. Caused by repeated bleeding from aneurysms, cavernous hemangiomas or rarely telangiectasias
- d. Demonstrated by gradient ECHO or susceptibility weighted MRI sequences

Arachnoiditis

1. Clumping together and scar formation of nerve roots
 - a. Secondary to:
 - i. Multiple surgeries
 - ii. No longer seen from myelography due to the use of water-soluble contrast media
 - iii. Clinical manifestations
 1. Severe burning pain in several dermatomal distributions
 2. Usually a regional rather than a clear radicular pattern
 3. CT/myelography demonstrates clumping of nerve roots or a featureless dural sac
 4. MRI demonstrates gadolinium enhancement of the scar
 5. Minimal weakness; burning pain predominates
 6. Asymmetric reflex loss
 7. Rare bladder involvement

Rarely caused by aneurismal rupture of a vertebral or anterior spinal artery.

Differential Diagnosis of Cancer vs X-RT Involvement of Cervical Nerve Roots

1. Usually X-RT treatment of head and neck cancer
2. Signs and symptoms are often delayed from six weeks to three months

Cancer

1. Painful (burning quality)
2. C8, T1 roots are primarily involved
3. Horner's syndrome
4. Pancoast tumor of the lung apex (adenoma or squamous cell carcinomas)

Cervical X-RT

1. Dysesthesias or paresthesias of the involved roots
2. C5, C6 roots are primarily involved
3. No Horner's syndrome
4. Myokymia of the muscles in the involved dermatomes
5. X-RT of the breast, Hodgkin's disease, head and neck cancers are the most common systemic illnesses treated
6. Often missed by conventional x-ray; MRI for diagnosis
 - a. Segmental radiculopathy
 - i. Pain is usually the most prominent symptom
 - b. Burst fracture of the vertebral body:
 - i. Vertebral body star fracture (radiation of fracture lines from the center of the vertebral body)
 - ii. Bilateral radicular pain
 - iii. Fractured bone fragment may be displaced into the spinal canal or foraminal exit area

- iv. Concomitant spinal cord direct injury and compression

- c. Lateral vertebral body translocation:
 - i. Severe high impact trauma (most often MVA)
 - ii. Bilateral radicular pain
 - iii. Associated severe spinal cord injury

7. Anterior vertebral body compression fracture:
 - a. Middle-aged and elderly women

Thoracic Root Disease

Disc Disease

General Characteristics

1. Trauma
 - a. Severe trauma (high impact MVA, heavy lifting, direct spinal injury)
 - b. Dull boring midline ache with episodes of radicular lancinating pain
 - c. Intercostal or abdominal radiations
 - d. Exacerbated by specific movements
 - e. Radicular pain associated with signs of compressive myelopathy

Traumatic Thoracic Radicular Disease

General neuroimaging features:

1. Jumped facet joint:
 - a. Overriding of the inferior over the superior facet joint
 - b. Traction or direct injury of the segmental root
2. Rotary subluxation of the facet joint
 - a. Facet joint is twisted; synovial interfacet is breached with metabolic bone disease (osteoporosis)
 - b. Due most often to minimal trauma
 - c. Lancinating radicular pain at the involved segmental level

Rarer Causes of Thoracic Root Disease

Syrinx

1. Atrophy at the segmental level
2. Early hyperhidrosis followed by anhidrosis of the affected segments
3. Dissociated sensory loss at the segmental level (destruction of spinothalamic fibers as they decussate in the anterior ventral commissure)
4. Long tract motor and sensory signs below the syrinx

Post-Traumatic Syrinx

1. Further cystic degeneration of the spinal cord
2. Usually, there is a 2 to 3 segment loss of function above and below the level of injury
3. Bilateral root involvement at the involved segmental level

Chest Surgery

1. Open heart

2. Lung surgery
3. Retraction (neuropractic or direct radicular injury; post-thoracotomy syndrome)
4. Prolonged and often refractory neuropathic pain of the involved roots or intercostal nerves

Thoracic Nerve Root Involvement from Systemic Disease

Diabetes Mellitus

1. Infarction or ischemia of the thoracic nerve roots (vasa vasorum) or usual etiology of diabetic polyneuropathy occurs in:
 - a. Elderly type II diabetics
 - b. Associated with weight loss
 - c. Abrupt onset
2. Diabetic “dying back” neuropathy:
 - a. Shield sensory loss on the chest wall
 - b. Associated with distal dying back neuropathy of the extremities
 - c. Single or multiple dermatomal involvement of the chest or abdomen
 - d. Sensory loss is in the distribution of the anterior rami (dorsal root component) or posterior rami (paravertebral sensory territory); the sensory loss may be in various combinations of the territories of these rami

Amyloid Neuropathy

1. Associated with primary amyloid neuropathy; also the TTR met 30 mutation (transthyretin)
2. Familial oculoleptomeningeal amyloidosis (FOLMA)
3. Denervation of the segmental disc (rarely associated with a Charcot’s joint)
4. Radicular pain due to root irritation

Ochronosis

1. AR; homogentisic acid synthetase deficiency
2. Dark urine (homogentisic aciduria)
3. Calcification and degeneration of multiple thoracic discs
4. “Rugger-Jersey” x-ray evaluation (calcification of the discs)
5. Differential diagnosis of calcified thoracic discs
 - a. May be asymptomatic
 - b. Ankylosing spondylitis
 - c. Hyperparathyroidism
 - d. Toxins

Immune-Mediated Processes That Affect Thoracic Roots

1. Acute inflammatory demyelinating polyneuropathy (AIDP):
 - a. GMI, Gd1b, Gal-Nac-GD1a antibodies
2. Chronic inflammatory demyelinating polyneuropathy (CIDP)
3. Sjögren’s disease:
 - a. Primarily a dorsal root ganglionitis
 - b. Involvement of the dorsal primary ramus or its medial or lateral divisions

Sicca Complex

1. Dry eyes, mouth, serous membranes
2. Segmental and regional sensory loss
3. Segmental and regional anhidrosis
4. Radiculopathy with increased sed rate
 - a. Poorly defined process
 - b. Usually, the lumbosacral roots are involved

Cancer and Benign Tumors

1. Leukemia
2. Hodgkin’s disease and non-Hodgkin’s disease lymphoma
3. Carcinomatosis of the meninges
4. Metastatic cancers

Tumor

1. Anterior mediastinal tumors (rarely involve thoracic roots)
 - a. Thymoma and thymic carcinoma are usually locally invasive
 - b. Thymic carcinoid (associated with multiple endocrinopathy type I);
 - c. MEN (multiple endocrinopathy) associated with:
 - i. Thymic lipoma
 - ii. Hodgkin’s and non-Hodgkin’s lymphoma (NHL)
2. Primary mediastinal germ cell tumors:
 - a. Mature teratoma
 - b. Seminoma
 - c. Non-seminomatous germ cell tumors

Posterior Mediastinal Tumors

1. Peripheral nervous system benign and malignant neoplasms are more frequent in the posterior mediastinum
2. They develop from peripheral nerves, sympathetic and parasympathetic ganglia, as well as neural tube embryonic remnants and include:
 - a. Schwannoma
 - b. Neurofibroma
 - c. Melanotic Schwannoma
 - d. Ganglioneuroma
 - e. Granular cell tumor
 - f. Malignant melanocytic nerve sheath tumor
 - g. Neuroblastoma
 - h. Neurofibrosarcoma (non-Recklinghausen’s disease)

Metastatic Disease (to the Cervical Root)

1. Multiple myeloma
2. Osteoclastic myeloma
3. Plasmacytoma
4. Paget’s disease (sarcomatous degeneration)
5. Multiple myeloma (vertebral fractures with secondary radicular involvement)
6. GI cancer (sacral bone involvement with colon cancer; lumbar and sacral roots > thoracic root involvement)
7. Giant articular bone cyst (vertebral fracture)
8. Osteoid osteoma:

- a. Refractory to narcotics the pain responds to prostaglandin inhibitors
- b. Involve the posterior elements of the vertebral body (pedicles and facets)
- c. Radicular symptoms
9. Vertebral body sarcoma
10. Chondrosarcoma
11. Enchondroma
 - a. Involves the nerve root exit foramina
12. Chordoma:
 - a. Approximately 4% involve thoracic vertebrae
13. Brown bone cyst:
 - a. Occurs with hyperparathyroidism
 - b. Bone resorption, fracture and pain
14. Hemangioma of the vertebral body
 - a. Most often they are an incidental bone finding on MRI T2-weighted sequences
 - b. May weaken the vertebral body
 - c. The lesions are extremely vascular
 - d. May compress the exiting nerve root
15. Thoracic meningioma in women
 - a. Extremely rare location for meningioma in men
 - b. Increased growth of the tumor in pregnancy and with breast cancer
16. Schwannoma:
 - a. Typically enlarges the foramina nerve root exit canal
 - b. Scalloping of the affected vertebral body (a sign of chronic pressure)
 - c. A dumbbell tumor (both enlarging the nerve root and expanding in the intradural extramedullary space)
17. Neurofibroma
4. Gram-negative disc space infection following surgery:
 - a. Involvement and signs of infection may be delayed for up to six weeks from the procedure
 - b. Pain, swelling, erythema and edema at the operative site
 - c. Invariably high sediment rate and C-reactive proteins
5. Tuberculosis:
 - a. T4–T6, T11–T12, L1–L2, the usual location of the infection
 - b. The infection is more common in the cervical spine in Asian patients
 - c. Disc space is infected > than the vertebrae; bony sclerosis of the vertebral body and endplates on neuroimaging
 - d. Pott's disease
 - i. Acute kyphotic angulation
 - ii. Occurs from vertebral body collapse and loss of disc integrity
 - iii. May cause spastic paraparesis
 - e. Cold abscess may occur along the iliopsoas muscle; T10–T11 root may be involved; blurring of the psoas stripe on x-ray of the abdomen
6. Actinomycosis:
 - a. Extension of active lung infections into thoracic vertebrae
 - b. Abscess with radicular symptoms
 - c. Characteristic sulfur granules in the abscess
 - d. Rural population
7. Nocardia:
 - a. Occurs in immunocompromised patients
 - b. Epidural vein involvement
 - c. The fungus is often in a lung abscess
 - d. Associated with osteomyelitis

Infections Involving Thoracic Roots

1. HZ (Herpes Zoster)
 - a. Thoracic dermatomes are most commonly involved
 - b. Clinical symptoms (similar to that of cervical roots)
 - c. A dorsal root ganglionitis
 - d. Rarely a hemorrhagic spinal cord infarction is associated (paraparesis is most often at the T4–T6 level)
2. HIV
 - a. Usually, the cervical cord is involved
 - b. Vascular degeneration of the cord
 - c. Rare radicular complaints
3. Staphylococcus aureus
 - a. Young IV drug abusers; there are end arteries to the disc
 - b. The disc space is infected:
 - i. Enhancement of the disc with contrast on MRI
 - ii. The vertebral body is spared: there is often pre- and postvertebral ligament inflammation (enhancement with gadolinium on T1-weighted sequences)
 - iii. Disc space infection causes severe lancinating radicular pain; minimal movement initiates pain (touching the patient's bed)
 - iv. Spinal cord involvement by contiguous spread or by venous infarction

Lumbosacral Root Disease L1–L5; S1–S5

General Characteristics

1. Higher lumbar root pathology:
 - a. Autoimmune processes
 - b. Connective tissue diseases
 - c. Retroperitoneal processes (tumors, hemorrhage, fibrosis)
 - d. Diabetes mellitus
 - e. Vasculitis

Lower Root Involvement (L4–S1)

1. Degenerative disc disease
2. Lumbar spondylosis
3. Lumbar spondylolisthesis
4. Spinal stenosis
5. Facet hypertrophy and tropism
6. L5–S1 lateral recess syndrome
7. Surgical procedures

Combined Lumbosacral Root Disease

1. Tumors (metastatic)
2. Surgical and post-surgical complication
3. Arachnoiditis
4. Congenital abnormalities

Congenital Defects of Lumbosacral Roots*Scoliosis*

General Characteristics

1. Congenital scoliosis is the failure of normal vertebral development during the 4th to 6th week of gestation

Associated Conditions

1. May occur in isolation
2. Occurs with systemic anomalies in approximately 60% of patients that include:
 - a. Cardiac defects – 10%
 - b. Genitourinary defects – 25%
 - c. Spinal cord malformations
 - d. Associated with syndromes that include:
 - i. VACTERL syndrome
 - ii. Oculo Auricular Vertebral syndrome
 - iii. Jarcho-Levin syndrome/spondylocostal dysostosis
 - iv. Klippel-Feil syndrome
 - v. Alagille syndrome

Clinical Manifestations

1. Localized lumbar pain usually in the nerve roots on the contralateral side
2. Patients are more susceptible to further compression by disc, bone, or ligament

Neuropathology

1. A developmental defect in the formations of the mesenchymal component of the vertebra
2. Failure of formation:
 - a. A normal fully segmented hemivertebra (normal disc space above and below)
 - b. Semisegmental hemivertebra
 - i. Hemivertebra fused to the adjacent disc on one side
 - c. In segmented hemivertebra:
 - i. Hemivertebra fused to vertebra on each side
 - d. Incarcerated hemivertebra:
 - i. Fused within the lateral margins of the vertebra above and below
 - e. Unincarcerated hemivertebra:
 - i. Laterally positioned
 - f. Wedged vertebra
3. Failure of Segmentation:
 - a. Block vertebra:
 - i. Bilateral bony bars
 - b. Bar body:
 - i. Unilateral unsegmented bar is common
 - c. Mixed:
 - i. Unilateral unsegmented bar with contralateral hemivertebra
 1. Progresses the most rapidly

Neuroimaging

1. MRI:

- a. All patients with congenital scoliosis to evaluate the complete neuraxis to rule out associated other anomalies that occur in 20–40% of patients and include:
 - i. Chiari malformations
 - ii. Tethered cord
 - iii. Syringomyelia
 - iv. Diastematomyelia
 - v. Intradural lipoma
- b. 3D CT
 - i. Best delineation of posterior bony anatomy

Laboratory Evaluation

1. Renal ultrasound or MRI
2. Echocardiogram

Adult Scoliosis

General Characteristics

1. Definition: a spinal deformity with a Cobb angle of more than 10° in the coronal plane in a skeletally mature patient
2. Separated into 4 categories:
 - a. Type I (primary degenerative scoliosis)
 - i. Disc or facet joint arthritis that affects the spinal column asymmetrically
 - b. Type II (idiopathic adolescent scoliosis) which progresses to adulthood
 - i. Combined with secondary degenerations
 - ii. Surgical or no surgical treatment
 - c. Type III (secondary adult curves) in addition to:
 - i. Oblique pelvis due to leg length differences or hip pathology
 - ii. Idiopathic, neuromuscular, or congenital scoliosis
 - iii. Lumbosacral junction asymmetry anomalies
 - d. Context of metabolic bone disease (primarily osteoporosis) combined with asymmetric arthritic disease or vertebral fracture Type IV (no identifiable cause)

Clinical Manifestations

1. Low back pain
2. Signs of contra or lateral spinal stenosis
3. Radicular pain at the appropriate level
4. Claudication (neurogenic) symptoms

Neuropathology

1. Asymmetric degeneration leads to spinal load imbalance with bone remodeling and further degenerative changes
2. Destruction of facet joints, joint capsules, disc and ligaments
3. Multi-segmental instability

Neuroimaging

1. MRI and CT evaluation:

- a. Degenerative facet joint changes (hypertrophy and tropism); thickened ligaments

- b. Central and lateral spinal stenosis
- c. Disc desiccation with degeneration and loss of disc height

Laboratory Evaluation

- 1. Bone metabolism evaluation
- 2. Extensive medical evaluation of older patients prior to surgery

Lordosis

General Characteristics

- 1. Increased angulation of the spine, the anterior pelvic tilt angle

Clinical Manifestations

- 1. Postural pain
- 2. Radiculopathy at the segmental level (usually L3–L5)
- 3. Facet pain

Neuropathology

- 1. Increased compression of the apophyseal joint
- 2. Increased anterior shear force at the lumbosacral junction
- 3. Possible precursor to spondylolisthesis

Neuroimaging

- 1. MRI or CT:
 - a. Measurement of the lordosis angles in relation to the anterior pelvic tilt
 - b. A sharp angle of L5 in relation to S1; the closer to 180-degree plane > traction on L4, L5, and S1 nerve root

Conjoined Nerve Roots

General Characteristics

- 1. Two adjacent nerve roots that share a common dural envelope during their course from the dural sac
- 2. The incidence by CT, MRI and myelography vary widely 2–17% in patients studied with spine imaging

Clinical Manifestations

- 1. Straight leg raising test may be negative
 - a. A distinguishing clinical feature from disc herniation
- 2. Usual presentation is sciatic pain
- 3. The L5 and S1 roots are most frequently involved. L4 and L5 are next in frequency
- 4. Claudication pain rather than that of a fixed radiculopathy; radicular symptoms with rest pain are more common with disc herniation
- 5. Neurologic deficits (motor and sensory) are more common with disc disease

Neuropathology

- 1. The dorsal roots may be more commonly involved than the ventral roots
- 2. Bifurcation occurs close to the intervening pedicles; they then enter their respective foramina

- 3. Abnormal root anastomosis is caused from a connection of a band of nerve fibers or a distal union in a common sheath
- 4. There is decreased mobility of the root which increases its risk of neuropractic or direct injury during neurosurgical procedures

Neuroimaging

- 1. Features typical of conjoined roots include:
 - a. MRI:
 - i. Equal density of the nerve root anomaly and the thecal sac
 - b. Asymmetry of the subarachnoid space (pouching out) in the axial view at the level of the anomaly that may be above the intervertebral disc space
 - c. Possible specific MRI signs:
 - i. Asymmetric morphology of the anterolateral corner of the dural sac
 - ii. Intervening extradural fat between the asymmetric dura and the nerve root
 - iii. Visualization of the entire course of the nerve root at the disc level
 - iv. Focal lateral recess and foraminal stenosis

Perineural Cysts (Tarlov Cyst)

General Characteristics

- 1. Naba classification:
 - a. The cysts are located in the perineural space between the endoneurium and perineurium
 - b. Type I cyst:
 - i. Extradural meningeal cyst without spinal nerve root fibers
 - c. Type II
 - i. Spinal extradural meningeal cyst with spinal nerve roots
 - d. Type III
 - i. Spinal intradural meningeal cysts
- 2. Cystic dilatations of the lumbosacral roots at or distal to the junction of the posterior root or DRG
- 3. Incidence in adults is between 4–9%; there is no sex predilection
- 4. CSF filled

Clinical Manifestations

- 1. Most often they are asymptomatic
- 2. A ball valve mechanism from hydrodynamic CSF forces causes the perineural cyst to fill with CSF and expand
- 3. Back pain
- 4. Radicular pain
- 5. Rarely bowel and bladder dysfunction
- 6. Leg weakness
- 7. Sexual dysfunction
- 8. Infertility

Neuropathology

- 1. The cysts are frequently multiple

2. Arachnoidal proliferation around the lumbosacral involved root
3. Putative absence of dura mater during development
4. Possible hemorrhage with hemosiderin deposition leading to venous drainage into the perineurium
5. Lining of the cyst contains nerve fibers and/or ganglion cells; they have a synovial lining; pseudo-stratified columnar epithelium

Neuroimaging

1. MRI
 - a. Fluid filled lesion with low signal on T1-weighted sequences and high signal in T2-weighted images
2. May erode bone; particularly prominent with sacral cysts
3. There may be communication of the cysts with the subarachnoid space

Cysts of the Ligamentum Flavum

General Characteristics

1. Ligamentum flavum cyst is a juxtafacet cyst; synovial and ganglion cysts that are adjacent to facet joints or that arise from the ligamentum flavum
2. A classification of juxtafacet cysts by location has been proposed:
 - a. Flavum cyst
 - b. Facet cyst
 - c. Posterior longitudinal ligament cyst
3. The ligamentum flavum is attached above and below to the lamina and laterally to the articular facet
 - a. Dorsal in the intervertebral foramen
 - b. Fused with the capsule in the lateral surface of the superior articular process in the lumbar spine
4. Most common level is L4–L5 > L5–S1 > L3–L4

Clinical Manifestations

1. Usual presentation is that of radiculopathy
2. Often asymptomatic
3. Back pain

Neuropathology

1. Collagen fibers in the cyst wall without a synovial lining

Neuroimaging

1. MRI:
 - a. Isointense or variable intensity on T1-weighted sequences; isointense with T2-weighted sequences
2. No communication with the facet joint
3. May present with intraluminal hemorrhage or with air or gas in the cavity

Differential Diagnosis of Cystic Lesions of the Ligamentum Flavum

1. Granuloma
2. Intraligamentous amyloid deposition
3. Ossification

4. Myxomatous degeneration and hematoma
5. Perineural cyst
6. Intraspinal dermoid cyst
7. Neurofibroma
8. Hydatid cyst
9. Cysticercosis

Achondroplasia

General Characteristics

1. The most common form of non-lethal skeletal dysplasia
2. Genetics:
 - a. Mutation of the fibroblast growth factor receptor 3-gene (FGF R3); autosomal dominant
3. Prevalence is 0.36 to 0.6 per 10,000 live births
4. Defining clinical features are:
 - a. Short stature
 - b. Disproportionately shorter proximal limb bones
 - c. Narrow trunk
 - d. Macrocephaly
 - e. Prominent forehead and flattened midface
 - f. Short broad hands; trident fingers
5. General medical complications:
 - a. Musculoskeletal
 - b. Cardiorespiratory
 - c. Ear, nose, and throat
6. Neurological complications:
 - a. Cervicomedullary spinal cord compression
 - b. Sleep apnea
 - c. Disordered respiration
 - d. Myelopathy
 - e. Hydrocephalus
 - f. Ligament laxity

Clinical Manifestations (Lumbar Stenosis)

1. 80% of individuals are symptomatic by age 60
2. Radiculopathy with claudication
3. Compressive cervical myelopathy

Neuropathology

1. Narrow spinal canal
2. Short pedicles
3. Narrowed exit foramina
4. Block vertebra
5. Abnormal chondrocyte proliferation and differentiation in the growth plate

Neuroimaging

1. MRI evaluation of neuropathological bone changes as above
2. Foramen magnum stenosis
3. T11–T12 spinal stenosis

Laboratory Evaluation

1. Sleep studies to evaluate for sleep apnea
2. Evaluation for cervical medullary decompression emergent surgery if there is disorder breathing

Congenital Spinal Stenosis

General Characteristics

1. Developmental lumbar spinal stenosis is a maldevelopment primarily of the dorsal spinal elements
 - a. Short pedicles
 - b. Trefoil bony spinal cord

Clinical Manifestations

1. Similar clinical symptomatology as acquired stenosis but presents at an earlier age
2. Subtle clinical signs of spondylosis

Neuropathology

1. Multilevel involvement with L3, L4, and L5 most severely involved
2. Severe stenosis at L1, L2, and S1 is rare

Neuroimaging

1. Shorter pedicle length
2. Smaller cross-sectional spinal canal area
3. Block vertebra
4. Narrowed exit foramina

Lateral Recess Syndrome

General Characteristics

1. The lateral recess may be the principal site of pathology in lumbar canal stenosis
2. Anatomy:
 - a. Bordered laterally by the pedicles, posteriorly by the superior articular facet and ligamentum flavum and anteriorly by the vertebral body, endplate margin and disc margin
 - b. It is funnel shaped and is narrowest in its cranial extent at the superior portion of the pedicle

Clinical Manifestations

1. Radicular signs and symptoms
2. If the compression is in the intervertebral foramen, extension of the trunk in conjunction with ipsilateral side bending and rotation reproduces the symptoms

Neuropathology

1. Two morphologic forms cause root compression in the lateral recess:
 - a. A congenital trefoil-shaped lateral recess becomes smaller; the superior articular facet hypertrophies or the disc margin enlarges from an endplate spur or a disc bulge
 - b. Angular pinch-like encroachment of the lateral margin of the canal from facet endplate and disc margin alterations
 - c. Composition of osteophytes that cause lateral recess encroachment:
 - i. Fibrous and hyaline cartilage and cancellous bone
 - ii. Intramembranous bone formation possibly due to segmental instability

Neuroimaging

1. CT measurement of the posterior edge of the vertebral body and the anterior part of the articular facet in the pedicular slice at the level of the upper vertebral platform
 - a. Lateral recess stenosis occurs when the nerve root is trapped in the bony margins of the lateral recess or exit foramen

Tethered Cord

General Characteristics

1. Traction of the conus medullaris and cauda equina by a tight thickened filum terminale
2. Two clinical categories:
 - a. Asymptomatic in childhood and present for the first time in adult life
 - b. Patients with pre-existing static skeletal/neurologic abnormalities that progress in adult life

Clinical Manifestations

1. Pes cavus (uni- or bilateral)
2. Cutaneous stigmata (strawberry hemangioma; cutaneous dimple) over the sacrum
3. Back pain; may have anal and perianal pain; genital or diffuse leg pain
4. Motor and sensory radicular deficits of lumbar and sacral roots
5. Sphincter alterations
6. Symptomatic with specific positions; particularly the dorsal lithotomy position
7. Symptomatic following delivery or vaginal surgery (primarily due to the dorsal lithotomy position)
8. Urodynamic features:
 - a. Hyper-reflexia of the bladder (neurogenic bladder)
 - b. Internal and external detrusor dyssynergia
 - c. Decreased bladder sensation and compliance
 - d. Hypocontractility of the detrusor muscle
9. General hyper-reflexia of both upper and lower extremities
10. Associations with tethered cord:
 - a. Terminal syringomyelia (caudal 1/3 of the spinal cord)
 - b. Diastematomyelia
 - c. Lipoma of the conus and lipomyeloschisis
 - d. Unilateral pes cavus

Neuropathology

1. Combination of thickening of the filum terminale with:
 - a. Low or dilated conus medullaris
 - b. Spinal lipoma
 - c. Dermoid cyst
 - d. Diastematomyelia
 - e. Hydromyelin
 - f. Sacral agenesis

Neuroimaging

1. MRI:

- a. Tethered cord; tip of the conus medullaris is below the body of L2 instead of the L1–L2 disc space
- b. Most commonly associated with intra- or extradural lipoma

Classification of Lumbosacral Nerve Root Anomalies with a Tethered Cord

1. Type I and II
 - a. One or more nerve roots exit the thecal sac at a more cranial (Type I) or caudal (Type II) level
2. Type III
 - a. Two or more nerve roots emerge from the thecal sac through a closely adjacent dural opening
3. Type IV
 - a. Two or more roots emerge from the dural sac as one nerve trunk
4. Type V
 - a. Two or more nerve roots are connected by an anastomotic branch often exiting the dural sac

Clinical Characteristics of Congenital Nerve Root Anomalies

1. Anomalies occur primarily at L4–L5
2. 20% of patients have other lumbosacral anomalies; rarely congenital absence of a facet joint on the side of the anomaly
3. They may be asymptomatic
4. May be associated with failure of back surgery for herniated disc or spondylosis as they are less mobile
5. In association with lumbar spondylosis and foraminal stenosis
 - a. The affected roots are compressed between the transverse process of the last lumbar segment and sacral ala (S1) or in various relationships to the inner side of the pedicle and facet joint
6. Conjoined lumbosacral roots:
 - a. Are found in approximately 1% of lumbar disc operations
 - b. Most often at L5–S1
 - c. Often not associated with a herniated disc
 - d. Radiographic features:
 - i. Asymmetric subarachnoid space at the affected root level
 - ii. Widened nerve root sleeve
 1. Two or more individual nerve roots may be identified in the axillary pouch (3 Tesla MRI or CT myelography)

Differential Diagnosis of Degenerative Diseases Affecting Lumbosacral Nerve Roots

1. Degenerative disc disease (desiccated hard disc)
2. Spondylosis (degenerative disc disease in association with bone remodeling and osteophytes in the nerve root exit foramina)

3. Degenerative spondylolisthesis
4. Foraminal exit osteoarthritis (osteophytes)
5. Lateral recess syndrome
6. Facet hypertrophy (tropism and rotation)
7. Stenosis (disc; spondylosis; ligamentous hypertrophy)
8. Juxta facet joint cysts (cysts of the ligamentum flavum; synovial cysts)

Benign Bone Tumors Affecting Lumbosacral Nerve Roots

Osteoid Osteoma

General Characteristics

1. A primary benign bone lesion; it constitutes 10% of all primary benign bone tumors and 3% of all primary bone tumors

Clinical Manifestations

1. Most often they are seen in the first 3 decades; 3× more common in men
2. Predilection:
 - a. Long bones; particularly of the lower extremities
3. Major symptom is pain:
 - a. Localized and more severe at night
 - b. May be exacerbated or relieved by movement
 - c. Relieved by non-steroidal anti-inflammatory drugs (block prostaglandin activation of primary nociceptors in the lesion)
 - d. Scoliosis occurs in 70% of patients when it involves the spine:
 - i. The most common cause of painful scoliosis in adolescents particularly if located in the thoracic or lumbar spine
 - e. If located in a pedicle, it may involve the exiting nerve root

Neuropathology

1. A highly vascularized nidus or connective tissue surrounded by sclerotic bone
2. The nidus is approximately 10 mm in diameter which is smaller than that seen in an osteoblastoma

Neuroimaging

1. CT is the best diagnostic modality to visualize the nidus
2. MRI:
 - a. Increased signal intensity on T2-weighted sequences or enhanced T1-weighted sequences
 - i. Correlates with the degree of vascularity of the fibrovascular nidal stroma
 - ii. Correlates with the quantity of osteoid substance within the nidus
 - iii. Visualizes the soft tissue and bone marrow around the nidus

Differential Diagnosis

1. The major tumor to be differentiated is osteoblastoma

Osteoblastoma

General Characteristics

1. Rare benign osteoid-producing primary bone tumor
2. Affects the long bones
3. Males > females most often seen in the second decade
4. 36% occur around the spine

Clinical Manifestations

1. Cervical vertebrae are rarely affected
2. Similar clinical signs and symptoms to osteoid osteoma
3. More aggressive than osteoid osteoma and erosion into the vertebral artery has been reported; blindness has been reported from occlusion of the artery
4. May extend into the neuronal exit foramina

Neuroimaging

1. Similar to that of osteoid osteoma although a major differential point is these lesions are usually larger than 2 cm whereas osteoid osteomas are <2 cm

Osteochondroma

General Characteristics

1. The most common benign bone tumor
2. 35% to 50% of benign bone neoplasms and 10% to 15% of all primary bone tumors

Clinical Manifestations

1. Involvement of the spine occurs in 2 to 5% of patients; male > female 2.5:1
2. Spine involvement is often seen in the setting of multiple osteochondromatosis
3. Usual occurrences are in long bones
4. Usual spine predilection is for cervical or upper thoracic levels
5. Patients described at L4 and L5 with radicular involvement
6. Often asymptomatic

Neuropathology

1. A developmental enchondromatous hyperplasia
2. Formation of cartilage-capped bony protrusions from a bony focus

Neuroimaging

1. CT:
 - a. Differentiates the cartilaginous and bone components of the tumor
2. MRI
 - a. Demonstrates spinal cord or nerve root compression; a lobulated lesion
3. Conventional radiograph:
 - a. Enchondromas present as oval shaped, linear and/or pyramidal osteolytic lesions
 - b. Well defined margins
 - c. Metaphysis and/or diaphysis of long tubular and flat bones

Differential Diagnosis

1. Atypical cartilage tumor
2. Chondroblastoma
3. Chondromyxoid fibroma
4. Ollier disease:
 - a. Enchondromatosis
5. Maffucci syndrome:
 - a. Hereditary multiple exostoses
 - b. Associated multiple cavernous hemangiomas

Hemangioma

General Characteristics

1. Occur primarily in the thoracic spine
2. Usually, they are asymptomatic
3. Symptoms may occur from:
 - a. Epidural extension
 - b. Expansion of the involved vertebra
 - c. Spontaneous epidural extension
 - d. Pathologic burst fracture

Clinical Manifestations

1. Thoracic hemangiomas produce more cord compression than lumbar ones
2. Intracanalicular root compression from extraosseous extension
3. Spinal stenosis from vertebral bone expansion

Neuropathology

1. Hamartomatous proliferation of vascular tissue of endothelial origin
2. Most often in the vertebral body of thoracic and lumbar vertebrae; they may be multiple

Neuroimaging

1. Reduced bone density between denser vertical trabeculae
2. MRI:
 - a. Active lesions have low signal intensity on T1-weighted sequences with high signal intensity on T2-weighted sequences; quiescent lesions have high signal intensity in both sequences

Differential Diagnosis

1. Giant cell tumor
2. Aneurysmal bone cyst
3. Metastasis

Aneurysmal Bone Cyst

General Characteristics

1. A benign non-neoplastic expansile cystic bone lesion
2. Most common location is long bones but approximately 12–30% involve the spine
3. Lumbar spine is the most frequent location followed by the thoracic spine; 2% involve the cervical spine
4. Incidence is 114/100,000 people; age (1–59 years)

Clinical Manifestations

1. Most frequently encountered between 10–20 years of age
2. Most commonly found in the metaphyseal areas of long bone
3. Presenting symptoms:
 - a. Well defined somatic pain, stiffness, and swelling
 - b. Pathologic fracture may cause spinal cord compression and radiculopathy

Neuropathology

1. An expansible, tumor-like osteolytic lesion consisting of blood filled cavities separated by connective tissue septa; there is a surrounding thin cortical bone shell
2. May aggressively destroy and expand bone
3. Usually, a small lesion causes a pathologic fracture of a vertebra

Neuroimaging

1. Arise in the posterior elements of a vertebra and spreads in the pedicles and body
2. May involve the spinal canal
3. CT-3D reconstruction
 - a. Pedicle and vertebral body integrity
4. MRI:
 - a. Multilocular cysts that are fluid filled; T2-weighted sequences have high-intensity signal
 - b. Multiple cysts may have varying signal intensities on T1- and T2-weighted sequences due to different oxidation levels of blood and their breakdown products

Giant Cell Tumor (GCT)**General Characteristics**

1. Comprise approximately 5% of primary bone tumors and approximately 20% of benign bone tumors
2. Slightly higher incidence in females
3. Majority are seen in patients older than 20 years
4. Primary location is the long bones of the extremities; a small proportion occurs in the pelvis, skull and spine

Clinical Manifestations

1. Pain and swelling at the lesion site are the most common symptoms
2. The tumor may be locally aggressive and impinge on a nerve root
3. Skull lesions (often sphenoid and temporal bones, rarely the occiput) produce symptoms by their location

Neuropathology

1. Osteoclastic-like nuclear giant cells in a fibrohistiocytic stroma between osseous spicules
2. May also have foreign body-like giant cells
3. Histiocytes may be positive for CD68
4. Endochondral ossification

Neuroimaging

1. CT:

- a. Ground glass appearance; cystic lesion

- b. Expands bone

2. MRI:

- a. T1-weighted sequence equal intensity with muscle; T2-weighted sequence slightly intense signal

Differential Diagnosis

1. Chondroblastoma
2. Chondrosarcoma
3. Aneurysmal bone cyst
4. Dermoid cyst
5. Eosinophilic granuloma
6. Pigmented villonodular synovitis

Dermoid Cyst**General Characteristics**

1. Congenital non-neoplastic lesions that originate from totipotent ectodermal cells which remain within the developing neural tube
2. Between the 3rd and 5th weeks of gestation
3. In approximately 50% of patients, there is a dermal sinus tract

Clinical Manifestations

1. Cysts are usually intradural in the lumbar and sacral spine
2. Symptoms may occur from tethering of the spinal cord in association with congenital nerve root abnormalities
3. Rupture causes chemical arachnoiditis
4. Infection of the cyst or sinus tract causes meningitis
5. May occur at the site of meningocele repair
6. Rarely they develop after a lumbar puncture or trauma

Neuroimaging

1. MRI:
 - a. T1- and T2-weighted sequences demonstrate variable signal intensities according to the tissue in the cyst

Eosinophilic Granuloma**General Characteristics**

1. Eosinophilic granuloma (EG) is one of the Langerhans cell histiocytosis
2. Incidence of 1:150,000 people/year
3. The most common site is the skull; vertebral involvement is approximately 7%
4. EG is a self-limited disease

Clinical Manifestations

1. Most often patients are younger than 15 years of age
2. In addition to the skull and vertebrae, the pelvis, mandible and ribs may be involved
3. Thoracic vertebrae are most often affected followed by lumbar (35%) and cervical vertebrae (11%)
4. Male to female is 2–5:1
5. Usually, the neurologic deficits are rare:
 - a. Pain may occur at the site
 - b. Spinal cord compression may occur from cervical tumors
 - c. Radiculopathy

Neuropathology

1. Single or multiple skeletal lesions
2. Lung involvement
3. Accumulation of pathologic Langerhans cells
4. Anti-CD1a immunolabeling

Neuroimaging

1. Lytic lesion often with osteoblastic activity on X-ray and CT
2. PET evaluation has 90% sensitivity and a specificity of 65%–80%
 - a. False positive results occur from benign disease with an inflammatory component such as fibrous dysplasia or aneurismal bone cysts
 - b. Low-grade tumors

Rare Benign Bone Lesions That Can Affect the Axial Skeleton with Consequent Radiculopathy

1. Neurofibroma
2. Leiomyoma
3. Chondromyxoid fibroma
4. Fibrous histiocytoma
5. Differential points for malignancy or benignity:
 - a. Pedicle change with expansion is most often malignant
 - b. Normal marrow preservation of a collapsed vertebral body on T1-weighted MRI sequences is most compatible with an osteoporotic fracture

Malignant Bone Tumors of the Lumbosacral Spine**Chordoma****General Characteristics**

1. Rare tumors with an incidence of one/million people
2. Approximately 4% of primary malignant bone tumors and 20% of primary spine tumors
3. Divided into:
 - a. Clival (skull base)
 - b. Sacrococcygeal
 - c. Cervical, thoracic and lumbar
 - d. Almost equal distribution by site
4. Sacrococcygeal tumors have a male predominance of 2:1
5. Brachy gene in chordoma
 - a. A diagnostic marker that differentiates the tumor from myoepithelioma and chondrosarcoma
6. Classification:
 - a. Notochordal hamartomas
 - i. Benign counterpart of chordoma
 - b. Chondroid chordoma:
 - i. 5–15% of all chordomas
 - ii. Spheno-occipital areas of the skull base
 - c. Differentiated chordoma:
 - i. <10% of chordoma
 - d. There is a correlation between the histological characteristic of a chordoma and its ability to metastasize
 - i. Chondroid chordomas are the least aggressive while de-differentiated chordomas are the most aggressive

Clinical Manifestations

1. Sacral chordomas
 - a. May be associated with large exophytic soft tissue masses
 - b. Bowel and bladder dysfunction (sacral roots)
 - c. Severe back pain; painful sacral mass
 - d. Intralesional surgery has a high rate of recurrence

Neuropathology

1. Physaliferous cells are characteristic; foamy appearance of the cytoplasm that contains multiple vacuoles which ultra structurally are divided into smooth-walled and villous
2. Tumors stain for vimentin, the S100 protein, epithelial membrane antigen and low molecular weight cytokeratins
3. Chondroid chordomas:
 - a. Histological features of both chordoma and chondrosarcoma
 - i. Approximately 1/3 of cranial chordomas
 - ii. Express chordoma markers
4. De-differentiated chordoma:
 - a. Sarcomatous regions comprised of spindle-shaped polygonal cells
 - b. Metastasizes late

Neuroimaging

1. MRI:
 - a. T2-weighted sequences demonstrate a hypointense, non-enhancing, interosseous lesion

Liposarcoma**General Characteristics**

1. Liposarcoma is a common adult soft tissue sarcoma composed of three histologic subtypes:
 - a. Well- and de-differentiated
 - b. Myxoid/round cell
 - c. Pleomorphic
2. Z1C1 overexpression
 - a. A transcription factor important for neuronal development

Clinical Manifestations

1. Well-differentiated and de-differentiated liposarcomas occur:
 - a. Retroperitoneum > extremities > paratesticular areas and trunk
2. De-differentiated tumors may metastasize (lungs primarily)
3. Retroperitoneal tumors may be >30 cm and invade viscera and the lumbosacral plexus; local recurrence is common
4. Myxoid/round cell tumors:
 - a. Translocation of chromosome 12 and 16
 - b. Interferes with adipocyte differentiation
 - c. Present in younger patients and its primary location is the proximal lower extremities

- d. Metastasizes to the skeleton
- 5. Pleomorphic liposarcoma:
 - a. Chromosomal gains, losses, duplications, and rearrangements have been described
 - b. Usually, present with lower extremity involvement; rarely the retroperitoneum and mediastinum
- 6. All types may involve lumbar and sacral roots

Neuropathology

- 1. Dependent on subtype
- 2. Pleomorphic liposarcoma resembles a non-adipocytic soft tissue sarcoma (malignant fibrous histiocytoma)
- 3. Myxoid/round cell liposarcoma
 - a. Abundant extracellular myxoid tissue
- 4. Well and de-differentiated tumors:
 - a. Adipocytomas (WD Type)
 - b. DD Types have an adipocyte-rich region that is demarcated from highly cellular spindle cell area

Neuroimaging

- 1. Intradural lesion that may diffusely invade the vertebral bodies and encase the cauda equina

Ewing Sarcoma

General Characteristics

- 1. Primitive neuroectodermal tumors (PNET) and Ewing sarcoma are in the same family of malignant small, round cell neoplasms whose origin is soft tissue or bone
- 2. Usual sites for EWS-PNET are the chest wall, pelvis, and the extremities
- 3. Incidence rate is approximately 3 patients/1,000,000 people
- 4. Approximately 10% of EWS arise in extraskelatal soft tissue
- 5. Caused by rearrangements involving the EWS gene on chromosome 22q 12 and fusion partners from the ETS oncogene family; 95% of EW sarcoma family tumors have fusion of the central exons of the EWSR1 gene (Ewing Sarcoma Breakpoint Region 1)

Clinical Manifestations

- 1. The tumor may arise from the pedicles of L4–5, and L5 S1
- 2. Primarily involves lumbar and sacral roots in the spine
- 3. Cerebral and lung metastasis occur

Neuropathology

- 1. Poorly differentiated small round cell tumors
- 2. ES and PNET represent a single entity
- 3. Light microscopy reveals small round blue cells with hyperchromatic nuclei and minimal cytoplasm
- 4. EWS-PNETs coexpress:
 - a. CD99 (the glycoprotein MIC2) and vimentin

Neuroimaging

- 1. CT scan EWS-PNETs

- a. Heterogeneous masses that invade surrounding tissue including bone

2. MRI:

- a. The mass is isointense to muscle on T1-weighted sequences and hyperintense on T2-weighted sequences

Osteosarcoma

General Characteristics

- 1. Osteosarcoma is the most common primary malignant bone tumor in children and young adults
- 2. Older adults may usually be affected from sarcomatous transformation of Paget's disease of bone
- 3. Incidence of 1/100,000 people

Clinical Manifestations

- 1. Pain and a painful mass lesion
- 2. Pathologic fracture
- 3. Secondary causes include:
 - a. Ionizing radiation
 - b. Hereditary:
 - i. Retinoblastoma
 - ii. Paget's disease of bone
 - iii. Enchondromatosis
 - iv. Hereditary multiple exostoses
 - v. Fibrous dysplasia
- 4. Presents between 5 and 30 years of age; a second peak occurs in the fifth and sixth decade
- 5. Pathologic fracture of vertebrae and compressive myelopathy and radiculopathy

Neuropathology

- 1. A malignant spindle cell neoplasm that produces osteoid
- 2. Classified into 4 subtypes:
 - a. Osteoblastic
 - b. Fibroblastic
 - c. Chondroblastic
 - d. Telangiectatic
- 3. Classification is based on the predominant type of tumor matrix

Neuroimaging

- 1. Radiographs:
 - a. An ill-defined mixed sclerotic and lytic lesion that arises in the metaphyseal region of the involved bone
 - b. Destruction of the bone cortex
 - c. Soft tissue mass with ossification
 - d. Periosteal new bone formation with elevation of the cortex (Codman's triangle)
- 2. CT assessment is superior to MRI for assessment of new bone formation
- 3. MRI:
 - a. T1- and T2-weighted sequences with fat suppression for the extent of bone and soft tissue involvement
 - b. Macroscopic tumor emboli may be found in regional large vessels
 - c. Telangiectatic osteosarcoma may present as a sacral mass

Chondrosarcoma

General Characteristics

1. Less than 10% of chondrosarcomas are in children; 0.5% of low-grade tumors arise from benign chondroid lesions
2. They are 27% of all primary bone tumors
3. Central tumors arise in the medullary cavity or periosteum

Clinical Manifestations

1. Most patients present between 40–70 years of age
2. Patients with Ollier disease, Maffucci syndrome, and hereditary multiple exostoses have a higher incidence
3. Insidious worsening pain that is most pronounced at night
4. Approximately 20% present as a pathologic fracture
5. Primary sites are the shoulder, pelvis or proximal femur
6. Rare spinal compression from pathologic fracture or radiculopathy

Neuropathology

1. Chondrocytes with small to slightly enlarged dense nuclei on a background of chondroid stroma
2. Neoplastic chondrocytes are arranged in lobar cords and clumps which cause endosteal scalloping

Neuroimaging

1. Radiograph:
 - a. An expansile mixed sclerotic and centrally lucent lesion, with a narrow transitional zone and thin sclerotic margin
 - b. Arcs and Wings calcifications
2. CT:
 - a. Non-mineralized portion of the tumor is hypodense to muscle (high water content of hyaline cartilage)
3. MRI:
 - a. Low to intermediate signal intensity on T1-weighted sequences; T2-weighted sequences the lesion is hyperintense

Differential Diagnosis

1. May arise from an osteochondroma
2. Enchondroma (secondary chondrosarcoma)
3. Giant cell tumor
4. Bone cyst

Epidural and Vertebral Metastasis

General Characteristics

1. Metastatic tumors are the most common neoplasms of the intraspinal canal and nerve roots
2. Locations:
 - a. Epidural > leptomeningeal > intraspinal
3. Epidural metastases occur primarily from direct extension of metastatic vertebral tumors; rarely a metastasis grows through the intervertebral foramina or directly metastasizes to the epidural space

4. Radiculopathy is secondary to direct compression by the tumor, metabolic and cytokine expression or a pathologic fracture that compresses the cauda equina
5. Differential diagnosis of common tumors that metastasize to vertebrae:
 - a. Lung
 - b. Breast
 - c. Prostate
 - d. Ovary
 - e. Melanoma
 - f. Renal cell
 - g. Sarcoma
 - h. Multiple myeloma
6. The most frequent sites of metastases are: thoracic > 70%; lumbosacral > 20%; cervical 10%

Clinical Manifestations

1. Local pain is the initial symptom. It is particularly evoked by mechanical stimuli (first percussion over the involved vertebra)
2. Radicular pain:
 - a. Thoracic metastasis usually present with bilateral radicular pain
 - b. Lumbosacral roots most often have a unilateral presentation
 - c. Cervical spine:
 - i. C8–T1 (from Pancoast) tumor or metastasis may present with C8/T1 radicular pain, a Horner's syndrome and anhidrosis or hyperhidrosis
 - ii. C8–T1 innervates the eye and T2 is the level for extremity sympathetic innervations (irritation or destruction)
 - d. Herpes Zoster may be reactivated at the site of the lesion
 - e. Deep boring pain that is worse at night
 - f. Weakness, sensory loss, and atrophy with depressed or absent reflexes at the affected level

Neuroimaging

Solitary Vertebral Collapse

1. Malignant features by MRI:
 - a. Ill-defined lesion margin
 - b. Pedicle involvement
 - c. Heterogeneous enhancement pattern
 - d. Irregular nodular paravertebral soft tissue lesion
 - e. Erosion of the endplate
 - f. Star burst pattern of fracture is more likely traumatic

Benign CT Features of an Acute Vertebral Lesion

1. Cortical fractures of the vertebral body without cortical bone destruction
2. Retropulsion of a bone fragment of the posterior cortex of the vertebral body into the spinal canal
3. Fracture lines within the cancellous bone of the vertebral body

4. Intervertebral vacuum phenomena
5. Thin diffuse paraspinal soft tissue mass

Malignant Features of Spine Lesions by CT and SPECT

1. The posterior portion of the vertebral body is involved
2. Concomitant vertebral body and pedicle involvement
3. Extensive abnormalities that involve the vertebral body and vertebral arch, but spare the pedicle are benign
4. Destruction of the anterolateral or posterior cortical bone of the vertebral body
5. Destruction of the cancellous bone of the vertebral body

Specific Patterns of Metastasis by Tumor Type

Lung Cancer

1. Multiple vertebral levels are involved
2. The most common metastatic lesion
3. Thoracic vertebrae > lumbosacral > cervical spine
4. Cortical and cerebellar metastasis are often concomitant
5. A common cause of carcinomatosis of the meninges
6. Rarely anti-Yo antibodies with paraneoplastic cerebellar degeneration
7. Often bilateral lumbosacral roots are involved

Gastric and Colon Cancer

1. Colon cancer may destroy the sacrum and involve lower sacral roots
2. Kruckenberg metastasis (dropped metastases to the ovaries) from the stomach
3. Associated non-bacterial thrombotic emboli (NBTE) with stroke (mucinous adenocarcinoma is the most common tumor)
4. Extremely dense lesions on neuroimaging (mucin)
5. Hypercoagulable state may be associated

Lymphoma

1. Predilection for paravertebral lymph nodes
2. Intertwines with the lumbosacral roots
3. Often arises in the epidural space with consequent spinal cord compression
4. May be associated with a very dense vertebra

Breast Cancer

1. Multiple vertebral bodies are involved
2. Has been associated with thoracic meningioma (only in women)
3. Carcinomatosis of the meninges is prominent
4. May have delayed onset (years often a bilateral mastectomy)

Prostate Cancer

1. Osteoblastic and lytic bone destruction occur concomitantly
2. Multiple levels are involved
3. May metastasize through the paravertebral venous plexus (no valves; Bateson's plexus to the posterior fossa)

4. Most often radiculopathy and spinal cord compression are the neurological signs (lumbosacral roots)
5. Metastasizes to the petrous apex (Bateson's plexus)
6. Midline vertebral pain

Ovarian Cancer

1. L1–L3 nerve roots > L4–S1
2. Associated with peritoneal implantation (a marble vertebra)
3. L1–L3 > L5–S1 roots; the entire cauda equina may be involved
4. Rare associations:
 - a. Paraneoplastic neuropathy
 - b. Cerebellar degeneration
 - c. Limbic encephalopathy

Melanoma

1. Usually multiple cerebral metastases
2. Unusual adhesive qualities of the tumor allow it to metastasize to the cardiac and intestinal surfaces
3. Almost never solitary
4. Cord compression rather than radicular presentation

Intrinsic Spinal Cord Tumors That Involve the Lumbosacral Roots

Differential Diagnosis

1. Ependymomas (myxopapillary)
2. Glioma of the filum terminale
3. Neurofibroma of the cauda equine
4. Cauda equina tumors:
 - a. Hemangioblastoma
 - b. Paraganglioma
 - c. Ganglioneuroma
 - d. Schwannomatosis
 - e. Neurofibroma

Systemic Disease Affecting Lumbosacral Nerve Roots

1. Diabetes mellitus
 - a. Diabetic amyotrophy (femoral nerve or thoracolumbar plexitis from infarction)
 - b. Vasculopathy of the vasa vasorum
 - c. Clinical features:
 - i. Patients > 60 years of age
 - ii. Present with pain of neuropathic quality
 - iii. Prominent weakness
 - iv. Concomitant weight loss
 - v. Thoracoabdominal nerve root involvement
2. Sarcoid
3. Periarthritis nodosa:
 - a. Proximal L1–L3 nerve root involvement; all roots may be affected
 - b. Asymmetric involvement
4. Meningeal amyloid
5. Acute intermittent porphyria

6. Coproporphyrinuria
7. Variegate porphyria
8. Necrotizing arteritis
9. Hypertrophic pachymeningitis (IgG4)
10. All collagen vascular disease
11. Carcinomatosis of the meninges
12. Mixed collagen vascular disease

Immune-Mediated Processes That Affect Lumbosacral Roots

AIDP

1. May affect proximal, distal and terminal somatosensory afferents
2. May present with apparent radiculopathy

CIDP (Chronic Inflammatory Demyelinating Polyneuropathy)

1. L5–S1 roots may be initially affected

Multiple Sclerosis

1. Affects the dorsal root entry zone at a junction of central and peripheral myelin; anterior horn cell damage
2. Amyotrophy of the affected extremity (several segment involvement as occurring with NMO); gray matter lesions are common in the hemispheres (“black holes”)
3. Some major autoimmune epitopes:
 - a. GM1
 - b. MAG
 - c. GQ1b
 - d. GAL-NAc-GDT/1a
4. Radiculopathy with increased sed rate (usually at L5)
5. Post-vaccination
6. Post-viral infection
7. Acute disseminated encephalomyelitis (an overwhelmingly central demyelinating disease)

Infection Affecting Lumbosacral Roots

1. Herpes Zoster (thoracic; cervical and lumbosacral roots)
2. Brucellosis (L5 roots)
3. Lyme’s disease
 - a. *Borrelia burgdorferi* (spirochete) is the causative organism
 - b. Radiculopathy occurs early in the course of the illness
 - i. May be associated with cranial neuropathy (uni- or bilateral VII, rarely other cranial nerves and meningitis)
 - ii. Single or asymmetric multiple root involvement
4. Chronic radiculopathy:
 - a. Presents months after the initial infection
 - b. Mild motor and sensory loss; not associated with meningitis or VIIth nerve palsy
 - c. Distal paresthesia or radicular pain
5. CMV
 - a. General Characteristics

- i. Affects lumbar and sacral roots
- ii. Most commonly encountered in severely affected HIV patients (CD4⁺ count of <50 mm³)
- b. Clinical Manifestations
 - i. Rapidly progressive cauda equina syndrome
 - ii. Leg weakness, paresthesia and saddle region involvement, sphincter dysfunction that progresses to flaccid paralysis
 - iii. Severe low back pain
 - iv. Polymorphonuclear pleocytosis with elevated protein and viral titers in the CNS; positive PCR
 - v. Gadolinium enhancement on MRI of involved roots in 50% of patients
 - vi. If acute neurologic symptoms and signs need to rule out:
 1. Infection or many other lesions of the cauda equina and conus medullaris
 2. Lymphomatous infiltration of the lumbosacral roots
 3. Syphilis (in an HIV-infected patient)
 4. Herpes simplex (type II with sacral root involvement)
 5. HIV-related polyradiculopathy
 - vii. Herpes virus 8 (lumbar and thoracic roots)
 - viii. EBV (Isolated nerve roots)
 - ix. Tuberculosis (Cold abscess)
 1. L1–L3 roots
 2. Some ethnicities have primarily cervical root involvement (Asian patients)
6. Syphilis:
 - a. Dorsal root entry zone is the site of infection
 - b. Pachymeningitis cervicalis > lumbosacral involvement
 - c. Tabetic pain:
 - i. Thoracic > lumbosacral roots
 - ii. May simulate a thoracic or abdominal visceral emergency
7. HTLV-1:
 - a. Involvement is overwhelming in the cervical cord
 - b. Isolated roots may be involved
8. HIV: L5; sacral roots
9. Spinal epidural abscess
 - a. General characteristics:
 - i. Occurs in the thoracic > lumbosacral > cervical cord
 - ii. Chronic lesions occur in the thoracic cord
 - iii. Infecting organisms:
 1. *Staphylococcus aureus*
 2. Gram-negative rods
 3. Anaerobes
 4. Skin flora (spinal operations)
 5. *Mycobacterium*
 6. Fungi
 - b. Risk factors:
 - i. IV drug abuse
 - ii. Spinal surgery

- iii. Diabetes mellitus
- iv. Epidural steroids:
 - 1. Recent fungal contaminant of steroid injections
- v. Epidural catheters:
 - 1. Prolonged use for neuropathic pain patients
- vi. Immunocompromised patients
- c. Clinical Manifestations
 - i. Onset often occurs with severe back pain; delayed from the onset of the infection
 - ii. Spinal cord compression, infarction or parenchymal infection
 - iii. Deep boring midline pain in the spine with sudden radicular component
 - iv. Cauda equina involvement
 - v. Fever, leukocytosis and elevated sed rate
 - vi. MRI may demonstrate gadolinium enhancement of the involved roots
- a. Severe trauma (often motorcycle accidents)
- b. Most often cervical nerve roots and the brachial plexus are injured
- c. MVA affect lumbosacral roots and the lumbosacral plexus
- 9. Plate fixation and pedicle screw displacement
- 10. Complications of epidural and spinal anesthesia
 - a. General Characteristics
 - i. Toxic effects of anesthetic (usually 0.25% bupivacaine)
 - ii. Direct injury by needle or catheter
 - iii. Subarachnoid injection of anesthetic during epidural procedures
 - iv. Contamination of anesthetics with detergents, chemicals or organisms (bacteria or fungal)
 - v. Epidural abscess
 - vi. Risk of epidural anesthesia is increased with:
 - 1. Lumbar spinal stenosis ("Pooling") of bupivacaine around nerve roots
 - 2. Inadvertent subarachnoid injection of high volume of anesthetic
 - 3. A combination of general and epidural anesthesia
 - 4. Advanced age
 - b. Clinical Manifestations
 - i. Radicular pain and weakness
 - ii. Lower extremity myoclonus and severe spasm
 - iii. Cauda equina syndrome
 - iv. May clear after days to weeks (the cauda equina are peripheral nerves and have regenerative capacity)

Miscellaneous Involvement of Lumbosacral Roots

- 1. Endometriosis
 - a. Endometrial tissue is adherent to pelvic nerve roots (L5–S5)
 - b. Catamenial cyclical pain with bleeds from the aberrant tissue and irritation of the lumbosacral roots
- 2. Laparoscopy for pelvic and abdominal processes
 - a. L1–L3 > involvement than L5–S1 roots
- 3. Epidural catheter trauma
 - a. Prolonged exposure to bupivacaine (directly toxic to the nerve root)
 - b. Direct trauma to the root during catheter insertion
- 4. Arachnoiditis
 - a. General Characteristics
 - i. Clumped scarred nerve roots in the dorsal sac (MRI evaluation)
 - ii. Occurs following multiple surgeries or hemorrhage during myelography with pantopaque. Water-soluble contrast has eliminated this cause
 - b. Clinical Manifestations
 - i. Severe burning pain in several root distributions > motor weakness
 - ii. No exacerbating or relieving factors
 - iii. Asymmetric reflex loss
 - iv. Neurenteric cyst (usually asymptomatic)
- 5. Spina Bifida
 - a. May be associated with congenital defects of the pedicles, facets, and foraminal exit canals
 - b. Conjoined nerve roots
- 6. Myxopapillary Ependymoma
 - a. Asymmetric lumbosacral nerve root involvement
 - b. Lower extremity weakness
 - c. Bowel, bladder, and sexual dysfunction
- 7. Dropped Metastasis
 - a. Medulloblastoma
- 8. Traumatic nerve root avulsion

Differential Diagnosis of Radiculopathy

Differential Diagnosis of Cervical Radiculopathy

- 1. Congenital Defects:
 - a. Abnormalities of the odontoid process ossification centers (C1–C2 roots)
 - b. Failure of odontoid tip fusion (C1–C2)
 - c. Morquio syndrome (atresia of the odontoid process)
 - d. Platybasia (C1–C3)
 - e. Basilar impression (C1–C4)
 - f. Klippel-Feil syndrome (C4–C7)
 - g. Sprengel's deformity with Klippel-Feil syndrome (C4–C7)
 - h. Roos' cervical bands (C4–T1)
 - i. Cervical ribs (C8–T1)
 - j. Thoracic outlet syndrome:
 - i. C5–C6 components of the upper trunk
 - ii. C8–T1 major components of the lower trunk
 - k. Congenital defects of the spinal canal and posterior elements:
 - i. Stenosis of the canal

- ii. Shortened block vertebra
- iii. Vertebral fusions
- iv. Lateral recess trefoil configuration
- 1. Chiari malformation
 - i. High cervical roots suffer a neuropractic injury
- 2. Lax ligaments (hypermobility of the odontoid process) with neuropractic injury of cervical roots and spinal cord compression
 - a. Rheumatoid arthritis
 - b. Trisomy 21
 - c. Marfan's syndrome
 - d. Ehlers-Danlos syndrome
 - e. Type VI collagen defects
 - f. Trauma (rupture of ligaments and odontoid fracture from high impact flexion/extension injuries)
- 3. Ligament Hypertrophy (all cervical roots may be involved)
 - a. Acromegaly
 - b. Mucopolysaccharidoses
 - c. Posterior ligament ossification syndrome
- 4. Pachymeningitis
 - a. Syphilis (now rare; cervical > lumbar > thoracic)
 - b. IgG4 syndrome (a component of idiopathic pachymeningitis)
 - c. Lymphoma (all roots are involved, but predominance is lumbosacral)
 - d. Sarcoid (cervical > lumbar > thoracic)
 - e. Tuberculosis (root site of involvement depends on ethnicity; Asian populations cervical roots > lumbosacral)
 - f. Subarachnoid hemorrhage (lumbar > cervical > thoracic)
 - g. Arachnoiditis (lumbar > cervical)
- 5. Degenerative disease
 - a. Cervical spondylosis (C5–C7)
 - b. Spondylolisthesis (C4–C7)
 - c. Spinal stenosis (C4–C7)
 - d. Disc disease (C4–C5, C5–C6, C6–C7)
 - e. Foraminal exit osteophytes (C3–C4 – C8–T1)
 - f. Facet hypertrophy (uncovertebral joints); C3–T1
- 6. Tumors of Cervical Nerve Roots
 - a. Schwannoma
 - b. Neurofibroma
 - c. Meningioma
 - d. Hemangioma
 - e. Aneurysmal bone cyst
 - f. Osteoid osteoma
 - g. Osteochondroma
 - h. Chordoma
 - i. Ewing's sarcoma
 - j. Osteosarcoma
 - k. Chondrosarcoma
 - l. Pancoast tumor (squamous and adenoma cancer of the lung)
 - m. Lymphoma
 - n. Salivary gland (adenocarcinoma)
 - o. Metastatic (carcinomatosis)
 - p. Post-X-RT (sarcoma of plexus/roots)
 - q. Hodgkin's/non-Hodgkin's lymphoma
 - r. Leukemia (acute with hemorrhage into a root)
 - s. Lymphomatous B-cell
- 7. Immune-mediated radiculopathies of Cervical Roots
 - a. AIDP
 - b. CIDP
 - c. Post-vaccination
 - d. Demyelinating disease (dorsal root entry zone DREZ; components of neuropathy)
 - e. ADEM (acute disseminated encephalomyelitis; overwhelming CNS demyelination rarely DREZ lesions)
 - f. Specific epitopes:
 - i. GM1
 - ii. GAL-NAc-GDT1a
 - iii. GQ1b
 - iv. Gd1b
 - g. Hangman's fractures
 - h. Spondylolisthesis
 - i. Plate fixation/screw displacement
 - j. Epidural catheter trauma (mechanical and from prolonged 0.25% bupivacaine)
 - k. Avulsion of nerve roots (C5–C6; C8–T1)
- 8. Trauma of the Cervical Spine
 - a. "Jumped" facet joints (C3–T1)
 - b. Rotary facet subluxation
 - c. Disc disease (rare; usually degenerative)
 - d. Burst vertebral fracture
 - e. Anterior compression fracture
 - f. Jefferson fracture
 - g. Odontoid fracture (dens) C2
 - h. Atlanto-occipital dislocation
- 9. Infection of Cervical Roots
 - a. HIV
 - b. HTLV-1 I (mixed HTLV-1 and concomitant HIV infection)
 - c. Herpes Zoster
 - d. Herpes simplex
 - e. Brucella (usually L5)
 - f. Bacterial infection (overwhelmingly in the context of epidural abscess or meningitis)
 - g. Staphylococcus aureus (IV drug abuse)
 - h. Gram-negative bacilli (post-surgical procedures)
 - i. Fungal infection:
 - i. Immunocompromised patients
 - ii. Aspergillus
 - iii. Cryptococcus immitis
 - iv. Coccidiomycosis
 - v. Mucormycosis
 - j. Parsonage Turner syndrome (C5–C6) putatively viral
 - k. Poliomyelitis (neuronopathy)
 - l. Enterovirus >1

- m. Coxsackie serotype 6 and 9
- n. West Nile Virus
- o. Hepatitis C
- p. EBV
- q. Adenovirus
- 10. Systemic Diseases that Affect Cervical Nerve Roots
 - a. Diabetes mellitus
 - b. Acute intermittent porphyria
 - c. Variegate porphyria
 - d. Coproporphyrinuria
 - e. IgG4 (pachymeningitis)
 - f. Sicca complex
 - g. Wegener's disease
 - h. SLE
 - i. PAN
 - j. Amyloidosis: FOLMA/FAP-1
 - k. Necrotizing angitis
 - l. Mixed connective tissue disease
 - m. Sarcoid (dural involvement)
 - n. Hyperparathyroidism (vertebral collapse)
- 11. Vascular disease of Cervical Nerve Roots
 - a. AVM involving the nerve root
 - b. Dural AVM
 - c. Dilated vein (overlying the nerve root) with compression
 - d. Klippel-Weber-Trenaunay
- 12. Miscellaneous Disorders that Affect Cervical Nerve Roots
 - a. Plasmacytoma
 - b. Paget's disease (degenerates to osteosarcoma)
 - c. Toxins
 - d. Ankylosing spondylitis

Differential Diagnosis of Thoracic Root Disease

- 1. Trauma
 - a. Compression fracture (Osteoporosis; anterior wedge)
 - b. Burst fracture (thoracolumbar)
 - c. Chance fracture:
 - i. Thoracolumbar
 - ii. Fracture through facets and posterior elements
 - d. Chest surgery
 - e. Jumped facet
 - f. Rotary subluxation of the facet joint
 - g. Chronic regional pain syndrome
 - h. Trauma to T1 and T2
 - i. Spinal cord injury with syrinx
- 2. Infection:
 - a. HZ
 - b. HIV
 - c. Bacterial infection
 - d. In conjunction with epidural abscess
 - e. Tuberculosis (T12–L2)
 - f. Nocardia (immunosuppression)
 - g. Actinomyces (extension from the lung)

- h. Herpes simplex
 - i. Surgical disc space
 - j. Poliomyelitis (neuronopathy)
 - k. Enterovirus
 - l. West Nile Virus
 - m. Coxsackie serotype 6 and 9
 - n. Adenovirus
- 3. Systemic Diseases:
 - a. Diabetes mellitus
 - b. Amyloid
 - c. Sicca complex (Sjögren's disease)
 - d. Homogentisic aciduria (ochronosis)
- 4. Tumor:
 - a. Meningioma
 - b. Neurofibroma
 - c. Schwannoma
 - d. Malignant and benign tumors of bone similar to cervical root disease
 - e. Metastatic disease
 - f. Leukemia and lymphoma
 - g. Carcinomatosis of the meninges
- 5. Immune-Mediated:
 - a. AIDP
 - b. CIDP
 - c. Post-vaccination
 - d. Post-viral infection
 - e. Autoimmune epitopes (similar to cervical root disease)

Differential Diagnosis of Lumbosacral Root Disease

- 1. Congenital Defects
 - a. Conjoined nerve roots
 - b. Scoliosis/kyphosis
 - c. Achondroplasia
 - d. HSM I, III, V (compression of hypertrophied roots)
 - e. Perineural cysts (all lumbar and sacral roots may be affected)
 - f. Congenital spinal stenosis:
 - i. Small canal
 - ii. Short pedicles
 - iii. Trefoil shape
 - g. Lateral recess stenosis (L4–L5; L5–S1)
 - h. Congenital dermoid cyst with paravertebral dermal sinus
 - i. Deep lordotic curve (neuropraxis of L4–L5 roots)
 - j. Meningomyelocele (lumbosacral roots)
 - k. Diastematomyelia (T10–T12)
 - l. Reduplicated cord (L1–S5 roots)
 - m. Achondroplasia (L1–S5)
 - n. Spondylolysis (pars interarticularis defect (L4–L5; L5–S1)
 - o. Sacral agenesis; caudal regression syndrome (L4–S5)
- 2. Degenerative disease Affecting Lumbar and Sacral Roots
 - a. Disc disease (desiccation; hard discs)

- i. Rarely a free fragment extrudes through the posterior longitudinal ligament
 - ii. Schmorl's node (erosion of the midline vertebral vertebrae)
- b. Lateral recess syndrome (osteophyte)
- c. Spinal stenosis (Spondylosis, ligament hypertrophy, facet hypertrophy, vacuum disc disease, bulging annulus fibrosis)
- d. Facet hypertrophy (superior facet that rotates into the foraminal exit canal)
- e. Juxta-articular cysts:
 - i. From the synovium
 - ii. Ligamentum flavum
- f. Osteophyte formation in the foraminal exit canal
- g. Degenerative spondylolisthesis
3. Bone Tumors of Lumbosacral Vertebrae:
 - a. Osteoid osteoma
 - b. Enchondroma
 - c. Osteochondroma
 - d. Aneurysmal bone cyst
 - e. Hemangioma/hemangioblastoma
 - f. Brown tumor (hyperparathyroidism)
 - g. Dermoid
 - h. Giant cell tumor
 - i. Chordoma
 - j. Osteosarcoma (evolution from Paget's disease of bone)
 - k. Chondrosarcoma
 - l. Liposarcoma
 - m. Ewing's sarcoma
 - n. Metastatic disease
4. Cancer Affecting Lumbosacral Nerve Roots:
 - a. Carcinomatosis of the meninges (possible with all cancer)
 - b. Leukemia:
 - i. Acute (hemorrhage into a nerve root)
 - ii. Chronic (infiltration)
 - c. Hodgkin's and non-Hodgkin's lymphoma
 - d. Liposarcoma
 - e. Myxopapillary ependymoma
 - f. Dropped metastasis (medulloblastoma)
 - g. Metastasis from any solid tumor
5. Systemic disease:
 - a. Diabetes mellitus
 - i. Amyotrophy (partial femoral nerve infarction)
 - b. Vasculitis (primarily L2, L3, L4)
 - c. Connective tissue disease (similar to cervical and thoracic roots)
 - d. Amyloid
 - e. Acute intermittent, variegate and coproporphyrinuria
 - f. Endometriosis
 - g. Sarcoid
 - h. Retroperitoneal hemorrhage (trauma, bleeding diathesis and anticoagulation)
6. Immune disease (Similar to Cervical Root disease)
7. Toxins/Anesthesia
 - a. Epidural anesthesia (bupivacaine 0.25%; usually prolonged epidural catheter for severe pain of at least 3 days duration)
 - b. Pantopaque contrast (rarely relevant today due to water soluble contrast agents used for myelography)
 - c. Metronidazole (contrast)
8. Trauma of Lumbosacral Roots
 - a. Chance fracture (thoracolumbar)
 - b. Compression fracture (Wedge)
 - c. Burst/fracture (thoracolumbar)
 - d. Sacrum ala compression
 - e. Laparoscopic procedures (higher L1–L3 roots > L5–S1)
 - f. Instrumentation (plate and pedicle screw placement)
 - g. Obstetrical and GYN Surgery (retraction injury of upper lumbar roots)
 - h. Hip replacement surgery (L4–S1)
 - i. Decompressive laminectomy
9. Vascular disease (similar to cervical and thoracic roots)
10. Infection
 - a. Cytomegalic virus infection of the lumbosacral roots in late stage HIV patients
 - b. Brucellosis (L5 root)
 - c. Lyme's disease (L5 root)

Further Reading

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Chapter 6

Plexus

Cervical Plexus

Overview

The cervical plexus is derived from the anterior primary rami of C1–C4. It lies behind the sternocleidomastoid muscle and anteriorly to the scalenus medius and levator scapulae muscles. It forms anastomotic loops that are related to the spinal accessory (XI) and hypoglossal nerves (XII).

Its terminal cutaneous branches are:

1. The greater occipital nerve (C2) which innervates the skin of the posterior scalp
2. The lesser occipital nerve that innervates the mastoid process and lateral head; the mastoid innervations overlap that of the sensory innervation from cranial nerve VII
3. The greater auricular nerve (C2–C3) which innervates:
 - a. The skin of the lower cheek and the mandible (overlaps V2, V3)
 - b. The auriculotemporal and buccinator terminal nerves of cranial nerve V
 - c. It also innervates the neck below the external ear
4. The cutaneous branches of the transverse colli nerves (C2–C3) which innervate the neck (primarily anteriorly)
5. The supraclavicular nerve (C3–C4) which innervate the skin of the supraclavicular fossa (immediately above the clavicle)
6. C1 is a purely motor root
7. Anatomical variants include:
 - a. Great auricular nerve communication with the mandibular nerve
 - b. Spinal accessory nerve communication with C2

The innervations of the muscular branches of the cervical plexus include:

1. A loop formed by C1 which curves with the hypoglossal nerve and joins the fibers from C2 and C3 roots that innervate infrahyoid muscles:
 - a. Sternohyoid
 - b. Omohyoid
 - c. Sternothyroid
 - d. Thyrohyoid
 - e. Geniohyoid

These muscles are synergistic in head flexion and swallowing physiology:

1. The phrenic nerve which innervates the diaphragm (C3–C5); C4 is the dominant root
2. Branches to the middle scalene (C3–C4) that affects:
 - a. Lateral neck flexion
 - b. Levator scapulae muscles (C3–C4); rotation of the scapula
3. Branches to the spinal accessory nerve that include:

- a. C2 to the sternocleidomastoid muscle
 - b. C3–C4 to the trapezius muscle
 - c. These branches course with CNXI
4. Swallowing function
 - a. Hyolaryngeal complex

Hyolaryngeal Complex

An important component of the pharyngeal phase of swallowing is the elevation of the hyolaryngeal complex. This is accomplished by the submental muscles (mylohyoid, geniohyoid and anterior digastric and the thyrohyoid muscles). Hyolaryngeal elevation displaces the larynx above the food bolus, shortens the pharynx and opens the upper esophageal sphincter. The hyolaryngeal complex is comprised of the hyoid bone, thyrohyoid membrane and the laryngeal cartilages that are the attachment site for the cricopharyngeus muscle; the cricopharyngeus muscle forms the upper esophageal sphincter. Other muscles that may contribute to the elevation of the hyolaryngeal complex are the posterior digastrics, stylohyoid, and long pharyngeal muscles.

Anatomically, an anterior and posterior sling of muscles suspends the hyolaryngeal complex and along with the thyrohyoid muscle, elevates it during swallowing. The anterior component of the sling is composed of the mylohyoid, geniohyoid, and anterior digastric muscles that insert on the hyoid bone. The posterior digastricus and stylohyoid may also contribute to the anterior sling. The posterior ring is composed of the long pharyngeal muscles that include the stylopharyngeus, salpingopharyngeus and palatopharyngeus muscles that are stabilized by the levator veli palatini. The distal posterior ring muscles insert on the posterior edge of the thyroid cartilage and lateral pharyngeal walls proximal to the upper esophageal sphincter. The thyrohyoid muscle is intrinsic to the hyolaryngeal complex and approximates the thyroid and hyoid bone.

In summary, the submental muscles (mylohyoid, geniohyoid, and anterior digastric) and the thyrohyoid muscle primarily elevate the hyolaryngeal complex that opens the upper esophageal sphincter during the pharyngeal phase of swallowing. The ansa hypoglossi of the cervical plexus is pivotal in the innervations of many of the muscles required for the pharyngeal phase of swallowing.

Clinical Presentations of the Sensory Components of C2–C4 Branches of the Cervical Plexus

The Greater Occipital Nerve

General Characteristics

1. Innervates the skin of the occiput (posterior scalp)

Clinical Manifestations

1. Pain and paresthesias in the cutaneous territory it innervates
2. Severe C2 irritation:
 - a. Pain projected to the brow and behind the eyes
 - b. A frequent trigger of unilateral migraine headaches

Neuropathology

1. Entrapped by the semispinalis and trapezius muscle
2. Neurofibroma
3. Direct trauma

Neuroimaging

1. Ultrasound

*The Lesser Occipital Nerve***General Characteristics**

1. Pain and paresthesias of the mastoid, lateral and posterior head and lower portion of the occiput

Clinical Manifestations

1. Often symptoms in the C2 distribution primarily

Neuropathology

1. Associated with flexion-extension or rotary injury of the neck (motor vehicle accidents, falls, and athletic injuries)
2. Very frequently associated with upper trunk (C5–C6) brachial plexus traction injuries
3. Lacerations
4. Surgical procedures of the posterior triangle of the neck

*The Great Auricular Nerve C2–C3***General Characteristics**

1. Roots are C2–C3; overlaps the auriculotemporal nerve of the Vth cranial nerve as well as components of V2 and V3

Clinical Manifestations

1. Paresthesias and pain in the lower cheek, lower pinna of the external ear (overlaps the auriculotemporal nerve of the Vth cranial nerve)
 - a. Irritation of this nerve causes:
 - i. Neurogenic inflammation and vasodilation of the pinna; the probable genesis of the “red ear” syndrome (C3 root is involved)
 - ii. C-fibers within the nerve release substance P (which interacts with mast cells that release histamine) and calcitonin gene-related peptide. The former (SP) causes endothelial plasma leakage and the latter (CGRP) vasodilation of the affected vessels

Neuropathology

1. Damaged during surgical procedures to the neck or face:
 - a. Facelift
 - b. Parotid surgery
 - c. Carotid endarterectomy
 - d. Traction injury from MVA
 - e. Lacerations

Neuroimaging

1. Ultrasound guided

*Transverse Colli Nerves***General Characteristics**

1. Innervation of the anterior and upper neck (C2–C3 roots)

Clinical Manifestations

1. Pain in the anterior and upper neck

Neuropathology

1. Trauma (flexion, extension, and rotary neck injuries)
2. Surgical procedures in the neck

Neuroimaging

1. Ultrasonography

*Supraclavicular Nerves***General Characteristics**

1. Innervate the supraclavicular fossa and clavicle
2. May innervate the anterior chest wall to T2

Clinical Manifestations

1. Paresthesia and pain in its innervations territory
2. May give a false level following spinal cord injury

Neuropathology

1. Flexion-extension and rotary neck injuries (MVA and falls)
2. Biopsy of lymph nodes
3. Supraclavicular approach for first rib removal or neurectomy of the upper trunk of the brachial plexus in thoracic outlet surgery

Neuroimaging

1. Ultrasonography

Injury of the Motor Roots of the Cervical Plexus (Ansa Hypoglossi)*Ventral Root of C2***Clinical Manifestations**

1. Inability to elevate the hyolaryngeal complex during the pharyngeal component of swallowing:
 - a. Failure to adequately open the upper esophageal sphincter
 - b. Aspiration pneumonia
 - c. Weakness of infrahyoid muscles
2. Middle scalene muscle weakness
 - a. Decreased anterior and lateral head flexion
3. Weakness of the sternocleidomastoid muscle:
 - a. Depressed rotation of the head contralaterally
4. Weakness of the trapezius muscle:
 - a. Depressed shoulder elevation

*The Phrenic Nerve***General Characteristics**

1. Spinal accessory component (C2 innervation) involvement weakens the lateral half of the diaphragm
2. An anatomic variant in which the phrenic nerve receives an anatomic branch from the subclavian nerve; the diaphragm may be normal in this instance with a proximal phrenic nerve lesion

Clinical Manifestations

1. Unilateral paralysis causes dyspnea on exertion but not at rest
2. Bilateral phrenic nerve paralysis causes severe dyspnea on exertion and may lead to alveolar hypoventilation and hypercarbia

Neuropathology

1. May be involved with viral infections that include Parsonage-Turner syndrome or neuralgia amyotrophica
2. Rarely involved with traction injury but not infrequently damaged with scalenectomy and neurolysis procedures in thoracic outlet surgery (lies adjacent to the middle scalene muscle)
3. Aortic aneurysm (compression)
4. Intrathoracic neoplasm (infiltration)
5. Enlarged mediastinal lymph nodes
6. Subclavian vein or internal jugular vein catheterization (direct trauma)
7. Central vein catheter placement
8. Breast cancer (neck metastasis); if associated with damage to the sympathetic chain and recurrent laryngeal nerve it is Payne syndrome
9. Injured during coronary by-pass surgery (neuropraxis or dissection of the internal mammary artery)
10. Clipped in association with the inferior vena cava during liver transplantation
11. Amyotrophic lateral sclerosis
12. Diabetes mellitus
13. Critical care neuropathy (difficulty removing a patient from mechanical ventilation)
14. Mediastinal X-RT
15. Herpes Zoster
16. AIDP
17. Hypophosphatemia

Neuroimaging

1. X-ray
 - a. Elevated diaphragm on the affected site
2. The diaphragm paradoxically moves upward with inspiration (fluoroscopy)

Pharyngeal Plexus*General Characteristics*

1. Lies in the retropharyngeal space between:
 - a. Anteriorly:
 - i. Superior and middle pharyngeal constrictor muscles
 - b. Posteriorly:
 - i. Longus capitis and colli muscles
 - ii. Prevertebral fascia
 - iii. Second and third cervical vertebrae
2. Composed of:
 - a. Sensory fibers of IX and X
 - b. Motor fibers of IX and X

3. Experimental information suggests:

- a. Stimulation of the pharyngeal plexus elicits vocal cord adduction
- b. Glottic closure reflex is affected (in porcine model) by the inferior superior laryngeal nerve. Some studies reveal that the external branch of the superior laryngeal nerve, the communicating nerve of Galen and the recurrent laryngeal nerve also may play a role in the innervations of the thyroarytenoid muscle (pivotal in the glottic closure reflex)
- c. The lingual branches of the glossopharyngeal nerves are thickened and course through a slit between the constriction pharyngis superior and medius muscles, where they may be compressed

Clinical Manifestations

1. Failure of the glottic closure reflex affected by the thyroarytenoid muscle (reflex)
2. Complaints that food gets stuck in the back of the throat and difficulty initiating deglutition

Neuropathology

1. Direct injury from surgical and dental procedures
2. Head and neck X-RT for malignancy
3. Associated with brachial plexus and cervical plexus neuropractic injuries

Neuroimaging

1. MRI (primarily utilizing defined landmarks rather than direct visualization of the plexus)

The Brachial Plexus*Overview*

The brachial plexus derives from the anterior primary rami of spinal segments C5, C6, C7, and T1. It is approximately 0.5 cm long in adults and extends from the spinal column to the axilla. Its detailed anatomy in this course is important as to which of its components are injured or affected by its varied pathologies. It is divided into roots, trunk, division, cords and branches. The C5–C6 roots coalesce to form the upper trunk; the C7 primary anterior ramus forms the middle trunk and the anterior primary rami of C8–T1 the lower trunk. In approximately 60% of patients, the C4 spinal root is a component of the upper trunk. In this instance, the plexus is prefixed, as all of the spinal root contributions are placed up one level. In this situation, the T1 spinal root of the lower trunk is less prominent. In approximately 7% of patients, C5 contributes minimally to the plexus and spinal roots are shifted down one level. If this occurs, T2 contributes to the lower trunk and C7 to the upper trunk.

The C5–C6 roots course downward and coalesce to form the upper trunk between the scalenus medius and scalenus anterior muscles. The anterior division of the upper and middle

trunk fuses and forms the lateral cord, while the anterior division of the lower trunk becomes the medial cord. The three posterior divisions of the upper, middle, and lower trunks form the posterior cord.

The brachial plexus is in close proximity to mobile components of the neck and shoulder that make it susceptible to traction injuries. The trunks are superficial in the supraclavicular fossa. The lower trunk is adjacent to the subclavian artery and the apex of the lung. The divisions of the plexus are retroclavicular and lie between the clavicle and the first rib. Infraclavicularly, the cords surround the axillary artery and are close to the proximal humerus and the glenohumeral joint. Cords are situated below the clavicle in the axilla and are the longest components of the plexus. There are anatomic variations between the cords.

The spinal nerves derived from the cords and trunks may be purely sensory, motor or mixed sensory motor. The nerves that arise directly from spinal roots include the dorsal scapular nerve, the long thoracic nerve and a branch to the phrenic nerve. The subclavian and suprascapular nerves arise from the upper trunk. The subscapular and thoracodorsal nerves arise from the posterior cord that terminates as the axillary and radial nerves. The proximal medial cord gives rise to the motor branch that innervates the pectoral muscle. The distal medial cord gives rise to the medial brachial and medial antebrachial cutaneous nerves. The medial cord gives a small branch to the median nerve and makes up the ulnar nerve. The proximal portion of the lateral cord gives rise to the lateral pectoral nerve. The termination of the lateral cord is the musculocutaneous nerve. It also gives off a lateral branch that joins the branch from the medial cord to form the median nerve.

The median, ulnar, radial, axillary nerves take origin in the peripheral axilla. The proximal portions of the median, ulnar and radial nerves are adjacent to the proximal humerus and the axillary artery. Plexus trunks form at the lateral border of the anterior and middle scalene muscles.

The major blood supply of the brachial plexus derives from the subclavian artery. The supraclavicular components of the plexus are supplied by the ascending cervical, deep cervical and the superior intercostal arteries. The roots are supplied by branches from the vertebral artery. The infraclavicular plexus and cords are supplied by the subclavian, axillary, and subscapular vessels.

Terminal Nerves That Arise from the Cervical Roots

1. The phrenic nerve
 - a. As noted earlier, the major root that innervates the diaphragm is C4. It receives contributions from C3 and C5. The phrenic nerve crosses the anterior scalene muscle to enter the thorax
2. Dorsal Scapular Nerve: Arises from the C5 nerve root immediately after it emerges from the intervertebral foramen, courses between the middle and posterior scalene muscle to innervate the levator scapular and the major and minor rhomboid muscles

3. The long thoracic nerve arises from the C5, C6 and C7 roots, descends along the lateral chest wall to innervate the serratus anterior muscle

Nerves That Arise from Brachial Plexus Trunks

Suprascapular Nerve

1. The suprascapular nerve arises from the upper trunk, descends posteriorly between the omohyoid and the trapezius muscle, through the scapular notch to innervate the supra- and infraspinatus muscles
2. Nerve to the subclavius muscle: May arise from the C5 root or the upper trunk to innervate the subclavius muscle that lies between the clavicle and the first rib
3. Medial pectoral nerve: Arises from the medial trunk whose major roots are C8 and T1. It innervates the pectoralis major and minor muscles

Nerves That Arise from the Brachial Plexus Cords

Lateral Pectoral Nerves

The major roots contributing to the nerve are C5, C6, and C7. The nerve usually arises from the lateral cord.

Anatomic variations occur and include:

1. Origin from the anterior division of the upper and middle trunks

Subscapular Nerves

The primary roots of the nerves are C5 and C6. The upper and lower subscapular nerves arise from the posterior cord in the axilla. The subscapularis nerve innervates the subscapularis muscle; the lower subscapular nerve innervates both the subscapularis and the teres major muscles.

Thoracodorsal Nerve

The major roots comprising the nerve are from C5–C7. The primary root is C7. The nerve takes origin from the posterior cord to innervate the latissimus dorsi muscle.

Anatomic variants include origins from:

1. The radial nerve
2. The axillary nerve

Medial Cutaneous Nerve of the Arm

The nerve originates from the medial cord to innervate the medial upper arm above the elbow.

Medial cutaneous nerve of the forearm usually arises from the medial cord. An anatomic variant is an origin from the medial cutaneous nerve of the arm. It innervates the medial forearm to the wrist.

Musculocutaneous Nerve

The musculocutaneous nerve is the termination of the lateral cord. It innervates the coracobrachialis, biceps brachii, and the brachialis muscles. Its major contributing roots are C5 and C6. In some patients, there is a contribution from C7. It terminates as the lateral cutaneous nerve of the lateral forearm from the elbow to the wrist.

A lateral branch fuses with a branch from the medial cord to form the median nerve.

An anatomic variant in a small number of patients includes:

1. An origin of the nerve from the anterior division of the upper trunk
 - a. In this instance, the lateral branch to the median nerve arises from the middle trunk

Axillary Nerve

The axillary nerve is one of the terminal branches of the posterior cord and is primarily composed of the C5 and C6 spinal nerves. It transverses the quadrilateral space (teres major inferiorly, triceps laterally, the humerus medially, and the teres minor superiorly). It innervates the teres minor and deltoid muscles. Its cutaneous branches innervate the lateral proximal arm over the deltoid muscle.

Radial Nerve

The spinal nerves that comprise the radial nerve are from C5–C8. T1 contributes in approximately 10% of patients. It is the termination of the posterior cord. A branch arises in the axilla, the posterior cutaneous nerve, which innervates the posterior upper arm to the elbow. In the upper arm, it descends medially to the humerus between the medial and long heads of the biceps muscle in the spiral groove. Its branches in the upper arm innervate the medial, lateral, and long heads of the triceps brachii and the anconeus muscle. At the lateral aspect of the upper arm (often exiting the spiral groove), it innervates the brachioradialis, extensor carpi radialis longus and a small component of the brachialis muscle (whose main innervation is the musculocutaneous nerve). It gives off the posterior antebrachial cutaneous nerve that innervates the posterior forearm. At the elbow, it divides into the sensory superficial radial nerve and the motor posterior interosseous nerve. The posterior interosseous nerve transverse the radial tunnel at the elbow that is composed of the radius, the capsule of the radiocapitular joint and the tendons of the biceps brachii and brachialis muscles medially and the brachioradialis, extensor carpi radialis and the extensor carpi ulnaris that form the anterior and lateral walls. A fibrous band around the superficial head of the supinator muscle forms the Arcade of Frohse that is the end of the radial tunnel. The superficial radial nerve travels into the forearm underneath the brachioradialis muscle outside of the radial tunnel. The nerve innervates the extensor surfaces of the hand and fingers (with the exception of the fingertips that are innervated by the median and ulnar nerves) as well as the medial dorsal hand and medial fingers that are innervated by the dorsal ulnar cutaneous nerve. The posterior interosseous nerve courses through the radial tunnel and descends under the Arcade of Frohse. It innervates the supinator, extensor digitorum communis, extensor digiti minimi, extensor carpi ulnaris, abductor pollicis longus, extensor pollicis longus and brevis and the extensor indicis proprius.

Median Nerve

The median nerve is composed of spinal nerves C5–T1 and is formed from the fusion of branches of the medial and lateral cords. Its sensory components are primarily derived from spinal segments C6 and C7. Rarely the C5 spinal segment is a component of the nerve. Sensory fibers arise from the upper and middle trunks to the lateral cord. Motor fibers course through all of the trunks and the medial and lateral cords. The median nerve reaches the antecubital fossa through the anterior compartment of the upper arm. It passes through the two heads of the pronator teres muscle and between the flexor digitorum superficialis and profundus muscles to reach the wrist. It innervates the pronator teres, flexor carpi radialis, palmaris longus, and flexor digitorum superficialis from branches given off in the forearm. It gives off the purely motor anterior interosseous nerve that innervates the flexor digitorum profundus 1 and 2, flexor pollicis longus and the pronator quadratus muscle. Prior to entering the carpal tunnel at the wrist, it gives off the palmar cutaneous nerve that innervates the thenar eminence. The nerve then enters the carpal tunnel that is composed of the carpal bones and a dorsal transverse ligament. It also contains nine flexor tendons to the fingers as well as the median nerve. Either within or just distal to the tunnel the recurrent branch of the nerve arises to innervate the abductor pollicis brevis, opponens pollicis, and the superficial head of the flexor pollicis brevis. The nerve supplies the first and second lumbrical muscles and digital branches to the volar and dorsal tips of the thumb index and long finger as well as the medial one-half of the ring finger.

Ulnar Nerve

The ulnar nerve is comprised primarily of spinal nerves C8 and T1, but in over 50% of patients, there is a contribution from the C7 spinal nerve that innervates the flexor carpi ulnaris muscle. This innervation derives from a branch of the lateral cord. The nerve is the termination and then continuation of the medial cord. It descends anteriorly to the teres major and latissimus dorsi muscles to enter the upper arm. It courses down the posterior compartment of the upper arm to the ulnar groove of the elbow. The ulnar groove comprises the medial epicondyle of the humerus and the olecranon process of the ulna. The ulnar collateral ligament bounds it inferiorly. Distal to the ulnar groove (1–2.5 cm), the nerve courses under a fibrous aponeurosis that connects the humeral and ulnar heads of the flexor carpi ulnaris muscle. The ulnar groove and the aponeurosis form the cubital tunnel. There are no branches from the ulnar nerve in the upper arm. The nerve traverses between the flexor carpi ulnaris and flexor digitorum profundus to the wrist. Its forearm branches innervate the flexor carpi ulnaris and the flexor digitorum profundus III and IV. The dorsal ulnar cutaneous nerve innervates the dorsum of the medial hand and fourth and fifth fingers. Prior to entering Guyon's canal at the wrist, it gives off the palmar branch that gives sensory innervation to the hypothenar eminence and innervates the palmaris brevis muscle. Guyon's

canal is formed radially by the hook of the hamate bone and the pisiform bone on its ulnar side, the pisohamate ligament inferiorly and the transverse carpal ligament superiorly. Either within or immediately distal to Guyon's canal the ulnar nerve gives off its terminal branches. The superficial sensory branch innervates the volar components of the fifth finger and the ulnar half of the fourth finger as well as the dorsal distal aspects of these digits. The deep motor branch of the ulnar nerve innervates the hypothenar muscles, the third and fourth lumbricals, the interossei, adductor pollicis and the deep head of the flexor pollicis brevis muscle.

Clinical Manifestations of Brachial Plexus Disorders

1. Supraclavicular Level:
 - a. Supraclavicular lesions present in myotomal and dermatomal distributions
 - b. Cervical root derived terminal nerves:
 - i. Phrenic nerve (C3–C5); C4 is the predominant root
 - ii. Dorsal scapular nerve:
 1. Arises from the C5 root as it exits the intervertebral foramen
 2. Innervates the major and minor rhomboid muscles and the levator scapuli
 3. The muscles pull the scapulae medially, rotate it and hold it against the chest wall
 - iii. Long thoracic nerve:
 1. Arises from C5, C6 and C7 spinal nerves
 2. Innervates the serratus anterior muscle
 3. Function:
 - a. Pulls the scapula forward around the thorax to achieve anteversion of the arm
 - b. Compresses the scapula against the wall of the thorax
 - c. Assists with elevation of the ribs with respiration
 - d. A component of arm elevation
 - e. Protraction of the scapula
 - f. Role in upward rotation of the scapula in synchrony with the trapezius muscle
 - c. Upper trunk lesions:
 - i. Suprascapular nerve
 1. Arises from the upper trunk immediately after it forms
 2. Function:
 - a. Abducts the arm at the shoulders, it is the main agonist of this movement for the first 10–15 degrees of its arc. Beyond 30 degrees the deltoid muscle is the primary arm abductor
 - b. Stabilizes the shoulder joint by effecting pressure medially that helps to hold the humeral head in the glenoid fossa
 - c. Provides sensory innervations to the acromioclavicular and glenohumeral joints

- d. The infraspinatus muscle:
 - i. Externally rotates the humerus
 - ii. Stabilizes the shoulder joint
- e. Diagnostic points:
 - i. Lesions at the level of the formation of the trunks:
 1. The serratus anterior and the rhomboids are normal
 2. Lesions at mid or upper trunk segments:
 - a. The supra- and infraspinatus muscles are normal

Lateral Cord Lesions

1. Lateral pectoral nerves:
 - a. Most often arise from the lateral cord. Anatomic variants are its origin from the anterior division of the upper and middle trunks
 - b. Function:
 - i. Innervates the pectoralis major muscle that is also innervated from the medial pectoral nerve
 - ii. Flexion and adduction of the humerus
 - iii. Rotates the humerus medially
 - iv. Sensory innervations of the anterior chest wall

Musculocutaneous Nerve

1. Most often is the termination of the lateral cord:
 - a. Gives off a branch that combines with a branch from the medial cord that forms the median nerve
 - b. Its major spinal nerves are C5 and C6 although there is a contribution from C7 in greater than 50% of patients
2. It innervates:
 - a. Coracobrachialis
 - b. Biceps brachii
 - c. Brachialis
 - d. Forms the lateral cutaneous nerve of the forearm
3. Function:
 - a. Coracobrachialis:
 - i. Flexes and adducts the arm
 - ii. Medial rotation of the humerus
 - iii. Stabilization of the humeral head within the glenoid fossa
 - b. Biceps brachii:
 - i. Supination of the forearm
 - ii. Flexion of the forearm
 - iii. Minor functions:
 1. Forward flexion of the shoulder
 2. Aids abduction of the arm
 3. Short head contributes to adduction of the arm
 4. Stabilization of the shoulder
 - iv. Lateral cutaneous nerve of the forearm
 1. Sensation from the lateral elbow to the wrist (laterally)

Medial Cord

1. Medial pectoral nerve:

- a. Innervates both the pectoralis major and minor muscles
- b. Function:
 - i. Adduction and medial rotation of the arm
 - ii. Poland syndrome (congenital absence of the muscle) may be asymptomatic
- 2. Medial cutaneous nerve of the arm
 - a. Provides sensation to the medial upper arm to the elbow
- 3. Medial cutaneous nerve of the forearm:
 - a. May arise from the medial cutaneous nerve of the arm
 - b. Function:
 - i. Innervates the medial forearm to the wrist

Posterior Cord

- 1. Thoracodorsal Nerve:
 - a. Most often arises from the posterior cord. Rarely its origin is the radial or axillary nerves
 - b. Its major spinal nerve is C7, but it receives contributions from C5 and C6
 - c. Function:
 - i. Extension and adduction of the arm
 - ii. Horizontal abduction of the arm
 - iii. Internal rotation
 - iv. Flexion from an extended position
 - v. Synergistic for extension and lateral flexion of the lumbar spine
- 2. Suprascapular nerves:
 - a. The upper suprascapular nerve innervates the subscapularis muscle. Derived from C5, C6 spinal nerves
 - b. Function:
 - i. Rotates the head of the humerus medially
 - ii. Draws the humerus forward and downward if the arm is raised
 - iii. Prevents displacement of the humerus

Lower Subscapular Nerve

- 1. Supplies the lower part of the subscapularis muscle as well as the teres major
- 2. Its spinal nerves are C5 and C6
- 3. Function:
 - a. The subscapularis is the major and most powerful muscle of the rotator cuff
 - b. Stabilizes the glenohumeral joint

Axillary Nerve

- 1. One of the terminal branches of the posterior cord. Its spinal nerves are C5 and C6. It innervates the teres minor and deltoid muscles. Its sensory innervation is the lateral proximal arm over the deltoid muscle
- 2. Function of the deltoid muscle:
 - a. Anterior fibers:
 - i. Shoulder abduction
 - ii. Medial rotation of the humerus
 - b. Posterior fibers:
 - i. Transverse extension
 - ii. Lateral rotation

- c. Lateral fibers:
 - i. Shoulder abduction
 - ii. Stabilizes the humeral head
- 3. Teres minor muscle:
 - a. Part of the rotator cuff that stabilizes the humeral head in the glenoid fossa
 - b. Is synergistic with the posterior fibers of the deltoid to laterally rotate the humerus
 - c. Transverse adduction and extension of the arm

Radial Nerve

- 1. The continuation of the posterior cord following branching of the axillary nerve. Its major spinal nerves are C5–C8 although approximately 10% of patients have a contribution from T1
- 2. Innervates:
 - a. The long, medial and lateral head of the triceps and the anconeus muscle
 - b. Brachioradialis, extensor carpi radialis longus and the brachialis (major innervations is from the lateral cord)
 - c. In the axilla, it gives off the posterior cutaneous nerve that innervates the posterior arm to the elbow. The posterior antebrachial cutaneous nerve innervates the posterior forearm. The superficial radial nerve innervates the extensor surface of the hand and fingers except for the distal fingertips. The dorsal ulnar cutaneous nerve supplies the dorsal medial hand and medial fingers
 - d. In the forearm it innervates the extensor carpi radialis brevis, supinator, extensor digitorum communis, extensor digiti quinti, extensor carpi ulnaris
 - e. Above the wrist branches innervate the abductor pollicis longus, extensor pollicis longus and brevis and the extensor indicis
 - f. In the hand, it gives off dorsal digital nerves
 - g. At the elbow the motor posterior interosseous nerve

Function of the Radial Nerve

Triceps Muscle

- 1. Primary extensor of the elbow joint
- 2. Fixates the elbow when the hand is used
- 3. Long head:
 - a. Used for sustained force
 - b. Synergistic for control of the shoulder and elbow
 - c. Retroversion and adduction
- 4. Lateral head
 - a. High-intensity force
- 5. Medial head:
 - a. Used during low force precise hand movements

Anconeus Muscle

- 1. Assists in elbow extension and supports the elbow in full extension
- 2. Protects the elbow joint capsule in the olecranon fossa during extension of the elbow
- 3. Abducts the ulna

Brachioradialis Muscle

1. One of the few muscles that receives innervations directly from the radial nerve (the triceps, anconeus, and extensor carpi radialis are the others). The other radial nerve innervated muscles receive their innervations from a deep branch of the nerve
2. Function:
 - a. Flexes the forearm at the elbow
 - b. Stabilizes the elbow during rapid flexion and extension
 - c. Synergistic with the brachialis and biceps muscles

Supinator Muscle

1. Curved around the upper 1/3 of the radius and innervated by the deep branch of the radial nerve
2. Function:
 - a. Supinates the forearm

Extensor Carpi Radialis Longus

1. Innervated by the radial nerve. All other major extensor muscles in the superficial layer of the posterior compartment of the forearm are innervated by the posterior interosseous nerve and include:
 - a. Extensor digitorum
 - b. Extensor carpi radialis brevis
 - c. Extensor carpi ulnaris
 - d. Extensor digiti minimi
2. Function:
 - a. Extension of the wrist
 - b. Radial abduction of the hand at the wrist

Extensor Carpi Radialis Brevis

1. Innervated by the posterior interosseous nerve
2. Function:
 - a. An extensor and abductor of the hand at the wrist

Extensor Digitorum Communis

1. Innervated by the posterior interosseous nerve
2. Function:
 - a. Principal action is extension of the proximal phalanges, the middle and terminal phalanges are extended by the interossei and lumbricals
 - b. Extends the phalanges, the wrist and the elbow (weak)

Extensor Carpi Ulnaris

1. Innervated by a deep branch of the radial nerve (C7, C8 spinal segments)
2. Function:
 - a. Extends and adducts the wrist

Extensor Indicis, Extensor Pollicis Longus and Brevis, Extensor digiti quinti

1. Innervated by the posterior interosseous nerve
2. Function:
 - a. Extension of the thumb (metacarpophalangeal and interphalangeal joints)
 - b. Extension of the index finger and wrist (extensor indicis) and extension of the little finger at all joints (extensor digiti quinti)

Median Nerve

1. Formed by fusion of branches from the medial and lateral cords (spinal segments C6–T1)
 - a. Motor fibers arise primarily from C6–T1 spinal segments
 - b. Sensory fibers from C6–C7 spinal segments
 - c. The sensory fibers transverse the upper and middle trunks to the lateral cord
 - d. Motor fibers traverse all of the trunks to both the medial and lateral cords
 - e. In the forearm the median nerve innervates:
 - i. Pronator teres
 - ii. Flexor carpi radialis
 - iii. Palmaris longus
 - iv. Flexor digitorum superficialis

2. Pronator Teres:

- a. A forearm pronator (C6–C7)

3. Flexor carpi radialis (C6–C7)

- a. A radial flexor of the hand

4. Palmaris longus (C7–T1)**5. Flexor digitorum superficialis (C7–T1)**

In its descent and after it passes between the two heads of the pronator teres the purely motor anterior osseous nerve takes origin to innervate:

1. Flexor pollicis longus (C7–C8)
2. A flexor of the terminal phalanx or the thumb
3. Flexor digitorum profundus and (C7–C8)
 - a. A flexor of the terminal phalanges of the second and third fingers
4. Pronator quadrates (C7–C8)
 - a. A forearm pronator

The median nerve divides into its terminal branches at the distal end of the carpal tunnel. The motor branches innervate the first and second lumbricals and the thenar muscles.

1. First and second lumbricals (C8–T1):
 - a. Flexors of the proximal and extensors of the two distal phalanges of the second and third fingers
2. Abductor pollicis brevis (C8–T1):
 - a. An abductor of the metacarpal of the thumb (possibly the best muscle to test for median nerve weakness)
3. Opponens pollicis (C8–T1)
 - a. Brings the metacarpal of the thumb into opposition
4. Superficial head of the flexor pollicis brevis (C8–T1)
 - a. Flexes the proximal phalanx of the thumb

Variations in the Innervation of Intrinsic Hand Muscles

1. Riche-Cannieu Anastomosis
 - a. Anastomosis between the motor branch of the median nerve and the deep ulnar nerve branch in the radial aspect of the hand
2. Adductor pollicis and first dorsal interosseous muscles may be exclusively supplied by the median nerve in 2% of patients
3. The abductor pollicis brevis and flexor pollicis brevis may be supplied exclusively by the ulnar nerve in 2% of individuals

Ulnar Nerve

The ulnar nerve derives from the C7, C8, and T1 spinal nerves and is the main branch of the medial cord. In its descent into the arm, it traverses the axilla beneath the pectoralis minor muscle and lies medial to the brachial artery in the upper arm. The C7 component arises from a branch of the lateral cord to innervate the flexor carpi ulnaris muscle. It enters a groove in the distal arm between the medial humeral epicondyle and the olecranon process. The dorsal component of this osseous fibrous canal is an aponeurosis between the olecranon and medial epicondyle. It is bound inferiorly by the medial ligament of the elbow joint. This canal is the cubital tunnel. Distal to the elbow joint originate its first two muscular branches.

1. The flexor carpi ulnaris (C7–T1)
 - a. Flexor of the wrist
2. Flexor digitorum profundus III and IV (C7–C8)
 - a. A flexor of the terminal phalanges of the fourth and fifth fingers

In the distal forearm, it gives off the palmar cutaneous branch that innervates the skin of the hypothenar eminence. Shortly thereafter, it gives off the dorsal cutaneous branch that innervates the dorsal ulnar hand and the dorsal components of the fifth finger and one-half of the fourth finger. The ulnar nerve proper enters the wrist lateral to the tendon of the flexor carpi ulnaris muscle and gives off the superficial terminal branch. This sensory branch innervates the distal ulnar palm and the volar aspect of the fifth and one-half of the fourth finger. The nerve then traverses Guyon's canal whose medial component is the piriform carpal bone and the hook of the hamate carpal bone laterally to become the deep muscular branch.

It innervates intrinsic muscles of the hand that includes:

1. Palmaris brevis (C8–T1)
 - a. Tenses the skin of the palm on the ulnar side of the hand to deepen the hollow of the palm
2. Abductor digiti minimi (C8–T1)
 - a. An abductor of the fifth finger
3. Opponens digiti minimi (C8–T1)
 - a. An opposer of the fifth finger
4. Flexor digiti minimi (C8–T1)
 - a. A flexor of the fifth finger at the metacarpophalangeal joint
5. Lumbricals III and IV (C9–T1)
 - a. Flexors of the metacarpal phalangeal joints and extensors of the proximal interphalangeal joints of the fourth and fifth fingers
6. Interosseous muscles:
 - a. Flexors of the metacarpophalangeal joints and extensors of the proximal interphalangeal joints. The four dorsal interossei muscles are finger abductors. The three palmar interossei muscles are finger adductors
 - i. Variants are:
 1. Innervation of the first dorsal interosseous by the median nerve (1% of individuals)
 2. First dorsal interosseous is innervated by the radial nerve (Froment-Rauber nerve)

7. Adductor pollicis (C8–T1)
 - a. An adductor of the thumb
 - b. It receives median nerve innervations in approximately 2% of individuals
8. Deep head of the flexor pollicis brevis (C8–T1)
 - a. A flexor of the first phalanx of the thumb

Clinical Manifestations

1. Total Brachial Plexus Paralysis:
 - a. There is paralysis of the entire arm that hangs limply at the patient's side. There is severe atrophy of all muscle groups
2. Anesthesia of the arm distal to a line extending obliquely from the tip of the shoulder to the medial arm approximately $\frac{1}{2}$ way to the elbow
3. Areflexia of the upper extremity

Upper Plexus Lesions

Most commonly involve the C5 and C6 spinal nerves of the upper trunk of the plexus.

1. Motor signs:
 - a. C5–C6 spinal nerve innervated muscles are paretic or paralyzed and atrophic. These muscles include:
 - i. Deltoid
 - ii. Biceps
 - iii. Brachioradialis
 - iv. Brachialis
 - b. If the lesion is very proximal the supraspinatus, infraspinatus and subscapularis may be involved. The arm is internally rotated and adducted and the forearm is extended and pronated. The palm faces out and backward. There is weakness of:
 1. Shoulder abduction:
 - a. Deltoid and supraspinatus
 2. Elbow flexion:
 - a. Biceps brachioradialis and brachialis
 3. External rotation of the arm:
 - a. Infraspinatus
 4. Forearm supination:
 - a. Biceps
 5. Very proximal lesions involve the rhomboids, levator scapulae, serratus anterior and scalene muscles
2. Sensory signs:
 - a. Sensation is often intact
 - b. Sensory loss does occur over the lateral/upper arm and the deltoid muscle in some patients
3. Reflex signs
 - a. Depression of the biceps and brachioradialis reflexes

Middle Plexus Lesions

1. Lesions of the middle trunk or the individual anterior primary ramus of C7 are involved
2. Motor signs:
 - a. Involvement of C7 innervation to the radial nerve is primarily involved which causes weakness or paralysis of extension of the forearm, hand, and fingers

- b. The paretic or paralyzed muscles are:
 - i. Triceps
 - ii. Anconeus
 - iii. Extensor carpi radialis and ulnaris
 - iv. Extensor digitorum
 - v. Extensor digiti minimi
 - vi. Extensor pollicis longus and brevis
 - vii. Abductor pollicis longus
 - viii. Extensor indicis
- c. Forearm flexion is maintained by the brachioradialis and brachialis (C5–C6 spinal nerves)
- 3. Sensory signs:
 - a. Patchy sensory deficit over the extensor surface of the forearm and the dorsum of the hand
- 4. Reflexes:
 - a. Triceps reflex is depressed or absent

Lower Plexus Lesion

- 1. Primary injury involves the C8–T1 spinal nerves or the lower trunk of the plexus
- 2. Motor signs:
 - a. Musculature supplied by the C8–T1 spinal nerves is affected. There is weakness of wrist and finger flexion and in the intrinsic hand muscles. There is usually severe hand atrophy leading to the “claw” hand deformity
- 3. Sensory signs:
 - a. Decreased sensation of the medial arm and forearm and the ulnar side of the hand
- 4. Reflex signs:
 - a. Loss of finger flexion
- 5. If T1 is damaged, sympathetic fibers to the superior cervical ganglia are interrupted which causes a Horner’s syndrome. If T2 is damaged, there is an interruption of the sympathetic innervation of the arm

Lesions of the Lateral Cord

Usually, result in weakness of the muscles innervated by the musculocutaneous and lateral head of the median nerve.

- 1. Motor signs
 - a. Weakness of the biceps brachii and brachialis
 - i. Flexion of the elbow
 - b. Coracobrachialis:
 - i. Supination of the forearm
 - c. Median nerve innervated muscles:
 - i. Pronator teres
 - 1. Pronation of the forearm
 - ii. Flexor carpi radialis:
 - 1. Radial wrist flexion
 - iii. Palmaris longus:
 - 1. Flexion of the wrist
 - iv. Flexor digitorum superficialis:
 - 1. Flexion of the middle phalangeal joints (second through fourth digits)
 - v. Flexor digitorum profundus I and II:

- 1. Flexion of the distal phalanges of the second and third fingers
- vi. Pronator quadratus:
 - 1. Pronation of the forearm
- 2. Sensory signs
 - a. Loss of sensation in the distribution of the lateral cutaneous nerve of the forearm:
 - i. Sensory loss in the lateral forearm
 - ii. Branch of the musculocutaneous nerve
- 3. Reflexes
 - a. Depression or absence of the biceps reflex

Lesions of the Medial Cord

- 1. Cause weakness of the muscles innervated by the ulnar nerve and the medial component of the median nerve
- 2. Ulnar innervated muscles that are weak include:
 - a. Flexor carpi ulnaris:
 - i. Ulnar flexion of the wrist
 - b. Flexor digitorum III and IV:
 - i. Flexion of the terminal digits of the fourth and fifth fingers
 - c. All of the ulnar innervated small intrinsic hand muscles
- 3. Median innervated muscles include:
 - a. Abductor pollicis brevis
 - i. Metacarpal abduction of the thumb
 - b. Opponens pollicis:
 - i. Opposition of the thumb
 - c. Superficial head of the flexor pollicis brevis:
 - i. Flexion of the proximal phalanx of the thumb
 - d. Lumbricals I and II:
 - i. Flex the first two metacarpophalangeal joints and extend the digits of the second and third fingers
- 4. Sensory Signs
 - a. Loss of sensation of the medial arm and forearm due to injury of the medial cutaneous nerves of the arm and forearm
- 5. Reflexes
 - a. Loss of the finger flexor reflex

Proximal Lesions of the Medial Cord

- 1. Injury of the medial anterior thoracic nerve
 - a. Weakness of the lower sternocostal portion of the pectoralis major muscle and the pectoralis minor muscle

Lesions of the Posterior Cord

Posterior cord lesions cause weakness in the muscles innervated by the subscapular thoracodorsal, axillary and radial nerves.

- 1. Motor signs:
 - a. Subscapular nerve innervated muscles:
 - i. Weakness of the teres major and subscapularis muscles
 - 1. Internal rotation of the humerus
 - b. Thoracodorsal innervated muscles:
 - i. Latissimus dorsi weakness:

1. Extension, adduction, transverse extension (horizontal abduction), flexion from an extended position and internal rotation of the shoulder joint
2. Synergistic role (therefore weakness) in extension and lateral flexion of the lumbar spine
- c. Axillary nerve innervated muscles:
 - i. Deltoid:
 1. Arm abduction
 - ii. Teres minor:
 1. Lateral rotation of the shoulder joint
 - iii. Sensory loss:
 1. Distribution of the lateral cutaneous nerve of the arm that includes a diminished sensation of the lateral arm

Radial Nerve

1. Weakness of elbow extension, wrist extension, supination of the forearm and finger extension. There is a minimal contribution to elbow flexion. Proximal lesions cause triceps reflex loss
2. Sensory signs: sensory loss in the extensor surface of the arm and forearm, dorsum of the hand and first four fingers distribution
3. Reflexes:
 - a. Depression of triceps and radial reflexes

Neuropathology of Nerve Injuries

Neuropraxis

1. Neuronal dysfunction due to transient conduction block
2. Compression of a nerve may cause segmental ischemia. If of short duration there may only be a reversible physiologic conduction block that lasts for minutes to hours. There may also be paranodal and then segmental demyelination. In this instance, recovery may take several weeks and is effected by remyelination

Axonotmesis

In this instance, the axon is interrupted, but the epineurium is preserved. The axon distal to the lesion degenerates over 7–10 days. Regenerating nerve sprouts from the proximal portion of the injured nerve attempt regeneration. The intact epineurium enhances the chance of reinnervation. Axons grow at a rate of 1 mm/day, so this process may require months to over a year.

Neurotmesis

1. The axon and epineurium are interrupted. The difference between axonotmesis and neurotmesis can only be determined by direct vision (surgery). Scarring from overlying tissue damage often prevents reinnervation

Neuropathology

1. Dependent on the particular process affecting the plexus

Neuroimaging

1. Primarily high resolution MRI
2. Ultrasound is useful for focal neuropathies

Laboratory Evaluation

1. EMG:
 - a. The EMG is essential in evaluating radiculopathy, plexopathy, and mononeuropathy
 - b. Combined with motor and sensory NCVs, it supports the localization determined by the clinical examination

Traumatic Brachial Plexus Injury

Overview

1. The longitudinal excursion of the brachial plexus is 15.3 mm
2. The greater the traction on the plexus, the greater the injury (neuropraxia, axonotmesis to neurotmesis)
3. The primary roots are the most susceptible to traction injury (they are arranged in parallel bundles rather than a lattice structure and therefore have decreased tensile strength)
4. Shoulder depression and lateral head flexion contralaterally injure the upper and middle trunk
5. Traction on the hyperabducted arm causes traction on the lower > middle > upper trunk
6. Preganglionic injuries are usually caused by avulsion of the root
7. Traction injuries may affect all or a portion of the plexus to a varying degree
8. C5 and C6 rupture occur close to the exit foramina. C8–T1 rupture is often closer to the spinal cord
9. The pathology is categorized as neuropraxic axonotmesis and neurotmesis
10. Treatment (surgical intervention) is dependent on the type and severity of the injury:
 - a. Most closed injuries are neuropraxic or axonometric that may recover spontaneously
 - i. Upper trunk lesions usually demonstrate signs of recovery in 2–3 months
 - ii. Four to five months are required for recovery in middle and lower trunk lesions
 - b. High impact injuries and those causing near total paralysis need to be evaluated earlier for possible surgery (3 weeks to 3 months)
 - c. Injuries that more likely sever nerves such as lacerations or gunshot wounds need to be evaluated for possible surgical repair within 72 hours
 - d. Associated conditions that cause neurological worsening after injury:
 - i. Hematoma
 - ii. Concomitant bone and vascular injury
 - iii. Compartment syndromes

Avulsion Injury

General Characteristics

1. C5–C6 root lesions after severe trauma

- a. 27% avulsions; 33% ruptures
- 2. Most often are caused by high impact trauma
 - a. MVA (motorcycle injuries are the most common)
 - b. Football, skiing, mountain climbing accidents and falls
- 3. C8–T1 root lesions:
 - a. 98% are avulsion, and 1–2% are ruptures

Clinical Manifestations

1. Total plexopathy may occur with high impact trauma:
 - a. Avulsion is greater in C8–T1 roots > C5, C6 and C7 roots
2. Early severe burning pain in an otherwise anesthetic hand; most severe proprioceptive loss if any sensation is present
3. Horner's syndrome is present in C8–T1 avulsion
4. Paralysis of the serratus anterior, rhomboids, infra- and supraspinatus muscles
5. Negative supraclavicular Tinel's sign
6. May have associated spinal cord symptoms and signs

Neuropathology

1. Neurotmesis of the roots

Neuroimaging

1. Traumatic meningocele
2. Fracture of a transverse process
3. Flattening of the root sleeve
4. Extravasation of contrast through the torn root sleeve during myelography
5. High resolution MRI may demonstrate the lesions and is now more commonly used than myelography
6. Ultrasound is used for focally associated neuropathies

Laboratory Evaluation

1. EMG:
 - a. Sensory, motor and mixed sensorimotor nerve conduction studies
 - b. SNAP (sensory nerve action potentials) are normal if the lesion is distal to the dorsal root ganglion
 - i. It requires 7–10 days for SNAPs to disappear with a completely severed nerve
 - c. Positive sharp-wave and fibrillation potentials in affected muscles and paraspinal muscles:
 - i. May require one week to appear in paraspinal muscles and three weeks following axonal injury
 - ii. The MUAPs voluntarily recruited are immediately affected

Obstetric Complications

General Characteristics

1. Incidence ranges from 0.38 to 2% per 1000 live births
2. Three types of injury occur:
 - a. Diffuse plexopathy
 - b. Upper trunk plexopathy (Erb's)
 - c. Lower trunk plexopathy (Klumpke's)
3. Risks for brachial plexus injury during childbirth:

- a. Diabetic, multiparous, obese mothers
- b. Greater than 4500 gram fetuses
- c. Mothers that are short
- d. Breech presentation
- e. Long and difficult labor
- f. Forceful downward traction of the head

Clinical Manifestations

1. Erb's palsy (C5–C6 roots; upper trunk)
2. The most common obstetrical brachial plexus injury:
 - a. Stretch of the upper trunk
 - b. Severe traction may avulse the C5 and C6 spinal nerves
 - c. Occurs with shoulder dystocia in a vertex presentation or the aftercoming head in a breech presentation
 - d. Upper trunk lesions cause weakness of muscles that include:
 - i. Supra- and infraspinatus
 - ii. Deltoid
 - iii. Biceps brachii
 - iv. Teres minor
 - v. Brachioradialis
 - vi. Extensor carpi radialis/longus/brevis
 - vii. Supinator
 - e. Weakness of the diaphragm or serratus anterior suggests root avulsion (proximal to the upper trunk)
 - f. Sensory loss < motor deficit

Klumpke's Paralysis (C8–T1 Roots)

1. Face presentation with hyperextension of the neck or with a breech delivery with hyperabduction of the arm
2. Weakness of hand muscles
3. Sensory loss < motor deficit

Neuropathology

- a. Primarily axonotmesis and neurotmesis (with avulsion)

Neuroimaging

- a. To assess for associated humeral or clavicular fracture; diaphragmatic paralysis
- b. MRI:
 - i. To assess for nerve root avulsion

Laboratory Evaluation

- a. EMG:
 - i. Determines the site and severity of the lesion

Thoracic Outlet Syndrome

Overview

The major components of the thoracic outlet are the sternocostovertebral space that forms the most proximal part of the thoracic outlet tunnel and is bound:

1. Anteriorly by the sternum
2. Posteriorly by the spine
3. Laterally by the first rib

The subclavian artery, subclavian vein, and C4 to T1 spinal nerves traverse this space. Associated structures include the apex of the lung and pleura, sympathetic trunk, jugular vein and lymphatics of the neck. It may be congenitally narrowed. The usual pathology of the sternocostovertebral space includes thyroid masses, an enlarged thymus, parathyroid mass, lymph nodes or lung tumors that cause the Pancoast syndrome (squamous or adenocarcinoma of the lung). The scalene triangle is bound by the anterior scalene muscle anteriorly, the middle scalene posteriorly with the first rib forming its base. The origins of the anterior scalene muscle are the transverse processes of C3–C6. The insertion of the anterior scalene muscles on the scalene tubercle of the first rib varies between the subclavian artery and vein and the pleural dome.

Variants of this insertion include:

1. Behind the artery
2. Between the artery and the brachial plexus
3. The entire base of the scalene triangle (which traps the neurovascular bundle). The anterior insertion may merge with the insertion of the middle scalene muscle in 20% of patients. The C5–C6 spinal nerves may traverse the anterior scalene muscle rather than descend between the anterior and middle scalene muscles

The origin of the middle scalene muscle is the transverse processes of C2–C7. It inserts on the retroarterial tubercle of the first rib (Chassaignac's tubercle). It may insert on the fibrous septum of the pleural dome in which case its lateral fibers insert on the second rib. The C8–T1 spinal nerves as the lower trunk of the plexus may be compressed by a more anterior or forward insertion (its sharp anterior edge). Rarely, congenital fibromuscular bands are noted along the anterior edge of the muscle that may also compress the C8–T1 spinal nerves.

The first rib forms the floor of the scalene triangle. The T1 spinal nerve is closest to the rib. Congenital rib anomalies, bony ridges, hypoplasia or inward curvature may compress the neurovascular bundle. There are congenital variations in the size of the base of the scalene triangle that may cause compression of components of the plexus. Its usual size is approximately 0.77 cm in men and 0.67 cm in women. The C5–C7 spinal nerves emerge from the apex of the triangle in association with interdigitation of the anterior and middle scalene muscles. This anatomical feature is noted in a large percentage of patients with neurogenic thoracic outlet syndrome. Adherence of the C5–C6 spinal nerves to the middle scalene muscle may also irritate these nerves and cause pain. Pathology in the costoclavicular and pectoralis minor space compresses the brachial plexus with various arm positions.

Anatomical Variations of the Thoracic Outlet

1. Bone defects:
 - a. Cervical rib
 - b. Abnormal or rudimentary first rib
2. Congenital bands or ligaments
3. Pectoralis minor insertion variations (hyperabduction syndrome)

4. Large subclavius muscle
5. Tight thoracic inlet
6. Scalene triangle congenital defects:
 - a. Narrow scalene triangle
 - b. Proximity of anterior and middle scalene muscles
 - c. High emerge of spinal nerves from the triangle
 - d. Interdigitated muscle fibers between the middle and anterior scalene muscles
 - e. Adherence of spinal nerves C5–C6 to the anterior scalene muscle
7. Congenital narrowness of the costoclavicular space
8. Clavicle anomalies (acromial head depression compresses the costoclavicular space)
9. A tight pectoralis minor space (below the insertion of the pectoralis minor tendon into the coracoid process); hyperabduction of the arm closes the space

Neurogenic Thoracic Outlet Syndrome

General Characteristics

1. The most frequent cause of TOS (hotly debated between neurologists, EMG specialists and thoracic and specific groups of orthopedic surgeons)
2. High percentage of patients has an underlying anatomical variant:
 - a. The four anatomical spaces of the thoracic outlet:
 - i. Sternocostovertebral space
 - i. Scalene triangle (most frequently involved)
 - ii. Costoclavicular space
 - iii. Pectoralis minor space
 - b. Congenital bands (12 types)
 - c. Cervical ribs
 - d. Long neck droopy shoulder
 - e. Tight thoracic inlet
 - f. Abnormal insertions of the anterior, middle or minimus scalene muscle

Clinical Manifestations

1. Abnormal posture of the affected extremity forward flexed and dropped shoulder as the position of comfort (weakness of the lower components of the trapezius muscle and the levator scapulae). There is often associated pathology of the ventral components of C2–C4
2. Positive stretch of maneuvers
 - a. Roos' abduction stress maneuver is positive in approximately 60–70% of patients in one minute; Wright's maneuver is also frequently positive. These maneuvers evoke heaviness and paresthesia in specific plexus sensory radiations within 1–2 minutes. Control patients can maintain these postures (surrender position of the arms) for at least three minutes
3. Positive Tinel's signs:
 - a. Erb's point (supraclavicular plexus)
 - b. Pectoralis minor space (lateral infraclavicular fossa)
 - c. Compression of the neurovascular bundle (against the proximal humerus)

- d. At the cubital tunnel (ulnar nerve)
- e. At the Arcade of Frohse (dorsal radial sensory fibers). This Tinel's sign is invariably misdiagnosed as "tennis elbow"
- f. Pronator canal (median nerve)
- g. Occasionally the carpal tunnel and Guyon canal areas are mechanically sensitive
- h. Sensory loss in specific plexus distributions:
 - i. Upper trunk
 1. Trapezius ridge, deltoid and medial scapula border (C5–C6 sensory radiations)
 2. Pain or tenderness at the tip of the scapula is notalgia and is a C6 sensory nerve radiation, not T6
 - ii. Lower trunk:
 1. Medial arm and forearm distributions (brachial and antebrachial cutaneous nerve distributions)
 2. Radiation into the complete 4th finger (the ulnar nerve splits the fourth finger and supplies a small triangular area above the wrist). The lower trunk innervates the entire medial forearm and arm. The lower trunk radiations are often misdiagnosed as ulnar nerve lesions
 3. Proximal lesions may be associated with a Horner's syndrome
 4. Lower trunk lesions are a common cause of chronic regional pain syndrome Type I and II that has severe somatosensory, motor, and autonomic features
 - iii. Lateral cord:
 1. Pain or paresthesia in the lateral forearm (lateral antebrachial cutaneous nerve) distribution
 2. Thumb, index and radial side of the third finger have decreased sensation or paresthesias
 - iv. Medial cord:
 1. Medial forearm (territory of the medial antebrachial cutaneous nerve); rarely the brachial cutaneous nerve territory of the medial proximal upper arm is involved
 2. The ulnar side of the third finger and the complete 4th and 5th finger comprise the medial cord sensory topology
 3. There is frequent involvement of intercosto-brachial nerve concomitantly with medial cord injury; this causes pain in the anterior chest wall (T1–T3) and the lateral chest wall (anterior axillary line); paresthesia and pain may radiate under the breast to the middle of the epigastrium at the xiphoid process. These radiations are often misdiagnosed as visceral pain radiations
 - v. Posterior cord:
 1. Paresthesias of the triceps muscle and back of the arm
 2. Radiations to the dorsal forearm and base of the thumb and parts of the dorsal hand (posterior antebrachial radial cutaneous nerve)
 - vi. Muscle weakness:
 1. Occurs in various components of the involved plexus; subscapularis, teres major, latissimus dorsi, deltoid, teres minor, triceps brachii, brachioradialis, extensor of the fingers and wrist, supinator and extensor and abductor muscles of thumb
 - vii. Reflexes:
 1. Most often they are normal
 2. They may be increased if CRPS I or II has supervened which is more common with lower trunk lesions (sympathetic hyperactivity induces contraction of the intrafusal muscle fibers of the nuclear bag of the muscle spindle complex)

Neuropathology

1. Neurogenic thoracic outlet syndrome comprises approximately 90% of all patients suffering the syndrome
 - a. Most patients have suffered trauma with flexion-extension injuries of the neck ("whiplash")
 - b. Repetitive movements commonly initiate the process
 - i. Falls on the outstretched arms are common
 - c. Most often, the process is neuropractic and recovers spontaneously. However, a small percentage of patients become chronic
 - d. Secondary concomitant CRPS I and II may be caused by lower trunk trauma most often
2. Specific anatomic causes of neurogenic TOS:
 - a. Cervical ribs: The incidence of cervical ribs in the population is estimated to be 0.3%
 - b. Women are affected two times more frequently than men are
 - c. Approximately 10% of patients with cervical ribs are symptomatic. Usually, symptoms are initiated by trauma
 - d. The Gruber classification of cervical ribs:
 - i. Type I – Protrudes slightly beyond the transverse process and attaches to the first rib by a tight fibrous band
 - ii. Type II – 2.5 cm in length:
 1. Attaches to the first rib by a tight fibrous band
 2. Rib and band lie within or on the medial border of the middle scalene muscle
 3. This configuration narrows the scalene triangle
 - iii. Type III:
 1. A complete rib with a fibrous connection to the first rib
 - iv. Type IV:
 1. A complete rib with a cartilaginous joint at the first rib

2. The complete rib causes the neurovascular bundle to arch over the rib
3. The neurovascular bundle is compressed when the shoulder girdle is depressed

Ligaments and Fibrous Bands That Compress Cervical Spinal Nerves

1. Twelve different fibrous structures can compromise the thoracic outlet
2. The most significant ligaments are:
 - a. Transverse process of C7 to the first rib
 - b. Tip of the cervical rib that inserts on the first rib
 - c. Ligaments that are within the body or on the anterior surface of the middle scalene muscle may affect C8–T1 spinal nerves of the lower trunk
 - d. Common anomalies:
 - i. Incomplete cervical rib on a long transverse process of C7 from which a tight band inserts on the first rib

Roos' Congenital Bands and Ligaments

1. Type I:
 - a. Tip of an incomplete cervical rib ligament that inserts posteriorly to the scalene tubercle
2. Type II:
 - a. The origin of the ligament is from the transverse process of C7 and inserts on the scalene tubercle
3. Type III:
 - a. A ligament that originates and inserts on the first rib; the origin is posterior and the insertion is anterior
4. Type IV:
 - a. The ligament originates within the middle scalene (C2–C7)
 - b. Courses on the anterior edge of the middle scalene
 - c. Inserts with the muscle on the first rib
 - d. The ligament is adjacent to C8–T1 spinal nerves
5. Type V:
 - a. Scalenus minimus muscle is the Vth band
 - b. Origin is in the anterior scalene muscle (lower fibers)
 - c. Courses behind the subclavian artery in front of the plexus to insert on the first rib
6. Type VI:
 - a. Scalenus minimus insertion into Sibson's fascia over the cupola of the lung rather than the first rib
7. Type VII:
 - a. A fibrous cord that courses on the anterior surface of the anterior scalene muscle
 - b. Inserts on the costochondral junction of the sternum
 - c. The band lies behind the subclavian vein that it may compress
8. Type VIII:
 - a. Origin of the ligament is the middle scalene muscle
 - b. Courses under the subclavian artery and vein
 - c. Inserts on the costochondral junction
9. Type IX:
 - a. A web of muscle and fascia that fills the posterior curve of the first rib

The Rib-Band Syndrome of Gilead

General Characteristics

1. Primarily a lower trunk plexopathy
2. Women are more often affected than men

Clinical Manifestations

1. Paresthesia of the 4th and 5th fingers, medial forearm to the medial humerus
2. Atrophy of the thenar > than hypothenar muscles of the hand

Neuropathology

1. A sharp fibrous band from the tip of an elongated C7 transverse process of true cervical rib to the first rib
2. A neuropraxic injury of the proximal lower trunk

Neuroimaging

1. Plain x-ray:
 - a. Prominent transverse process at C7
 - b. Cervical rib
 - c. The band cannot be appreciated by MRI

Laboratory Evaluation

1. EMG:
 - a. The median CMAP and medial antebrachial cutaneous SNAP amplitudes are reduced to a greater extent than the ulnar SNAP and CMAP
 - i. Ulnar studies primarily assess C8 fibers

Brachial Plexus Injuries

Brachial Plexus Surgery for Neurogenic Plexopathy

General Characteristics

1. No gender difference
2. Young and middle-aged patients are affected

Clinical Manifestations

1. Weakness of the intrinsic muscles of the hand noted immediately
2. Pain may be the predominant symptom
3. Lower trunk involvement is often associated with Type II complex regional pain syndrome

Neuropathology

1. Most lesions occur during transaxillary first rib resection; less frequently with scalenectomy and neurolysis of the upper trunk in the supraclavicular fossa
2. Direct surgical injury as traction (neuropraxis) plexus injury
3. Phrenic nerve may be involved concomitantly (particularly if the procedure involves the middle scalene muscle)
4. Site of the lesion:
 - a. Proximal lower trunk
 - b. C8–T1 spinal nerves

*Orthopedic Surgical Procedures That Injure the Plexus***General Characteristics**

1. Most common procedures are those for:
 - a. Recurrent anterior shoulder dislocation
 - b. Shoulder joint replacement
 - c. Arthroscopy of the shoulder
 - d. Surgical procedures that compromise the costoclavicular space
 - e. Direct trauma from arteriography and cannulas
 - f. Percutaneous cannulation of the subclavian and internal jugular vein
 - g. Percutaneous brachial plexus block

Clinical Manifestations

1. Chronic recurrent anterior shoulder dislocation:
 - a. Putti-Platt; Bristow procedures
 - b. During surgery:
 - i. Direct trauma to the musculocutaneous nerve is the most frequent injury
 - ii. Median, ulnar, radial, and axillary nerves may be injured with clinically expected motor and sensory deficits
 - c. Concomitant damage to the axillary artery and vein
 - d. Delayed onset of plexopathy following the modified Bristow procedure:
 - i. The bone screw that attaches the coronoid process to the glenoid rim works loose
 - ii. Axillary artery may be pierced with pseudoaneurysm formation that compresses the infraclavicular plexus

Shoulder Joint Replacement

1. Direct trauma to the axillary nerve and the supraclavicular plexus

Arthroscopy of the Shoulder

1. Direct trauma to the infraclavicular nerves:
 - a. Musculocutaneous
 - b. Axillary
 - c. Ulnar
 - d. Radial
2. Neuropraxis injuries of these nerves

Surgical Procedures That Compromise the Costoclavicular Space

1. Operations to correct Sprengel deformity
2. Midportion of the clavicle surgery (fracture repair or to obtain access to subclavian vessels); regeneration of the lateral clavicle with excess callus formation that compresses the upper trunk

Direct Trauma from Arteriography and Cannulas

1. Trauma to the infraclavicular brachial plexus:
 - a. Cords of the plexus are adjacent to the second segment of the axillary artery; the median nerve is on the surface of the artery

- b. Leakage of blood from the puncture site that causes direct compression of the terminal nerves: median > ulnar > radial
- c. Most often, there is a combination of median and ulnar nerve trauma
- d. Pain, paresthesia, and arm weakness in characteristic patterns
 - i. Onset of symptoms may be delayed for up to two weeks
- e. Nerve lesions may occur from pressure (hematoma) in the medial brachial fascial compartment that:
 - i. Extends from the axilla to the elbow
 - ii. Formed by the medial intramuscular septum and the surface of the medial upper arm
 - iii. Encloses the neurovascular bundle and fascial axillary sheath
- f. Percutaneous cannulation of the subclavian and internal jugular vein:
 - i. Direct instrumentation induced trauma
 - ii. Hematoma compression
 - iii. Rarely axillary mononeuropathy
 - iv. Rarely upper trunk plexopathy
- g. Percutaneous brachial plexus block:
 - i. Injuries may be caused by:
 1. The block itself
 2. Tourniquet-induced ischemia
 3. Post-operative casting
 4. The surgical procedure
 - ii. Axillary block approach causes more injuries than interscalene blocks
 - iii. Usual symptoms are paresthesia in the median and ulnar nerve distributions; usually slight weakness of the involved nerves
 - iv. May have delayed onset (up to two days) following the procedure:
 1. Bupivacaine at 0.25% may demyelinate nerves

*Median Sternotomy***General Characteristics**

1. Median sternotomies:
 - a. Primarily open heart surgeries
 - b. Thoracotomy
2. Affects up to 5% of patients that undergo the procedure

Clinical Manifestations

1. Primarily affects the lower trunk
2. Sensory loss of the medial forearm and hand
3. Weakness of intrinsic hand muscles

Neuropathology

1. Neuropraxis injury of the lower trunk; usually recovers in months

Neuroimaging

1. Ultrasound evaluation of the plexus

2. MRI not effective in visualizing lesions that are neuropractic
3. EMG:
 - a. Usually, demonstrates a lower trunk lesion

Post-Anesthesia Brachial Plexopathy

General Characteristics

1. Follows surgical procedures usually under general anesthesia
2. Abdominal operation (usually cholecystectomy or hysterectomy; now changing due to minimally invasive surgery)

Clinical Manifestations

1. Upper plexus more often involved than lower plexus; usually unilateral
2. Weakness and paresthesia are the predominant signs and symptoms
3. Rarely patients complain of pain
4. Rarely a Horner's syndrome
5. Recovery usually begins 2–3 weeks after onset and may require several months to be complete:
 - a. Sensory loss recovers first followed by lower plexus, then upper plexus and lastly motor function

Neuropathology

1. A neuropractic injury
2. Positions associated with post-operative paralysis:
 - a. Supine
 - b. Trendelenburg (steep and prolonged)
 - c. Abduction of one or both arms to 90 degrees or greater
 - d. Extension and external rotation
 - e. Rotation and lateral flexion of the head to the contralateral side
 - f. Lower shoulder and arm compressed
 - g. Flexed and prone position (back procedures)
 - h. Excessive abduction and arm flexion

Neuroimaging

1. MRI/MRA:
 - a. To evaluate soft tissue and vascular components in the surgical field
 - b. Ultrasonography to evaluate terminal nerves

Post-Operative Brachial Plexopathy

General Characteristics

1. Surgery for neurogenic brachial plexopathy particularly performed without a clear anatomic target such as a cervical rib is fraught with complications

Clinical Manifestations

1. First rib transaxillary resection:
 - a. Weakness and wasting in a lower trunk distribution
 - b. Paresthesias and burning pain in the 4th and 5th fingers and medial forearm
 - c. Less commonly:

- i. Flail arm with numbness and pain of the entire upper extremity
- ii. This pattern may evolve into a medial cord distribution of weakness

2. Anterior scalenectomy and neurolysis:

- a. Pain across the trapezius ridge and down the medial scapular border
- b. Minimal weakness of the rhomboids, supra- and infraspinatus and biceps muscles
- c. Occasional paresthesia of the lateral deltoid and the lateral forearm
- d. Occasional weakness of the ipsilateral phrenic nerve

Neuropathology

1. Neuropractic, axonotmesis, and neurotmesis

Neuroimaging

1. MRI:
 - a. To evaluate the surgical field for hematoma or bone defects (difficult to distinguish brachial plexus components with 1.5 Tesla magnet strength)
2. Ultrasonography to evaluate terminal nerves

Laboratory Evaluation

1. EMG:
 - a. After 14–21 days to evaluate the level and extent of the operative injury

Gunshot Wounds/Laceration Injuries

General Characteristics

1. Gunshot wounds:
 - a. 85% are in males; the average age is 28 years

Clinical Manifestations

1. 80% of injuries affect the cords or terminal nerves
2. Majority of patients have plexus lesions in continuity
3. Laceration injuries:
 - a. Knife injury or glass (fall through a glass window); propeller blades; chainsaw
 - b. Clinical manifestations:
 - i. Associated damage to blood vessels of the neck, axilla, and upper lung
 - ii. 33% of injuries the brachial plexus is in continuity
 - iii. Knife or glass injury tend to be focal

Neuropathology

1. Neuropractic (less often)
2. Usually neurotmesis injury

Neuroimaging

1. MRI/MRA
2. Ultrasonography

Laboratory Evaluation

1. EMG after 21 days demonstrates denervation in the injured components of the plexus

*Backpack Palsy***General Characteristics**

1. Noted in military personnel and civilians using improperly positioned heavy backpacks
2. Males affected more often than females
3. Related to backpack design and weight; multiple mechanical and time-dependent features
4. Possible congenital structural or prior trauma as predisposing factors

Clinical Manifestations

1. Preceded by transient episodes prior to the fully developed syndrome
2. Muscle weakness of the shoulder, arm or forearm > pain
3. Upper trunk > middle plexus innervated muscles are involved; the deltoid may be the most severely involved muscle
4. Sensory loss and reflex changes are less apparent

Neuropathology

1. Neuropractic and axonometric injury

Neuroimaging

1. MRI:
 - a. To rule out congenital defects and prior traumatic injury (excessive callus formation from a fractured clavicle)
2. Ultrasonography

Laboratory Evaluation

1. EMG:
 - a. To evaluate the location and severity of the injury

*Shoulder Injuries with Concomitant Brachial Plexus Involvement***General Characteristics**

1. Brachial plexus involvement is often overlooked in the context of shoulder pathology. Weakness is often ascribed to pain and joint pathology
2. The usual injuries are:
 - a. Humeral fracture or dislocation
 - b. Scapular fracture
 - c. Rotator cuff tear

Clinical Manifestations

1. Rotator cuff tear:
 - a. Approximately 30% of these injuries are associated with brachial plexopathy
 - b. All components of the plexus may be injured
 - c. Posterior cord and middle trunk > than upper trunk and lateral cord
2. Humeral fractures and dislocation:
 - a. Ischemic or a vascular compressive lesion
 - b. Posterior cord and middle and lower trunk may have the greatest deficit
 - c. Trunks and cords, as well as terminal nerves, may be involved with reductions of shoulder dislocations

3. Clavicular fractures with plexopathy:
 - a. Excess motion of the clavicle at the fracture site
 - b. Exuberant callus formation
 - c. Tight figure of eight brace
 - d. Delayed onset (months to years)
 - e. Anterior division and upper trunk involvement with weakness of the innervated muscles
 - f. Upper arm pain exaggerated by arm elevation

Neuropathology

1. Primarily neuropractic and axonometric injury

Neuroimaging

1. MRI (local pathology)
2. Ultrasonography (terminal nerves)

Laboratory Evaluation

1. EMG:
 - a. To evaluate location and extent of the injury

*Burner/Stinger Syndrome***General Characteristics**

1. Usual contact sports injury (shoulder trauma; face mask injury in football)

Clinical Manifestations

1. Severe pain and paresthesia in the arm without motor loss
2. Recovery within minutes

Neuropathology

1. Neuropractic
2. Neuroimaging and EMG
 - a. Not necessary unless symptoms persist

*Arterial Vascular Thoracic Outlet Syndrome***General Characteristics**

1. Extremely rare
2. May be seen in individuals that perform repetitive overhead/arm movements (butchers, using saws; pitchers in baseball)

Clinical Manifestations

1. Adson's maneuver less often positive than in patients with true neurogenic thoracic outlet syndrome
2. Ischemia of the hands and fingers rather than specific neurogenic plexopathy is most common; some patients complain of heaviness and weakness of the arm in abduction; primarily upper trunk distribution
3. May have severe ischemic pain

Neuropathology

1. Bony abnormalities of the clavicle and first rib cause post stenosis dilatation then aneurysm formation of the subclavian or axillary artery
2. Distal emboli from thrombi in the artery to the fingers

Neuroimaging

1. MRI:

- a. Evaluation of the local anatomy with particular reference to bony and congenital anomalies
2. MRA:
 - a. Evaluation of the arterial supply to the arm to rule out aneurysm of the subclavian or axillary arteries

Laboratory Evaluation

1. EMG:
 - a. Evaluation of the location and extent of any brachial plexus involvement

Effort Venous Thrombosis of the Upper Extremity (Paget-von Schroetter Disease)

General Characteristics

1. Thrombosis of the subclavian and axillary vein

Clinical Manifestations

1. Abrupt presentation
2. Upper extremity swelling cyanosis and livedo reticularis
3. Dilated venous collaterals over the chest and shoulder
4. Brachial plexus is not involved

Neuropathology

1. Prolonged compression of the axillary vein on a hard surface (arm outside of the window and resting on the door of a car)
2. May follow extreme exercise of the arm

Neuroimaging

1. MRA and MRV to evaluate the circulation to the arm

Immune-Mediated Brachial Plexopathy

General Characteristics

1. Terminology:
 - a. Acute brachial plexitis
 - b. Neuralgic amyotrophy
 - c. Parsonage-Turner syndrome
2. Evidence suggesting an immune basis includes:
 - a. May develop after an infection or vaccination
 - b. Following bone marrow transplantation
 - c. During treatment with immunomodulating agents
 - i. Interferons
 - ii. Interleukin 2
 - iii. Tumor necrosis factor alpha blockers
 - d. Antibodies against peripheral nerve myelin and soluble terminal complement complexes
 - e. Response to steroids
 - f. In association with some autoimmune diseases

Clinical Manifestations

1. Immune brachial plexus neuropathy usually presents with acute shoulder pain or forearm pain that is exacerbated by movement:
 - a. The intense pain may last for days to weeks but usually evolves to a dull ache that may be persistent for several years

2. Weakness is evident as pain dissipates and depends on the components of the plexus that is involved (trunks, divisions, cords or terminal nerves)
3. Patterns of weakness:
 - a. The most common pattern of weakness involves muscles innervated by the upper trunk or multiple mono-neuropathies that include:
 - i. Suprascapular nerves
 - ii. Long thoracic nerves
 - iii. Axillary nerves
 - b. There may be concomitant involvement of the phrenic and interosseous nerves. These nerves may be involved in isolation
 - c. Rarely cranial nerves IX, X, XI and XII can be involved
 - d. Isolated spinal accessory involvement has been described

Neuropathology

1. Biopsy of IBPN reveals:
 - a. Perivascular perineural and endoneurial inflammatory infiltrates
2. Antigens have not been identified, but electrodiagnostic studies suggest they are axonal rather than epitopes of myelin

Neuroimaging

1. MRI:
 - a. May demonstrate increased T2-weighted signal intensity of the plexus that suggests inflammation with edema

Laboratory Evaluation

1. CSF:
 - a. Approximately 10% of patients have increased spinal fluid protein with or without pleocytosis
2. EMG:
 - a. Electrodiagnostic studies depend on the component of the plexus that is involved
 - b. Nerve damage may be multifocal and is usually axonal
 - c. The upper trunk is primarily involved:
 - i. Median and ulnar motor studies are positive in approximately 15% of patients; median and brachial SNAPs may be abnormal
 - d. 50% of patients demonstrate:
 - i. Decreased CMAP from the deltoid, biceps, and serratus anterior muscles
 - ii. Decreased SNAPs of the lateral, antebrachial, cutaneous and median sensory nerves
3. CSF:
 - a. Slightly increased CSF protein with mid pleocytosis

Differential Diagnosis

1. Asymmetric form of chronic inflammatory demyelinating neuropathy
2. Multifocal acquired motor and sensory demyelinating neuropathy
3. Multifocal motor neuropathy

Hereditary Neurologic Amyotrophy

General Characteristics

1. AD; gene maps to chromosome 17q 25.3 (SEPT9)
 - a. Encodes the septin-9 protein
2. Severe form of hereditary neuralgic amyotrophy without SEPT9
3. A novel locus on chromosome 21q21

Clinical Manifestations

1. A history of one or more sudden onset painful attacks that involve the neck, shoulder or arm
2. Weakness in various affected components of the plexus
3. Associated features:
 - a. Hypertelorism
 - b. Occasional cleft palate:
 - i. Skin folds or creases on the neck or forearm
 - ii. Short stature
 - iii. Syndactyly

Neuropathology

1. Septins are involved in cytokinesis and cellular trafficking
2. Septin-9 protein localizes with other septins and with septin-intermediate filaments that interact with actin microfilaments and microtubules

Neuroimaging

1. MRI to rule out other causes of brachial plexopathy
2. Sonography

Laboratory Evaluation

1. EMG:
 - a. Similar to idiopathic brachial plexus neuropathy

Hereditary Neuropathy with Liability to Pressure Palsies

General Characteristics

1. PMP22 gene deletion; AD but gene de novo mutations occur; the gene is on chromosome 17p11.2
2. The deletion of the 1.5 MB region is the same that is duplicated in CMT
3. Prevalence of 7.3/100,000 to 16/100,000 people

Clinical Manifestations

1. Age of onset is the second and third decade (but has been described to the 8th decade)
2. 60–70% of patients present with a single, focal acute neuropathy
3. Rare cranial nerve involvement that includes V, VII, XII and components of X
4. Brachial plexus involvement (12–27%)
 - a. Possibly causative of backpack neuropathy
5. Painless recurrent plexopathy
6. Scapuloperoneal presentation (Davidenkov phenotype)
7. Muscle weakness and atrophy
8. Numbness in affected plexus distributions
9. Reduced or absent deep tendon reflexes (primarily ankle jerks)
10. Episodes may be preceded by minor compression of the affected nerve or the plexus

Neuropathology

1. Nerve biopsy demonstrates segmental demyelination with varying large-fiber loss
2. Tomacula:
 - a. Redundant or over folding layers of the myelin sheath of variable thickness are present
3. The 1.5 Mb deletion on chromosome 17p11.2 is found in approximately 85–90% of patients that are clinically affected
4. Mouse model demonstrates focal axonal constriction within tomacula

Neuroimaging

1. MRI:
 - a. CNS white matter lesions occur in isolated patients
 - b. Sonography reveals hypertrophy at entrapment sites
2. EMG:
 - a. Increase in distal motor latencies especially of the median and peroneal nerves
3. EMA:
 - a. Focal motor slowing at entrapment sites
 - b. NCV may be normal in some segments
 - c. Sensory nerve conduction velocities may be decreased with decreased SNAP amplitudes

Laboratory Evaluation

1. DNA testing for the deletion of the PMP22 gene
2. Focal motor slowing at entrapment sites
3. NCV may be normal in some segments
4. Sensory nerve conduction velocities may be decreased with decreased SNAP amplitudes

Neoplasms Affecting the Brachial Plexus

General Characteristics

1. Benign tumors:
 - a. Neuronal sheath tumors:
 - i. 60–80% of brachial plexus tumors are neuronal sheath tumors
2. Include:
 - a. Schwannoma
 - b. Neuroma
 - c. Neurofibroma

Clinical Manifestations

1. Present as mass lesions in the supraclavicular fossa or axilla
2. Pain and paresthesia are early symptoms (distortion of nerve fibers without conduction block, demyelination, or destruction of axons)
3. Later motor and sensory loss

Schwannoma

General Characteristics

1. Approximately 5% of benign and soft tissue neoplasms
2. Approximately 20% of tumors of the brachial plexus

Clinical Manifestations

1. Solitary
2. An adult tumor
3. Affects the upper plexus
4. Most often presents as a supraclavicular or axillary mass
5. May affect any organ and region including:
 - a. Nasal septum
 - b. Cervical sympathetic chain
 - c. Gingiva
 - d. All cranial nerves; may be plexiform
 - e. Base of the tongue
 - f. Cecum and gastric mucosa
 - g. Sublingual area
6. Affects the upper plexus most often
7. Sensory signs:
 - a. Tender to palpation; radiating paresthesia is common
8. Later mild motor and sensory deficit referable to the involved dermatome and myotome of the nerve

Neuropathology

1. Benign and well encapsulated
2. Usually, affect the proximal components of the plexus
3. Degenerative changes and variable admixture of spindle (Antoni A) areas and hypocellular microcytic (Antoni B) areas with macrophages and collagen fibers; located near vessels and have a well formed collagenous capsule
4. Express S100 protein and pericellular collagen type IV
5. Plexiform Schwannoma:
 - a. A subtype that occurs in superficial cutaneous or subcutaneous locations
 - b. Intraneuronal pattern of growth
 - c. Associated weakly with NF2 and Schwannomatosis (approximately 5% of patients); usually Antoine A pattern and is less encapsulated than classic Schwannomas

Neuroimaging

1. MRI:
 - a. Homogeneously isointense on T1-weighted sequences and hyperintense on T2 images
 - b. Cystic degeneration may be noted in the usual Schwannoma

Neurofibroma**General Characteristics**

1. Growth pattern is well-demarcated intraneural or diffuse infiltration of soft tissue at extraneural sites
2. Variants:
 - a. Based on architectural growth and include localized, diffuse and plexiform subtypes
 - i. Localized cutaneous neurofibroma is the most common
 1. May involve a major nerve to cause a fusiform expansion of the nerve trunk (intraneural subtype)
 2. Diffuse neurofibromas cause a plaque-like enlargement (usually in the head and neck region)

- ii. 10% of neurofibromas are seen with neurofibromatosis type I

Clinical Manifestations

1. Interdigitate more with nerve fibers within the nerve fascicle
2. In association with neurofibromatosis, they are often multiple and may affect a large portion of the brachial plexus
3. Demonstrate motor and sensory deficits depending on which component of the plexus is affected
4. Neurofibromas associated with NFI:
 - a. Occur both supra- and infraclavicularly
 - b. Are frequently multiple and plexiform
 - c. Present at an earlier age than Schwannomas
 - d. May extend intraspinally (dumbbell tumor) in the intradural extramedullary compartment
 - e. Equal male and female incidence

Neuropathology

1. Neoplastic proliferation with Schwann cell differentiation:
 - a. Wavy nuclear contours
 - b. S100 protein expression
2. Incorporate non-neoplastic peripheral nerve components that include axons, perineural cells, fibroblasts, mast cells, and lymphocytes

Neuroimaging

1. Plain films may demonstrate enlargement of an intraforaminal exit canal
2. MRI:
 - a. Bag of worms appearance from diffuse involvement along a nerve segment
 - b. Few flow voids within the lesion are seen in T2-weighted images
 - c. Plexiform neurofibromas may present on imaging with an intermediate signal compared to muscle on T1-weighted images and with a hyperintense signal on T2-weighted sequences

Perineuroma**General Characteristics**

1. Advanced perineural differentiation
2. Two types of tumor have been described:
 - a. Intraneural
 - b. Soft tissue

Clinical Manifestations

1. Localized solitary expansion of peripheral nerve due to involvement of one or more nerve fascicles
2. Remain stable over time or progress slowly

Neuropathology

1. Perineurial cell proliferation that extends into the endoneurium that surrounds individual nerve fibers and capillaries that produce "pseudo-onion bulbs"
2. Soft tissue perineuromas lack an associated nerve
3. The most commonly utilized immunohistochemical marker is epithelial membrane antigen (EMA)

Neuroimaging and Electrodiagnostic Features Have Not Been Delineated

Differential Diagnosis

1. Localized reactive Schwann cell proliferation (intraneural form)
2. Low-grade fibromyxoid sarcoma (soft tissue form)

Hybrid Benign Nerve Sheath Tumors

General Characteristics

1. Some arise in the setting of inherited syndromes the most common of which is NFI

Clinical Manifestations

1. A solitary painless nodule
2. Equal male to female incidence
3. Approximately 70% arise in the second to fifth decade
4. Wide distribution over the extremities and trunk

Neuropathology

1. Usually well circumscribed; features of Schwannoma and soft tissue perineuroma
2. Encapsulated and composed of spindle cells
3. EMA and S100 are histological markers
4. Neuroimaging and electrodiagnostic features have not been well delineated

Differential Diagnosis of Benign Non-Neural Sheath Plexus Tumors

1. Lipoma
2. Ganglioneuroma
3. Myoblastoma
4. Lymphangioma
5. Dermoid

Malignant Nerve Sheath Tumors That May Involve the Brachial Plexus

General Characteristics

1. Approximately 15% of neural sheath tumors are malignant
2. They are primarily neurogenic sarcoma and fibrosarcoma
3. Malignant transformation of benign neural sheath tumors:
 - a. Most common in von Recklinghausen's disease
 - b. Late transformation (20–40 years) to sarcoma in patients who have been irradiated for breast cancer or Hodgkin's disease

Metastatic Brachial Plexus Tumors

General Characteristics

1. Two-thirds originate from the lung or breast
2. Other metastatic lesions occur from:
 - a. Larynx
 - b. Pancreas
 - c. Colon
 - d. Bladder
 - e. Testes
 - f. Thyroid

- g. Esophagus
- h. Lymphoma
- i. Melanoma
- j. Ewing's sarcoma

3. Metastatic tumors have often metastasized extensively prior to plexus involvement

Clinical Manifestations

1. Known malignant disease (rare for plexus involvement as a presentation)
2. A long latency from treatment of the primary tumor is not uncommon
3. Pain in the arm and shoulder is often the first manifestation; weakness and sensory loss occur later
4. Associated extradural spread with cervical cord compression
5. Many breast cancer patients have received X-RT that involved the plexus prior to a metastatic disease presentation
6. Pancoast syndrome
 - a. Direct spread from the apex of the lung (superior sulcus or thoracic inlet tumor)
 - b. Usually, the syndrome is caused by a squamous cell carcinoma (rarely in the scar of a prior tuberculous infection) or an apical adenocarcinoma
 - c. Pain in the shoulder, scapula or 4th and 5th finger that is often burning in quality
 - d. Weakness wasting and sensory loss in the lower trunk distribution
 - e. Horner's syndrome
7. Primary lymphoma:
 - a. Arising from the cervical or axillary lymph nodes may infiltrate the plexus

Neuropathology

1. Metastatic lesions may grow along the components of the plexus
2. Symptomatology may derive from expression of inflammatory cytokines as well as direct invasion of the tumor

Neuroimaging

1. Demonstrates thickening of plexus components; often contrast enhancement is noted
2. 18-FDG-SPECT
 - a. May demonstrate primary and other metastatic sites; useful in following the course of treatment
3. Sonography

Laboratory Evaluation

1. Electrodiagnosis:
 - a. Dependent upon the components of the plexus that is affected

Radiation-Induced Brachial Plexopathy

General Characteristics

1. Women irradiated for breast cancer is the most frequent cause followed by lung cancer and lymphoma

2. Dosimetric considerations that induce lesions:
 - a. Field size
 - b. Amount of tissue irradiated:
 - c. Time period of the irradiation
 - d. Number of fractions delivered
 - e. Dose of each fraction
 - f. Total dosage
3. Latent period of 0 to 34 years may occur after x-ray treatment

Clinical Manifestations

1. Paresthesias in the C5–C6 spinal nerve, lateral cord, and median nerve distributions
2. Pain may develop late and is usually of moderate severity
3. Weakness of intrinsic hand muscles
4. All parts of the plexus may be involved, but the supraclavicular components of the plexus usually have greater involvement than the infraclavicular
5. Edema of the extremity may develop
6. Most patients have a progressive course although some patients plateau
7. Rare clinical manifestations:
 - a. Severe edema (possible compartment syndrome)
 - b. An acute onset ischemic process:
 - i. Injury to the subclavian artery
 - ii. Associated with painless weakness and sensory loss
 - iii. Segmental occlusion of the subclavian artery
 - c. Reversible Plexopathy:
 - i. Develops 2–14 months after X-RT
 - ii. Hand and forearm paresthesia; shoulder pain; mild hand weakness
 - iii. Chemotherapy after X-RT may be causative or associated

Neuropathology

1. Extensive demyelination
2. Proliferative endarteritis of the vasa vasorum
3. Progressive fibrosis in the irradiated field

Neuroimaging

1. MRI with three Tesla magnet field strength which develops 3D isotropic sequences
2. Gadolinium enhancement is positive for tumor

Laboratory Evaluation

1. EMG:
 - a. Myokymic discharges

Differential Points Between X-RT Damage and Recurrent Tumor

1. Tumor:
 - a. Primarily the C8–T1 roots or the lower trunk is affected; rapidly progressive
 - b. Severe burning pain and intrinsic hand muscle wasting
 - c. Horner's syndrome

- d. MRI:
 - i. May demonstrate thickening or mass in these plexus components
 - ii. Enhances with gadolinium
2. X-RT
 - a. Occurs primarily in the C5–C6 root or spinal nerve distribution
 - b. Greater paresthesias than pain and weakness
 - c. MRI:
 - i. Fibrosis of the plexus and surrounding tissue
 - ii. No enhancement with gadolinium
 - d. EMG:
 - i. Myokymic discharges

Lumbosacral Plexus Lesions

Overview of Lumbosacral Plexopathy

Upper lumbar plexus lesions demonstrate various combinations of deficits in the iliohypogastric, ilioinguinal, genitofemoral, femoral and obturator nerve distributions. Weakness is seen in hip flexion, knee extension (concomitant inability to lock the leg on standing) and adduction of the thigh. Sensory loss is noted in the lower abdominal wall, inguinal, labial, and scrotal areas as well as the thigh and medial lower leg. An absent or a depressed knee reflex is noted.

Lower lumbar sacral plexus lesions cause deficits within the innervation territories of the gluteal, sciatic, tibial, and peroneal nerves. Weakness occurs in hip extension, and abduction, knee flexion, and all intrinsic foot musculature. Sensory loss occurs in the posterior thigh, anterior and posterior aspects of the lower leg below the knee and most of the foot. There are diminished or absent ankle reflexes. Gluteal and sciatic nerve weakness localizes a lesion to the sacral plexus.

Plexopathies are recognized when motor, sensory, and reflex deficits occur in multiple nerve and segmental distributions that affect one extremity. Localization is often difficult due to the pathologies of the region, but usually in a broad sense can be divided into:

1. Lumbar plexopathy
2. Sacral plexopathy
3. Lumbosacral trunk lesions
4. Pan-plexopathy

In general, lumbar plexopathies evolve in a stepwise and dissociated manner.

In localization of lumbosacral plexopathies pathology of the cauda equina and conus medullaris has to be considered. Rarely, motor neuron disease may simulate plexopathy if deficits are without pain or sensory loss. Intraspinal lesions (lower spinal cord) tend to be bilateral with early bowel and bladder dysfunction rather than motor weakness. Cauda equina lesions are painful, and bladder dysfunction is seen early.

Differential points in the history or examination include:

1. Pain in the following territories define specific sensory roots and nerves:

- a. Hip (sclerotoma radiation of L5)
 - b. Buttock (L5–S1 root); often have tenderness in the sciatic notch
 - c. Proximal thigh laterally (L5); also may be caused by bursitis of the tensor fascia lata
 - d. L1, L2, L3 roots innervate the dorsal thigh; this is also the sclerotomal distribution of the recurrent nerve of Spurling of L5. The usual problem is disc herniation radiating to the dorsal thigh rather than its somatic dermatomal distribution
 - e. The medial thigh is innervated by the ilioinguinal nerve (L1, L2 roots)
 - f. The groin is innervated by T12 and L1. It may also have a projected sclerotomal radiation from S1. Thus S1 root irritation may radiate to the groin. This invariably is diagnosed as hip disease or an inguinal hernia
 - g. The straight leg raising test causes sciatic nerve pain (L5–S1 roots); the reverse SLR test stretches the femoral nerve (L2–L3 sensory roots are involved; often concomitant inguinal pain)
 - h. In plexopathy, the valsalva maneuver does not elicit pain as it frequently does with radiculopathy
 - i. In peroneal nerve neuropathy with foot drop:
 - i. Inversion of the foot is normal
 - ii. Toe flexion and hip abduction are normal
 - iii. The ankle reflex is preserved
 - j. Differential signs to distinguish lumbosacral trunk lesions from an L5 radiculopathy:
 - i. The lumbar trunk is formed primarily by the L5 spinal nerve with a contribution from L4; peroneal sensation is normal which favors a trunk lesion
 - ii. If the pattern of weakness is hip adductors, iliopsoas, and quadriceps a lumbar plexopathy rather than femoral or obturator nerve lesions is more likely
 - k. Simultaneous involvement of the lumbar and sacral roots is usual with external trauma; iatrogenic injury more often involves individual L5 plexus components
4. Sensory nerves of the lumbar plexus:
 - a. Iliohypogastric (L1 spinal root)
 - b. Ilioinguinal nerve (L1 root) innervates:
 - i. Upper medial thigh
 - ii. Base of the penis and labia majora
 - c. Genitofemoral nerve (L1–L2 root)
 - i. Innervates the upper anterior thigh
 - ii. Scrotum and labia majora
 - d. Lateral cutaneous nerve of the thigh (L2–L3)
 5. Lesions of the entire lumbosacral plexus:
 - a. Rare; most are incomplete
 - b. Paralysis or paresis of the entire lower extremity with hypo or areflexia
 - c. Sensory abnormalities that involve the entire lower extremity
 6. Lesions of lumbar segments:
 - a. Usually, are incomplete
 - b. Paresis and atrophy in the distribution of the femoral and obturator nerves:
 - i. Iliopsoas:
 1. Weakness of thigh flexion
 - ii. Quadriceps:
 1. Weakness of leg extension
 - iii. Sartorius:
 1. Weakness of thigh eversion
 - iv. Adductor muscles:
 1. Weakness of thigh adduction
 - c. Sensory signs:
 - i. Sensory loss in the inguinal area and over the genitalia
 1. Iliohypogastric, ilioinguinal, and genitofemoral nerves are involved
 - ii. Lateral thigh:
 1. Lateral femoral cutaneous nerve
 - iii. Medial thigh:
 1. Obturator nerve
 - iv. Anterior thigh:
 1. Femoral nerve
 - v. Medial part of the lower leg:
 1. Saphenous nerve that is derived from the femoral nerve

Anatomical Relationship of the Lumbar and Sacral Plexus

1. The L1, L2, L3 ventral rami are the primary components of the lumbar plexus with contributions from T11 and T12
 - a. They traverse the posterior portion of the psoas muscle anterior to the vertebral transverse processes:
 - i. Femoral nerve (L2–L4 primary spinal nerves) also supplies sensation to the thigh and leg by:
 1. Medial and intermediate nerve of the thigh
 2. Saphenous nerve which provides sensation to the medial calf
2. Obturator nerve (L2–L4 spinal nerves)
 - a. Innervates the adductor muscles of the thigh
 - b. Provide cutaneous innervations to the medial thigh
3. Muscular branches that derive directly from the plexus:
 - a. Iliopsoas (L2–L3 spinal nerves)
 - b. Iliacus (L2–L3 spinal nerves)

Reflexes

1. Depressed or absent patellar reflex:
 - a. Femoral nerve
2. Loss of cremasteric reflex:
 - a. Genitofemoral nerve

Sacral Plexus

General Characteristics

1. S1–S3 ventral rami are the major roots:
 - a. Contribution from L4–L5 and S4–S5 roots
2. The plexus overlies the lateral sacrum and the posterior lateral pelvic wall
3. Sciatic nerve (spinal nerves L4, L5, S1–S3):

- a. Innervates the hamstrings; all muscles below the knee
- b. All sensation below the knee except that supplied by the saphenous nerve (medial lower leg):
- c. At the sciatic notch it divides into the common peroneal and tibial nerves
- 4. Superior gluteal nerve (L4, L5, S1 spinal nerves):
 - a. Innervates the gluteus medius and minimus muscles
- 5. Inferior gluteal nerve (L5, S1, S2 spinal nerves):
 - a. Innervates the gluteus maximus muscles
- 6. Posterior femoral cutaneous nerve (S1, S2, S3):
 - a. Innervates the buttocks, perineum, posterior thigh
 - i. The cuneal branch innervates the posterior upper thigh and inferior buttock

Lesions of the Sacral Plexus

Complete Lesion

1. Motor signs:
 - a. Paralysis or paresis of muscles innervated by the superior gluteal, inferior gluteal and the sciatic nerves
 - i. “Flail foot” from paralysis of both the dorsal and plantar foot musculature
 - b. Weakness:
 - i. Knee flexion:
 - 1. Hamstrings
 - ii. Foot eversion:
 - 1. Peroneal
 - c. Foot inversion (L4–S1 spinal roots):
 - i. Tibialis anterior and posterior tibial nerve
 - d. Plantar flexion of the toes:
 - i. Medial plantar nerves (II–V digits)
 - ii. Tibial nerve innervates the flexor hallucis longus
 - e. Extension of the toes:
 - i. Peroneal nerve innervates the extensor hallucis longus; L5–S1 roots
 - ii. Deep fibular nerve (Extensor hallucis longus muscle – EHL)
 - f. Abduction and internal rotation of the thigh:
 - i. Superior gluteal nerve
 - g. Hip extension:
 - i. Inferior gluteal nerve

Sensory Signs

1. Loss of sensation in the sciatic nerve distribution
 - a. Outer leg
 - b. Dorsum, sole and inner aspect of the foot
2. Posterior thigh and popliteal fossa
 - a. Posterior femoral cutaneous nerve

Reflexes

1. Decreased Achilles reflex
 - a. Sciatic nerve
2. Depressed bulbocavernosus reflex

Sphincter Signs

1. Loss or dysfunction of bladder and bowel control
 - a. Pudendal nerve

Differential Diagnosis Features Between Root and Lumbosacral Plexus Lesions

1. Positive mechanical signs favor a root lesion:
 - a. Straight leg raising test (sciatic nerve and S1 root)
 - b. Reverse SLR (places traction on the femoral nerve); the leg is extended with the patient lying on his stomach
 - c. Valsalva maneuver that causes pain:
 - i. Root greater than plexus involvement
2. Warm dry and red foot:
 - a. Indicative of a plexus lesion
 - b. Involvement of the retroperitoneal lumbar sympathetic nerves
3. Proximal > distal leg muscle weakness suggests a plexus lesion
4. Gluteus muscle innervations arise directly from the plexus
5. Iliopsoas muscle is not involved in a femoral nerve lesion because its innervation is directly from the plexus

Trauma of the Lumbosacral Plexus

General Characteristics

1. The lumbosacral plexus is often injured with trauma to the pelvic ring:
 - a. Double fracture dislocation
 - b. Traction injury from dislocation of the hip joint
2. Femoral nerve compression due to position:
 - a. Occupies the gutter between the psoas and iliopsoas muscle above the inguinal ligament
 - i. Surgical retraction (medially)
 - ii. Injured laterally by a hematoma between the iliacus fascia and the nerve
3. The lumbosacral cords are vulnerable to compression at the:
 - a. Pelvis brim by the fetal head
 - b. Obstetric forceps
4. Aneurysm of the common iliac or hypogastric arteries in the presacral areas
5. The femoral nerve is compressed by:
 - a. Angulation under the inguinal ligament
 - b. Prolonged flexion abduction of the thigh (dorsal lithotomy position under anesthesia)
6. Fixation points of the common peroneal nerve are at the sciatic notch and fibular neck:
 - a. Vulnerable to traction injury

Clinical Manifestations

1. Fracture:
 - a. Double vertical fracture dislocations of the pelvic bony ring:
 - i. 50% of patients suffer neurologic deficits
 - b. The injury is usually ipsilateral to the iliac joint damage
 - c. The lumbosacral plexus cord level is affected by consequent compromise of L5–S1 spinal nerve innervated muscles
2. Rupture, compression and traction injuries affect:
 - a. Lumbosacral trunk:

- i. Primarily L4 and L5 spinal nerves (L5 primarily)
 - ii. The spinal nerves are contiguous with the sacrum adjacent to the sacroiliac joint
- b. Obturator and/or superior gluteal nerves are often concomitantly injured
- c. L5–S3 anterior rami may be affected
- d. Concomitant vertebral body rupture
3. Intra-arterial injections
 - a. Injections into the buttock:
 - i. Ischemic injury due to vasoactive drugs that are injected into the inferior gluteal artery causing ischemia of the sciatic nerve
 - ii. Weakness, pain, and sensory loss in the sciatic nerve distribution occur minutes to a few hours after the injection
 - iii. Widespread lumbar plexus injury may occur due to retrograde extension of gluteal artery spasm to branches of the internal iliac artery
 - iv. Buttock skin may be painfully swollen, cyanotic and develop gangrene
 - v. Painless lumbosacral plexopathy may follow cisplatin injection into the iliac artery
4. Obstetric and gynecologic procedures that damage the lumbosacral plexus:
 - a. Risk factors:
 - i. Short women with large babies
 - ii. Prima gravida
 - b. Post-partum weakness
 - i. Lumbosacral trunk injury (primarily L5 spinal nerve) compression at the pelvic brim over the sacroiliac joint:
 1. Cephalic pelvic disproportion
 2. Protracted labor
 3. Mid pelvic forceps delivery
 - c. Involvement of the quadriceps muscles:
 - i. Bilateral in 25% of patients
 - ii. Concomitant with an obturator neuropathy
 - d. Causes of peripheral femoral neuropathy:
 - i. Lithotomy position under anesthesia during vaginal delivery (compression under the inguinal ligament)
 - ii. Separation of the symphysis pubis with direct compression of the nerve by the fetal head
 - iii. Epidural anesthesia:
 - iv. Paracervical block that affects the posterior femoral nerve (pain may be delayed by several days)
 - v. Lumbosacral plexus compressed at the pelvic brim by a uterine leiomyoma (accelerated growth during pregnancy)
 - vi. Intrapelvic Schwannoma
 - e. Catamenial sciatic nerve pain:
 - i. Implantation of endometrial tissue either intra-abdominally or at the sciatic notch
 - ii. Endometrial deposits in the sciatic notch may be associated with an outpouching of a pocket of peritoneum
 - iii. Perimenstrual pain in the buttock or posterior thigh

Clinical Manifestations

1. Weakness, sensory loss, and reflex changes are dependent on the lumbosacral component or the terminal nerve that is affected
 - a. Motor, sensory and reflex deficits are evident in multiple nerves or segmental distributions in the affected extremity

Neuropathology

1. Neuropractic and axonometric injury occur with compression and traction injuries
2. Neuromeric injury is primary with high impact trauma and some surgical procedures

Neuroimaging

1. Ultrasonography of the plexus
2. MRI:
 - a. To evaluate the plexus and soft tissue
3. CT
 - a. To evaluate bone at the site of injury

Surgical Trauma of the Lumbosacral Plexus

1. Laterally placed retractor blades compress the femoral nerve between the iliac and psoas muscle during:
 - a. Vaginal hysterectomy
 - b. Modified lithotomy position (under anesthesia)
 - c. Pelvic procedures (ovarian tumors and cysts)
2. Hip joint replacement
 - a. Approximately 0.7–1% of hip replacement surgeries are complicated by femoral, obturator or sciatic palsies
 - b. Subclinical nerve damage occurs from:
 - i. Preoperative stretch injury due to hip dislocation
 - ii. Retroperitoneal hemorrhage
3. Other surgical complications
 - a. Heat
 - b. Toxicity from methyl methacrylate bone cement
 - c. Direct trauma and that from retractor blades
 - d. Post-operative aneurysm formation
4. Aneurysm of the iliac or hypogastric artery:
 - a. Rectal examination reveals a firm pulsatile mass
 - b. Surgical repair has been associated with ischemic plexus lesions
 - c. Hemorrhage from an aortic, iliac or a hypogastric aneurysm may compress the femoral nerve
 - d. Retroperitoneal hematoma occurs from abdominal aortic aneurysm leakage

Tumors of the Lumbosacral Plexus

General Characteristics

1. Occur in less than 1% of patients with neoplasms
2. Direct extension from the tumor occurs in approximately 75% of patients while metastasis from extra-abdominal sites in approximately 25%
3. In approximately 15% of patients, lumbosacral plexopathy is the initial presentation

4. The lumbar plexus is affected in approximately 1/3 of patients; the sacral plexus in 50% and the remainder both plexus bilateral involvement is seen in 25% of patients

Clinical Manifestations

1. Severe unilateral pain radiating into L1–L4 sensory root distributions or the costovertebral angle
2. Weakness of the iliopsoas and quadriceps muscle (L1–L4 ventral roots)
3. Lower extremity edema
4. A warm dry and red foot if the sympathetic chain is involved paravertebrally
5. Lymphomas and lymphosarcoma may attain a large size and present as an abdominal mass

Neuropathology

1. Tumors that involve the lumbosacral plexus:
 - a. Colorectal, prostate, cervical, ovarian are the primary tumors
 - b. They invade by local extension
2. Metastatic lesions:
 - a. Breast
 - b. Lymphoma
 - c. Sarcoma
 - d. Lung
 - e. Thyroid (rare)
 - f. Melanoma
 - g. Testicular
 - h. Multiple myeloma
3. Primary pelvic plexus tumors:
 - a. Neurofibroma
 - b. Schwannoma
 - c. Sarcoma (degenerations of a benign neurofibroma)
4. Benign tumors
 - a. Dermoid of the omentum
 - b. Uterine leiomyoma

Neuroimaging

1. CT scan and MRI are positive more than 80% of patients by the time of clinical presentation
2. Sacral bone involvement is often a sign of colorectal cancer

Radiation Therapy (X-RT)

General Characteristics

1. Median time to the onset of symptoms is variable; the usual is five years; in some patient, symptoms may appear 20–30 years after treatment
2. There is no apparent relationship between the amount of X-RT and the latent period to symptoms
3. Signs rarely occur with less than 40 Gy rads

Clinical Manifestations

1. Bilateral or unilateral slowly progressive leg weakness
2. Starts distally usually in the L5–S1 roots; muscle wasting and absent reflexes

3. Numbness and paresthesia may be the presenting symptoms
4. Mild pain as a late symptom (approximately 50% of patients); aching, burning and lancinating in character
5. May arrest after several years (usually five years)
6. Often associated bowel and bladder symptomatology treatment

Neuropathology

1. The usual cancers that are irradiated are:
 - a. Lymphoma
 - b. Testicular
 - c. Ovarian
 - d. Uterine
 - e. Cervical
2. X-RT may induce:
 - a. Malignant nerve sheath tumors
 - b. Post-irradiation lower motor neuron syndrome
3. A dose above 1 Gy effects can be seen in:
 - a. Schwann cells
 - b. Fibroblasts
 - c. Vascular and perineural cells
4. Injury may occur after:
 - a. External beam photon therapy
 - b. Intestinal or intracavitary radiation implants
 - c. Combined photon and proton beam
5. The effect is dose dependent:
 - a. Animal experiments demonstrate that the threshold dose is 20–25 Gy
 - b. Accumulated doses below 40 Gy with conventional fractionation of 1.8–2.0 Gy are considered to have a low risk of injury to nervous tissue
6. Late effects include proliferative endarteritis and fibrosis in the plexus and soft tissue; vascular permeability and venous exudation

Neuroimaging

1. MRI:
 - a. Demonstrates thickening of the plexus with tumor and atrophy with X-RT; no enhancement with gadolinium with X-RT
2. Diffusivity measurements differentiate malignant lesions from irradiation injury

Laboratory Evaluation

1. CSF:
 - a. CSF protein may be slightly elevated
2. EMG:
 - a. Myokymia may be demonstrated in approximately 60% of patients

Radiation vs. Tumor Invasion of the Lumbosacral Plexus

Radiation Plexopathy

1. Insidious onset and progression
 - a. Sensory symptoms may begin at two months; may resolve after several months

- b. Presenting symptoms and signs may be weakness
- c. Bilateral involvement
- d. Distal muscle weakness (L5–S1 roots)
- e. Atrophy and no enhancement on MRI; less diffusivity on DWI
- f. EMG may be normal or demonstrate myokymia and fasciculation

Tumor Invasion

- 1. Rapid onset and progressive course
- 2. Pain may be the initial symptom
- 3. Unilateral involvement
- 4. Proximal weakness (L1–L4 roots)
- 5. Enhancing mass on MRI (with gadolinium); destruction of bone

Post-Irradiation Lower Motor Neuron Syndrome

- 1. X-RT of the lower thoracic and lumbar spine
- 2. Painless wasting and fasciculation of leg muscles
- 3. May have a delayed onset from the end of treatment (months to years)
- 4. Sphincter function is normal
- 5. EMG:
 - a. Sensory nerve action potentials are normal
 - b. Denervation is seen in the affected muscles

Medical Causes of Lumbosacral Plexopathy

Diabetic Radiculoplexus Neuropathy

General Characteristics

- 1. Involves the nerve roots and the lumbosacral plexus most often in a setting of diabetic length-dependent neuropathy
- 2. Approximately 8% prevalence in type I and II diabetic patients
- 3. Rarely the presenting feature of diabetes
- 4. Often seen in Type I diabetic patients controlled by diet and oral hypoglycemic agents
- 5. Most common onset is the sixth to seventh decade
- 6. Rare to have concomitant nephropathy, retinopathy, or history of coma

Clinical Manifestations

- 1. Hip and anterior thigh pain are often the initial presenting symptoms
- 2. Leg weakness supervenes within a few days to weeks
- 3. Weakness predominates in a lumbar plexus distribution that affects:
 - a. Hip flexion
 - b. Adduction
 - c. Knee extension
- 4. Approximately 2/3 of patients have weakness in the L5 myotome; 50% are weak in the S1 dermatome in addition to the proximal muscles innervated by L1–L4 roots. L5 and S1 innervated muscle weakness may occur without involvement of proximal muscle weakness

- 5. Sensory loss is common but often not noticed due to pain and weakness
- 6. A small percentage of patients have neuropathy of the trunk
- 7. Approximately 50% of patients have involvement of the autonomic nervous system that includes:
 - a. Orthostatic hypotension
 - b. Urinary dysfunction
 - c. Impotence
 - d. Constipation or nocturnal diarrhea
- 8. 75% of patients have concurrent length-dependent neuropathy
- 9. There may be gradual improvement of weakness over months, and the pain diminishes over weeks; proximal muscles are more likely to recover

Neuropathology

- 1. Microvasculitis:
 - a. Epineural and perivascular inflammation
- 2. Multifocal fiber loss is demonstrated on nerve biopsy
- 3. The process is frequently bilateral
- 4. Impaired glucose tolerance has been demonstrated in a large percentage of patients with idiopathic plexopathy

Neuroimaging

- 1. MRI:
 - a. An early screen to r/o other pathologies
 - b. If malignant infiltration of the plexus is suspected CT should be added to imaging parameters as up to 40% of patients have epidural tumor extension

Laboratory Evaluation

- 1. EMG and nerve conduction velocities to evaluate the level and extent of the plexopathy as well as the often concurrent length-dependent neuropathy
- 2. Sed rate is elevated in 20% of patients
- 3. CSF:
 - a. Protein may be elevated (120 mg% suggests root involvement)

Idiopathic Lumbosacral Plexitis

General Characteristics

- 1. Phenotype is similar to that of diabetic radiculoplexus neuropathy
- 2. Lumbar plexus is more often affected than the sacral although pan-plexopathies occur
- 3. Age of onset is 30 months to 81 years of age
- 4. It is usually monophasic and mild but may be recurrent and have a progressive course
- 5. Bimodal incidence:
 - a. Prior to age 20 years of age
 - b. Between 40–60 years of age
- 6. Mild trauma, vaccination and viral illness have been reported to precede the illness in some patients
- 7. Children, in general, have a monophasic course; adults may have recurrences

Clinical Manifestations

1. Abrupt onset of unilateral pain in the anterior thigh (lumbar plexitis) and posterior thigh and buttock (sacral plexitis); some patients have a more prolonged onset with recurrent bouts of pain
2. Muscle weakness is observed within 5–10 days of onset of the pain; it may progress for days to weeks; the pain resolves as the weakness supervenes
3. Muscle weakness of L1–L4 roots is most common and is associated with a positive femoral reverse SLR nerve test and absent quadriceps reflex
4. Lower plexus involvement:
 - a. Positive Tinel's sign at the sciatic notch and popliteal fossa
 - b. Weakness of the anterior and posterior tibialis, everters of the ankle, foot flexors, and extensors
 - c. Absent Achilles reflex
5. The process may be bilateral
6. Recovery is often prolonged (over months) and is incomplete

Neuropathology

1. Impaired glucose tolerance has been reported in some patients
2. Nerve biopsy demonstrates demyelination and axon loss similar to diabetic patients
3. Probable microvasculitis; possibly immune-mediated

Neuroimaging

1. MRI:
 - a. To rule out compressive or invasive lesions
 - b. Gadolinium-enhanced lumbar and sacral roots, and trunks may be demonstrated

Laboratory Evaluation

1. EMG/NCV:
 - a. To delineate the location and severity of the process
2. HbA1c (must be negative)
3. Sed rate elevated in some patients
4. CSF:
 - a. Slight increase in protein has been demonstrated in some patients

Differential Diagnosis of Medical Causes of Lumbosacral Plexus Lesions**Vasculitis****General Characteristics**

1. Usually a necrotizing vasculitis

Clinical Manifestations

1. Develops acutely
2. Painful; weakness with fixed sensory loss
3. Progresses in a step-wise manner
4. Constitutional symptoms are associated that include:
 - a. Fatigue and weight loss

b. Associated conditions:

- i. Granulomas of the respiratory tract
- ii. Retinitis
- iii. Purpura
- iv. CNS involvement
- v. Eosinophilia

c. Specific entities:

- i. Diabetic microvasculitis
- ii. SLE
- iii. Periarteritis nodosa
- iv. Sarcoid
- v. Steroid responsive lumbosacral plexopathy
- vi. Wegener's granulomatosis
- vii. Hereditary temperature sensitive plexopathy (AD)

Infections Affecting the Lumbosacral Plexus**1. Abscess:**

- a. Bacterial abscess whose origin is in the psoas or paraspinal musculature

b. Perirectal abscess:

- i. Immunocompromised patients
- ii. Prior rectal surgery
- iii. Fever in association with groin, abdominal or back pain
 1. Usually sciatic nerve radiation
 2. L4–S2 motor/sensory deficits

2. Anogenital Herpes Simplex

- a. Less than 1% of women with primary anogenital infection develop plexopathy
- b. Most frequent incidence is in males with herpetic proctitis
- c. HS type 2 greater than type 1
- d. The primary anogenital lesion may be on the cervix
- e. Rare plexopathy with recurrent attacks
- f. Clinical features:
 - i. Dermatomal leg weakness and sensory loss
 - ii. Paresthesias and sensory loss in the perineum, buttocks, and posterior thigh
 - iii. Urinary retention, constipation, and erectile dysfunction
 - iv. Reduced tone of the anal sphincter; sensory loss in sacral dermatomes; loss of the bulbocavernosus reflex
 - v. May involve lower motor neurons of the sacro-coccygeal plexus
 - vi. Mild meningeal irritation
 - vii. Symptoms and signs last 10 days to 3 weeks often with good recovery

g. Laboratory evaluation:

- i. Diagnosis is confirmed by PCR
- ii. CSF may demonstrate a lymphocytic pleocytosis

3. Cytomegalic virus:

- a. Lumbosacral plexus noted in severely ill HIV patients
 - i. CD4⁺ count of <200 mm³
- b. Severe pain, paresthesia and weakness in a wide distribution

- c. Associated retinitis
- 4. Herpes Zoster:
 - a. L5–S1 roots
- 5. Tuberculosis:
 - a. Cold abscess; involves the psoas and iliacus muscle; (T12–L4 roots)
- 6. Pyelonephritis:
 - a. Upper > lower plexus
- 7. Appendicitis:
 - a. Upper roots of the lumbar plexus
 - b. Characteristic iliopsoas spasm
- 8. Iliacus muscle abscess:
 - a. Following laparoscopy
 - b. Upper plexus involvement
- 9. Lyme's disease:
 - a. L5 root most often affected
- 10. Brucellosis:
 - a. L5 root is most often affected
- 11. Syphilis:
 - a. Dorsal root entry zone; meninges are involved particularly involving cervical root
 - b. HIV-associated
- 12. Epidural abscess:
 - a. Surgery
 - b. Catheters (anesthesia for pain)
 - c. Osteomyelitis
- 13. IV drug abuse:
 - a. Pyogenic organisms
 - b. Staph aureus is most common
 - c. Affects the disc space (end arterial supply)
 - i. Severely painful (vibration of the bed causes pain)
 - ii. Very positive meningeal stretch signs
 - d. MRI:
 - i. Involvement of both the anterior and posterior longitudinal ligaments
 - ii. Enhancement of the disc space, the nerve roots, and the paravertebral muscle
 - e. Contiguous spread of infection to nerve roots from osteomyelitis is the most common route of infections
- 14. EBV Infection:
 - a. Upper lumbar plexus involvement

Retroperitoneal Hemorrhage

General Characteristics

1. The lumbar plexus may be compressed within the iliopsoas muscle
2. Femoral nerve in isolation may be compressed by an iliacus hematoma or hemorrhage (trauma or retractor)

Clinical Manifestations

1. Femoral nerve
 - a. The iliacus fascia is lighter than the psoas fascia; smaller hematomas produce femoral compression more frequently than diffuse lumbar plexopathy

2. Pain in the groin radiating to the anterior thigh and medial lower leg (primarily L3–L4 roots and the saphenous nerve)
3. Position of comfort is a flexed upper leg
4. Positive reverse straight leg raising test
5. Minimally painful Patrick's maneuver (internal/external rotation of the upper leg)
6. Weakness of the quadriceps; loss of sensation in the femoral nerve territory; loss of the quadriceps reflex
7. Grey-Turner's sign in approximately 5–10 days over the costovertebral angle (purple blood breakdown products)
8. Clinical manifestations of psoas muscle hematoma
 - a. Severe groin and lower abdominal pain
 - b. The upper leg is not usually flexed at the hip:
 - c. Negative reverse SLR test (forced upper leg extension)
 - d. Rarely hip flexion with external rotation of the leg is painful
 - e. No palpable hematoma; rarely a groin mass is palpable
 - f. Thigh adductor muscle weakness (obturator nerve)

Neuropathology

1. Iliacus and psoas hemorrhage; occur most often in anticoagulated patients
 - a. May be associated with an abrupt drop in hemoglobin
 - b. Rarely bilateral
 - c. Heparin has a greater incidence than Coumadin; the never anticoagulants have not yet been reported
 - d. Often there is no preceding trauma
 - e. Most often a neuropractic nerve injury

Neuroimaging

1. Loss of the psoas shadow on a routine abdominal flat plate
2. MRI demonstrates the hemorrhage

Differential Diagnosis of Hemorrhagic Plexus Lesions

1. Athletic injury; hyperextension and avulsion of the iliacus muscle from the ileum
2. Localized blunt trauma; pelvic fracture
3. Disseminated intravascular coagulation
4. Hemophilia and other clotting disorders
5. Leukemia
6. Aneurysmal rupture
7. Anticoagulation

Immune-Mediated Causes of Lumbosacral Plexopathy

1. AIDP (acute inflammatory demyelinating plexopathy) may involve the proximal plexus
2. CIDP (distal nerve involvement to a greater degree than proximal nerve roots)
3. Specific epitopes:
 - a. GMI
 - b. Gal-NAC-GTdla
 - c. Gd1b
 - d. MAG
 - e. SGPG
 - f. Anti-sulfatide

4. Paraneoplastic Antibodies
 - a. Anti-Hu
 - b. Anti-Yo
 - c. Anti-MA
 - d. Anti-TA
5. Post-vaccination
6. Post-serum infusion with anti-venoms antibody preparations

Toxins/Anesthetics

1. Lidocaine/bupivacaine
 - a. 0.25% or greater concentration usually delivered by epidural catheter for severe neuropathic pain; demyelinating lesions of the roots
 - b. Benzyl alcohol adjuvant of anesthetics
 - c. Heroin (IV drug abuse); the adulterants may be talc or quinine to which there is an autoimmune response
 - i. May have a delayed onset of symptoms and signs (1–2 days after infusion)
 - ii. Diffuse lower extremity pain
 - iii. Minimal weakness or sensory loss
 - iv. Pain clears prior to recovery of motor function
 1. May be associated with transverse myelitis of ten at T4

Differential Diagnosis of Gadolinium Enhancement of the Lumbosacral Plexus

1. Carcinomatous meningitis
2. AIDP
3. CIDP
4. Arachnoiditis
5. Infections (CMV in particular)
6. Sarcoid
7. Leukemia/lymphoma
8. Tumor invasion

Differential Diagnosis of Unusual Lumbosacral Plexus Lesions

1. Acute aortic occlusion:
 - a. Level of the lesion may be:
 - i. Conus medullaris
 - ii. Cauda equina
 - iii. Proximal nerve trunks
 - iv. Lumbosacral plexus
 - b. Clinical manifestation
 - i. Acute lower extremity monoplegia

Neuromuscular Choristoma

General Characteristics

1. Rare congenital lesions
 - a. Differentiated muscle intertwined with peripheral nerve and the lumbosacral plexus

Clinical Manifestations

1. Undergrowth of the affected limb
2. Primarily in the sciatic nerve:

- a. Progressive neuropathy
 - b. Shortened atrophic limb
 - c. Pes cavus
3. Undergrowth of bone with hip dysphasia

Neuropathology

1. Normal differential muscle within the affected nerve or plexus

Neuroimaging

1. Smoothly tapering fusiform enlargement of the sciatic nerve or brachial and/or lumbar plexus
2. T1 and T2 signal characteristics of muscle
 - a. Longitudinal bands of loss of T1 and T2 signal
3. Nerve fascicle thickening results in coccyx cable root presentation

Further Reading

Further Reading on Plexus Disorders

Cervical Plexus

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Chapter 7

Peripheral Neuropathy

Overview

The differential diagnosis of peripheral neuropathies can be based on the determination of the signs and symptoms of:

1. The predominant fiber size in the nerve that is affected
2. The patterns of motor or sensory loss
3. The time course of the illness
4. Associated medical conditions
5. Exposure to toxins and medications
6. Most importantly the individuals' genetic background

Approximately 30% of peripheral neuropathies remain undiagnosed after a sophisticated evaluation. This percentage will steadily decrease with modern techniques of high throughput genetic testing.

The patient's predominant symptoms and neurologic examination suggest the fiber size that is involved in the neuropathy that focuses the examination on the physical findings subserved by that fiber size. It is important to realize that damage to peripheral nerves cause dynamic changes in both the peripheral and central nervous system such that modality-specific sensory information such as touch may be perceived as pain. These changes are complex and involve responses of the injured nerve to its microenvironment (that includes immune cells, tachykinins, protons, and other proteins) with consequent changes at all levels of the peripheral and central nervous system. These changes from afferent input may activate genes that in turn induce structural changes in the central nervous system.

The smallest unmyelinated fibers are C-fibers (that are polymodal) and autonomic fibers that are approximately 1 μ in size. The predominant symptoms expressed by patients with involvement of these fibers are distal extremity burning pain and autonomic dysregulations.

Secondary signs and symptoms of C-fiber involvement may be:

1. Mechanical allodynia in which an innocuous stimulus (touch) is perceived as painful
2. Hyperalgesia in which a normally painful stimulus is amplified
3. Hyperpathia where the stimulus threshold to elicit pain is increased but once exceeded reaches maximal intensity too rapidly, is overwhelming, and is not stimulus bound

C-fibers are primarily involved in neuropathic pain but are also involved in other aspects of sensation such as pleasurable touch. A-delta thinly myelinated fibers may also be considered small fibers and mediate well-localized fast lancinating pain, the sensation of cold and deep muscle ache. Allodynia to mechanical and thermal stimuli, hyperalgesia and hyperpathia, characterize neuropathic pain which is a major symptom of many neuropathies.

Recent studies of mechanical allodynia reveal that after nerve injury:

1. Neurokinin-1 receptor expressing pain projection neurons of lamina I in the dorsal horn receive excitatory afferent input from somatostatin-containing interneurons via a pre-existing polysynaptic pathway
2. These somatostatin interneurons also receive input from nociceptors
3. This pathway under normal conditions is inhibited by dynorphin/GAD67 interneurons located in lamin II of the dorsal horn
4. These inhibitory GABA-ergic interneurons are normally modulated by polysynaptic projections from AB fibers as well as A-delta and C-fiber nociceptors
5. A-beta (touch fibers) are also linked to lamina I NKIR pain projecting neurons through PKC (phosphokinase C gamma/somatostatin) interneurons, central cells and somatostatin interneurons in outer lamina II of the dorsal horn
6. This pathway is modulated by glycinergic and dynorphin expressing interneurons. As noted above sensory processing in the dorsal horn is exceedingly complex and is not fully understood

It is clear that after a nerve injury touch and mechanical afferent input is relayed to nociceptive circuits in lamina I and II of the dorsal horn that are involved in mechanical allodynia.

Autonomic fiber symptomatology (unmyelinated fibers) derives from:

1. Autonomic dysregulation manifested by postural hypertension
2. Obstipation
3. Sexual dysfunction
4. Micturition abnormalities
5. Hypo- or hyperhidrosis
6. Pupillary alterations

Characteristically, small fiber neuropathies have decreased pain and temperature thresholds, minimal weakness, and atrophy with retained reflexes.

Large fiber neuropathies (12–22 μ fiber size) have deficits in motor, vibratory, proprioceptive, and discriminative touch. Patients demonstrate sensory ataxia, distal and proximal weakness, a positive Romberg sign, poor balance, and loss of reflexes.

In general, both large and small fibers are involved in neuropathies (recently small fiber deficits have been shown in Charcot-Marie-Tooth disease (CMT)) and demonstrate motor, sensory, and autonomic features to various degrees. Frequently sensory abnormalities are noted initially with the gradual development of motor and autonomic phenomena. Coldness of the effected extremities with sweating deficits are common symptoms and signs of autonomic involvement in a mixed peripheral neuropathy.

The distribution of the sensory loss is extremely important in differential diagnosis. Axonal metabolic dying back neuropathies (length dependent dying back neuropathy) affect

the longest axons initially. Patients develop deficits in the toes and distal legs initially, and the fingers become involved when the process crosses the knees. The center part of the chest is affected in a shield distribution. The dorsal root ganglia that subserve the central chest are in the thoracic spine and their most distal axons (that subserve the central chest) degenerate initially. Similarly, in the face, when the cervical nerve roots are affected, the chin and midface may be numb or dysesthetic prior to areas near the ear (C2 distribution). In general, these neuropathies progress symmetrically although initially, they may be slightly asymmetric. Some polyneuropathies demonstrate a proximal symmetric pattern of weakness. These include Guillain-Barré syndrome, acute intermittent porphyria, diabetes, and chronic inflammatory demyelinating polyneuropathy (CIDP). Rarely patients may have a proximal accentuation of weakness superimposed on distal weakness (from a distal length-dependent process such as occurs with diabetes and HIV).

Focal neuropathies occur with entrapments in various tunnels, mononeuritis multiplex from infarction or nerve compression. These may be genetic as is the case with hereditary neuropathy with compression palsy (deletion of chromosome 17) or mechanical from trauma, anesthesia, alcohol or coma. Mononeuritis multiplex (sequential involvement of large nerves) has recently been described as presenting as a distal symmetric polyneuropathy. Monoradiculopathies, polyradiculopathies, and plexopathies are distinguished by their characteristic patterns of involvement. Differential diagnosis becomes more difficult in situations where there are several simultaneous processes such as diabetes and multiradiculopathies from cervical and lumbar spondylosis. Almost all older patients have some degree of osteoarthritic involvement at C5–C6 and L4–L5 and L5–S1 levels. Shoulder trauma and repetitive movements may damage the brachial plexus, individual nerves, and nerve roots. Commonly diabetic and HIV-infected patients have nerve involvement at several levels. Almost all patients with complex regional pain syndrome (CRPS I/II) have multiple nerve, plexus and root components that maintain the illness.

As a general rule in the upper extremities, root disease is primarily felt proximally and rarely radiates to the fingers. The exception is C6 that radiates to the lateral forearm, thumb, and index finger. The C7–T1 spinal nerve almost never gets injured as this is a non-movement segment. Brachial plexus and upper extremity nerve problems radiate to the hand. In the lower extremities, the reverse is true. Radicular pain frequently radiates to the leg and foot while lumbosacral plexus problems are experienced proximally. Nerve pathologies are experienced both proximally and distally. At times, polyradiculopathies at L4–L5 and L5–S1 may simulate a neuropathy but most patients have had prior back, buttock and posterior thigh radiations at some point in their course. The examination demonstrates the particular motor and sensory deficits of the involved roots. Multifocal neuropathies may have characteristic distributions such as cold

parts of the body in leprosy (ear lobes, nose and dorsal aspects of extremities) and a regional distribution as in CRPS I.

The temporal profile of a neuropathy is extremely helpful in differential diagnosis and may be divided into:

1. Acute (progressing over days to weeks)
2. Subacute (6 months to one year)
3. Chronic (6 months to years)

Within the time frame, the process may be monophasic, intermittent or progressive.

Acute neuropathies are generally autoimmune mediated, toxic exposures, in the setting of critical care or metabolic as exemplified by acute intermittent porphyria. Subacute neuropathies may be autoimmune, paraneoplastic, metabolic or due to vitamin deficiency. Chronic neuropathies are often hereditary or metabolic (uremia, diabetes, liver failure).

Axonal neuropathies are characterized by digital muscle weakness, atrophy, and at times, fasciculation whereas demyelinating neuropathies demonstrate weakness and loss of deep tendon reflexes out of proportion to atrophy.

Hereditary neuropathies are suggested by pes cavus, a foreshortened foot and intrinsic foot muscle atrophy. The insertions of the gastrocnemius muscles in the lower extremities are too high, and there is often distal 1/3 of the quadriceps muscle atrophy. The patients' wrists and ankles are thin. Associated medical conditions include kyphoscoliosis, ataxia, cardiomyopathy and other dysmorphisms. The process evolves slowly. Patients may note that it was always difficult for them to stand in one place without shifting weight due to a deep ache in the legs. They may have had difficulty running and were clumsy in their adolescent years. Approximately 10% of hereditary neuropathies have abnormally flat or "rocker bottom feet." These patients along with those that have pes cavus suffer an undue number of twisted ankles due to peroneal muscle weakness. Family members are often affected but are unaware of the condition.

Almost all acquired neuropathies have a seminal feature that leads to a clinical diagnosis.

Hereditary Peripheral Neuropathies Charcot-Marie-Tooth Disease (CMT)

General Characteristics

1. Hereditary neuropathies comprise approximately 50% of undiagnosed neuropathies
2. CMT is the most common type of hereditary neuropathy and is classified by:
 - a. Nerve conduction velocity
 - b. Demyelinating or axonal primary pathology
 - c. Mode of inheritance:
 - i. Autosomal dominant
 - ii. X-linked
 - iii. AR
 - iv. Sporadic

- d. Age of onset
- e. Identification of the causative gene mutation
3. CMT1 is the demyelinating form and CMT2 is characterized by axonal degeneration
4. Overlapping phenotypes exist; CMT1 patients show signs of secondary axonal degeneration
5. Patients within each subtype may be unequally affected in regard to motor and sensory deficits
6. The genotype is heterogeneous, and there is complexity of phenotype/genotype correlation; greater than 900 mutations in various genes have been described
7. Clinical groups overlap and the same phenotype can be caused by mutations in different genes
8. CMT occurs in approximately 1:2500 individuals

Clinical Manifestations of CMT1

1. Ratio of CMT1 to CMT2 is approximately 2:1
2. Onset is usually from the first to third decade although a few patients may remain asymptomatic into later life
3. They are initially distally weak with an early predilection for the anterior compartment peroneal muscles with consequent foot drop; they suffer frequent falls and ankle sprains
4. Steppage gait
5. Rare complaints of numbness or tingling although patients may have difficulty standing still without muscle ache. Positive early sensory complaints are a strong differential point for an acquired neuropathy. There is decreased sensation to all modalities and recent studies demonstrate a small fiber component to the sensory loss
6. Muscle weakness and atrophy is severe below the knee and often effects the distal 1/3 of the quadriceps; rarely there is pseudohypertrophy of the calves which is asymmetric
7. Pes cavus or a foreshortened foot with hammer toes is most common; a small proportion has a flattened foot with no arch, a "rocker bottom" foot
8. Approximately 2/3 of patients have intrinsic hand muscle weakness and atrophy that may become severe in some patients in later stages of the illness; over time there is slight to moderate proximal muscle weakness
9. Respiratory difficulties rarely occur from phrenic nerve involvement
10. Reflexes are usually unobtainable
11. Hypertrophy of nerve roots rarely compresses the spinal cord or cauda equina
12. Nerve hypertrophy may be palpitated in the great auricular nerve, the supraclavicular nerves, ulnar and the peroneal nerve at the fibular head
13. Rare associated findings:
 - a. Deafness
 - b. Adie's pupil
14. Roussy-Levy essential tremor occurs in approximately 1/3 of patients

Neuropathology

1. Nerve biopsy:
 - a. Loss primarily of large diameter fibers
 - b. Diminished axon diameter with neurofilaments within atrophic axons
 - c. Recurrent demyelination and remyelination result in decreased intermodal length
 - d. Schwann cell proliferation causes the formation of onion bulbs
 - e. Loss of myelinated fibers in the posterior columns of the spinal cord

Neuroimaging

1. MRI:
 - a. Predominant early atrophy of the anterior compartment muscles

Laboratory Evaluation

1. EMG:
 - a. By 3–5 years of age, the nadir of nerve conduction velocity is reached and remains stable for the rest of the patient's life
 - b. Compound motor action potential amplitude (CMAP) progressively decreases over time (axonal loss)
 - c. Distal motor latencies increase until approximately ten years of age at which time they plateau
 - d. Motor nerve conduction velocities:
 - i. Motor NCV are less than 38 m/s; usually, they range between 20–25 m/s
 1. Point mutations in peripheral myelin protein 22 (PMP22) and those with mutations in myelin protein zero (MPZ) have NCV 10 m/s or less
 2. There is no conduction block or temporal dispersion
 3. Prolonged distal motor latencies
 4. F-waves latencies are usually absent or are extremely prolonged
 5. Sensory nerve action potentials (SNAPs) are unobtainable or of low amplitude; NCVs are very slow
2. Evoked potentials:
 - a. Somatosensory evoked potentials demonstrate slow central conduction
 - b. Visual evoked potentials reveal slow conduction in central optic pathways (in some CMTs)
3. Cerebrospinal fluid (in general)
 - a. Increased protein

Clinical Variants of CMT

CMT1A

General Characteristics

1. Approximately 85% of patients with CMT1A have a duplication within chromosome 17p11.2-12 in the PMP22 gene (3 gene copies)

- a. Patients with deletion of this chromosome segment (one gene copy remains) have hereditary neuropathy with liability to pressure palsies (HNPP)
- b. Most de novo duplications are paternally inherited
- c. Point mutations in the PMP22 gene
 - i. Phenotypically resemble Dejerine-Sottas

Clinical Manifestations

1. Classic features as described for CMT1

Neuropathology

1. Duplication of one of the alleles of the PMP22 gene
2. Toxic effect of PMP22 overexpression
3. Enlarged nerves with Schwann cell proliferation, loss of myelinated fibers (large diameter fibers), decreased internodal length
4. Disruption of multiple types of cell junction complexes in peripheral nerve with increased permeability of myelin and impaired action potential propagation
5. Increases in endoneurial extracellular matrix volume (synthesized by Schwann cells)
6. Abnormalities in fibronectin and tenascin
7. Increase in endoneurial collagen

Neuroimaging

1. MRI:
 - a. Anterior compartment (leg) muscle atrophy initially
2. Peripheral nerve ultrasound (in pediatric patients)
 - a. Increased cross-sectional area (1.9–3.5 fold increase compared to controls)
 - b. Disease severity correlated with cross-sectional area and age

CMT1B

General Characteristics

1. Approximately 20% of patients with CMT1 have CMT1B
2. Genetics:
 - a. Mutations in the MPZ gene are located on chromosome 1q22-23
3. MPZ is an integral myelin protein
4. Some mutations are associated with a severe demyelinating CMT3 phenotype (early onset); the later onset form is suggestive of the CMT2 axonal form

Clinical Manifestations

1. A severe early onset form with delayed walking (NCV < 10 m/s)
2. Later onset form with more axonal pathology
3. More commonly associated with Adie's pupil

Neuropathology

1. MPZ is an integral myelin protein that is a member of the immunoglobulin superfamily
2. Localizes to the tight, compact regions of myelin possibly maintaining tight compaction by forming links between adjacent myelin layers

3. Rarely tomaculae and uncompacted myelin are demonstrated

Neuroimaging

1. Similar to CMT1A

Laboratory Evaluation

1. Greater axonal characteristics on EMG than CMT1A

CMT1X

General Characteristics

1. The second most common form of CMT
2. Genetics:
 - a. Mutation of the gap junction protein beta 1 (GJB1) gene:
 - i. Encodes connexin 32 (CX32)
 - ii. Located on the X-chromosome
 - iii. There is no male to male transmission and males are more affected than females
 - iv. All amino acid mutations are pathogenic
 - v. Females have a spectrum of deficits putatively due to X-inactivation

Clinical Manifestations

1. Peripheral manifestations are similar to CMT1A and 1B characterized by progressive weakness, atrophy, and sensory abnormalities distally more often than proximally
2. A subgroup of patients has mild deafness and abnormalities on brainstem evoked potentials
3. Weakness and atrophy develop in the hands. Thenar atrophy and positive sensory symptoms and loss are more evident than in CMT1A
4. Males are clinically affected by ten years of age
5. CMT1X is an X-linked dominant trait:
 - a. It affects female carriers
 - b. Affected women have a later onset than men and have a milder phenotype
 - c. Women may be completely asymptomatic but obligate carriers have electrophysiological evidence of peripheral neuropathy

Neuropathology

1. Prominent features are age-related loss of myelinated fibers and regenerated axon clusters
2. Myelin sheaths are inappropriately thin for the axonal diameter which supports:
 - a. Segmental demyelination and remyelination
 - b. Remyelination after axonal regeneration

Laboratory Evaluation

1. EMG:
 - a. Men with CMT1X mutations demonstrate "intermediate" nerve conduction velocities with mildly prolonged distal motor and F-wave latencies

- b. Forearm motor NCV in males are 30–40 m/s and 30–50 m/s in females
- c. Conduction slowing in CMT1X is less uniform among nerves and dispersion is greater than in CMT1A
- d. Electrophysiological evidence of distal axonal loss

CMT1C

General Characteristics

1. Genetics:
 - a. Autosomal dominant, which is unusual for CMT, as most other forms are recessive
 - b. Mutations in the gene SIMPLE (also named LITAF, EET1, and PIG7) the small integral membrane protein of the lysosome/late endosome causes CMT1C
 - c. A putative role in endosomal regulation and vesicular trafficking which is fundamental for cargo entry, export and intracellular transport in cells
 - d. SIMPLE is secreted by the endosome pathway
 - e. The percentage of CMT1 with this mutations is 0.6%

Clinical Manifestations

1. Chronic CMT1 phenotype

Neuropathology

1. SIMPLE is an early endosomal protein rather than a late lysosomal/late endosomal protein
2. In genetically altered mice there is myelin unfolding that originates from paranodal regions near Schmidt-Lanterman clefts
3. The illness is caused by dominant effects of the mutant protein rather than haploinsufficiency of SIMPLE protein
4. Nerve biopsy of one patient demonstrated onion bulb formation

CMT1D

General Characteristics

1. Comprises less than 1% of molecularly defined cases of CMT1
2. Genetics:
 - a. Missense mutations in the early growth response 2 gene (also called Knox 20) located on chromosome 10
 - b. EGR2 is a transcription factor that is involved in the transcriptional regulation of myelin genes in Schwann cells
3. Localization with SOX10 genes

Clinical Manifestations

1. CMT1 phenotype

Neuropathology

1. Mutations interfere with the expression of genes required for myelination by Schwann cells

CMT1E

General Characteristics

1. Allelic to CMT1A
2. Point mutation in the PMP22 gene

Clinical Manifestations

1. CMT1 phenotype
2. Associated deafness

CMT1F

General Characteristics

1. Mutations in the neurofilament light chain gene NF-1
2. Located on chromosome 8p13-21
3. CMT1 phenotype

Laboratory Evaluation

1. EMG evaluation:
 - a. May be associated with low amplitude CMAPs and normal or only slightly slow NCVs and thus is often classified as CMT2F
 - b. Some patients have conduction velocities in the mid-twenties which classify them as CMT1F

Hereditary Neuropathy with Liability to Pressure Palsies (HNPP)

General Characteristics

1. Also known as tomaculous neuropathy is autosomal dominant
2. Caused by a 1.5 Mb deletion in chromosome 17p16.2
3. De novo deletions are paternally inherited
4. May also be rarely caused by mutations in myelin protein zero (MPZ)
5. The mutation affects peripheral myelin protein 22 (PMP22) the same region that is duplicated in CMT1A

Clinical Manifestations

1. Manifests within the second or third decade; rarely presents in the first decade and some patients remain asymptomatic
2. The usual presentation is painless numbness and weakness in the distribution of a peripheral nerve; rarely, there are cranial neuropathies and multiple mononeuropathies
3. Precipitants are most often trivial compression of a nerve or repetitive movements
4. The mononeuropathies usually resolve over weeks to months
5. The most common site of compression is the carpal tunnel, cubital tunnel, spiral groove and the fibular head. The brachial plexus may be involved from carrying a heavy load or clavicular pressure from a backpack

6. Rarely patients may suffer a progressive or relapsing sensorimotor peripheral neuropathy that may be misdiagnosed as a CMT or chronic inflammatory demyelinating polyneuropathy (CIDP)
 7. There is often sensory loss to all modalities primarily affecting large fibers, decreased reflexes throughout and pes cavus
 8. HNPP is approximately 6% of patients with CMT
- d. Proteins involved in lipid metabolism:
 - i. MTMR2, RAB7, SPTLC1, SPTLC2
 - ii. These genes are ubiquitously expressed and have pleiotropic functions:
 1. Chaperone activity
 2. Autophagy
 3. Vesicular transport
 4. Protein and lipid biosynthesis

Neuropathology

1. Focal globular thickening of the myelin sheath that resembles a sausage (tomacula). These are redundant loops of myelin
2. There is a decrease in large myelinated fibers, segmental demyelination and remyelination and axonal atrophy and degeneration
3. Patients have only one copy of the PMP22 gene
4. De novo deletions arise from unequal crossing over during meiosis
5. De novo mutations of female origin are from intrachromosomal rearrangement
6. Mutation within the PMP22 gene may cause the illness putatively by a loss of function of the gene

Laboratory Evaluation

1. EMG:
 - a. Sensory and motor NCVs (nerve conduction velocities) demonstrate prolonged distal latencies and slightly slow NCVs with normal or reduced amplitudes
 - b. Across entrapment sites, there is slowing of NCVs, conduction block, and temporal dispersion
 - c. There may be distal accentuation of slowing without compression
 - d. Asymptomatic family members may demonstrate slowing of NCVs

CMT2 Autosomal Dominant Axonal Neuropathies

General Characteristics

1. The axonal forms of CMT comprise approximately 50% of the illness which have been linked to over 15 gene mutations
2. The genes are involved in four major physiologic functions:
 - a. Neuron-specific:
 - i. Cytoskeletal organization
 - ii. Axonal transport
 - iii. NEFL, GAN1, and KIF1B
 - b. Code for heat shock proteins
 - i. HSPB1, HSPB3, HSPB8
 - c. Aminoacyl-tRNA synthetase
 - i. GARS, YARS, AARS, HARS, KARS

3. The canonical roles of heat shock proteins are:
 - a. Protein folding under stress conditions
 - b. Cytoskeletal regulation
 - c. Apoptosis
 - d. Autophagy
 - e. Oxidative stress

Clinical Manifestations of CMT2

1. CMT2, in general, has later onset than CMT1
2. Onset is usually in the second decade although some patients are asymptomatic until adulthood
3. Less severe involvement of the intrinsic hand muscles than patients with CMT1
4. CMT1 has more severe involvement of the peroneal, anterior tibialis, gastrocnemius and soleus muscles than patients with CMT2
5. Generalized areflexia is common in CMT1 and rare in CMT2
6. CMT1 may have tremor (Roussy-Levy syndrome)
7. 50–70% of CMT2 patients have decreased light touch, pain, joint position and vibration sensibility. Recent work has demonstrated small fiber sensory loss by quantitative sensory testing in CMT1 patients
8. Both CMT1 and CMT2 have loss of ankle jerks
9. Pes cavus and hammer toes are more severe in CMT1 patients
10. Approximately 25 to 30% of CMT2 patients have identified mutations

Seminal Manifestations of the Clinical Variants of CMT2

CMT2A2

General Characteristics

1. Is caused by mutations in the mitofusin 2 gene that is located on chromosome 1p36
2. It is the most common form of CMT2 and comprises approximately 20% of CMT2 patients
3. MFN2 mutation may account for 79% of severely impaired patients with CMT2
4. Associated neurologic findings include:
 - a. Optic atrophy
 - b. Pyramidal tract deficits
 - c. Hearing loss
 - d. Vocal cord paralysis (patients with severe disability)

Neuroimaging

1. MRI:
 - a. Subcortical white matter hyperintensities
 - b. A subgroup with spinal cord atrophy with or without hydromyelia

CMT2B*General Characteristics*

1. Mutations in the Rab7 gene have been identified as causative
 - a. Rab7 is a small G-protein that is involved in vesicular transport to late endosomes and lysosomes in the endocytic pathway
 - b. The mutant Rab7 proteins have impaired GTPase activity
 - c. Mutations in the SPTLC1 gene may also be causative

Clinical Manifestations

1. Foot ulcers and amputations of the toes on a background of sensory loss, distal muscle, and atrophy

CMT2B1*General Characteristics*

1. The disease is caused by a homozygous missense mutation at the LMNA locus at chromosome 1q21.2-q21.3
2. Patients come from Northwestern Africa (northwest of Algeria and east of Morocco)
3. The inheritance is autosomal recessive
4. Lamins A and C are allelic to limb-girdle muscular dystrophy
5. Other mutations in the lamins A and C protein cause:
 - a. Emery-Dreifuss muscular dystrophy
 - b. Fiber type disproportion
 - c. Limb-girdle muscular dystrophy
 - d. Dilated cardiomyopathy with conduction defect
 - e. Different forms of lipodystrophy and progeria

Clinical Manifestations

1. The age of onset is between 6 to 27 years
2. The cause can be variable with rapid progression of a proximal and distal muscle weakness and sensory loss or a milder phenotype that evolves slowly

CMT2C*General Characteristics*

1. The illness is caused by mutations in gene encoding the calcium-permeable ion channel TRPV4 (transient receptor potential vanilloid 4)
2. The TRPV spectrum disorders are autosomal dominant and show variable disease expression and reduced penetrance
3. The TRPV4 disorders are grouped into six neuromuscular disorders and skeletal dysplasia

4. The three neuromuscular disorders are:
 - a. CMT2C
 - b. Scapuloperoneal spinal muscular atrophy
 - c. Congenital distal spinal muscular atrophy (CDSMA)
5. There are six skeletal muscle dysplasias

Clinical Manifestations of CMT2C

1. The age at onset is variable and can begin in infancy
2. Disease in infancy:
 - a. Breathing difficulties and stridor
 - b. Phrenic nerves may be affected
 - c. In adults, vocal cord paralysis is evident which may begin with hoarseness
 - d. There is severe atrophy of the distal limbs, but proximal weakness may develop
 - e. Sensory loss to all modalities
 - f. Reduced or absent deep tendon reflexes
 - g. Some patients develop pes cavus but not to the same degree as is seen with CMT1, CMT2A or CMT2B
 - h. Patients have been reported as having hereditary distal spinal muscular atrophy with vocal cord paralysis
 - i. Patients may manifest skeletal dysplasia and peripheral neuropathy

CMT2D*General Characteristics*

1. Autosomal dominant inheritance
2. Mutations in the glycyl-tRNA synthetase (GARS) gene
 - a. 13 GARS mutations have been associated with CMT disease
 - b. Loss of function mutations
3. Patients with Silver syndrome from mutations in the BSCL2 gene can present similarly

Clinical Manifestations

1. Age of onset is between 12 to 36 years
2. The hands are more affected than the distal legs; there is prominent first dorsal interosseous wasting
3. The course is slowly progressive
4. There is distal sensory loss to all modalities
5. Areflexia slowly supervenes
6. One patient described with a GARS mutation had facial and respiratory muscle involvement
7. A subgroup of patients may develop pes cavus, hammer toes and scoliosis
8. The disorder is allelic to distal spinal muscular atrophy type B

CMT2E*General Characteristics*

1. The disease is caused by mutations in the neurofilament light chain NEFL gene; chromosome 8p21
2. Autosomal dominant inheritance
3. The phenotypic spectrum has not been fully elucidated

Clinical Manifestations

1. Manifests in the second and third decade
2. Distal leg weakness
3. Deafness in some patients
4. Sensory loss to all modalities
5. Pes cavus
6. Areflexia
7. One patient had post-partum exacerbation

CMT2F*General Characteristics*

1. Caused by mutations in the HSPB1 gene that encodes a small heat shock protein 27; chromosome 7q11-q21
2. Autosomal dominant inheritance demonstrated in a large multigenerational Russian family

Clinical Manifestations

1. Symmetric weakness and atrophy of distal leg muscles that is more severe than the arms
2. Onset is between 15 to 25 years

Neuroimaging

1. MRI evaluation:
 - a. A proximal to distal gradient of muscle involvement in male patients; less impairment of distal thigh muscles (3/5 patients)
 - b. Minimal or no muscle abnormalities were detected in female patients (2/5 patients)

CMT2G*General Characteristics*

1. The disease is caused by mutation the gene HSPB8 located in chromosome 12q12-q13.3
2. Evaluated in a Spanish kinship

Clinical Manifestations

1. Age of onset between 9 to 76 years
2. Most patients became symptomatic in the second decade of life (mean age of 29)
3. Classic CMT2 phenotype
4. Maybe allelic to CMT4H

CMT2H*General Characteristics*

1. Possibly allelic to CMT4A

CMT2L*General Characteristics*

1. The disease is caused by mutations in the gene HSPB8 which encodes heat shock protein 22:
 - a. The mutations are primarily in the Lys 141 residue; clinical heterogeneity occurs in patients with the Lys 141 mutation

2. Mutations (K141N and K141E) that occur in the α -crystallin domain of HSP22 cause distal hereditary motor neuropathy or CMT2L
3. The stress-induced molecular chaperones:
 - a. Assist in the correct folding of denatured proteins
 - b. Prevent aggregation of misfolded proteins

Clinical Manifestations

1. Distal limb atrophy, sensory loss (axonal loss in large myelinated fibers)
2. Areflexia
3. Classic CMT2 phenotype
4. The same genetic defect is noted in distal hereditary neuropathy 2A (dHMN2A)

Neuroimaging

- a. MRI imaging:
 - i. Lower extremity MRI reveals similarity between HSPB8 and HSPB1 in 1 patient

CMT2I/2J*General Characteristics*

1. The disease is caused by mutations in the myelin protein zero (MPZ gene)
2. MPZ:
 - a. Is an essential structural protein that is required for peripheral nerve myelination
 - b. It has a single extracellular transmembrane and cytosolic domain which bind to adjacent molecules that form tetramers which link to opposing tetramers on adjacent wraps of myelin
 - c. Mutations are dominant-negative (frameshift, missense or nonsense)
3. There are two major forms:
 - a. Early childhood onset
 - b. Late adult onset

Clinical Manifestations

1. Early onset form:
 - a. Presents in infancy with hypotonia and delayed motor milestones
 - b. Nerve conduction studies demonstrate severe slowing of less than 15 m/s
 - c. There may be a slight elevation of CSF protein
2. The demyelinating phenotype CMT1B presents in the first decade with gait abnormalities ("steppage"), falls and pes cavus
3. The adult form (CMT2I, CMT2J)
 - a. Presents usually between 18 to 50 years of age
4. CMT2J
 - a. In addition to phenotypic CMT2 axonal neuropathy has:
 - i. Adie's pupil
 - ii. Hearing loss
5. CMT2I
 - a. Electrophysiology is more associated with a demyelinating pattern

*Neuropathology***Mechanism 1**

1. Length-dependent axonal loss with/without segmental demyelination
2. Pathogenesis of MPZ neuropathies:
 - a. The mechanism of MPZ mutations is failure of the protein to reach the plasma membrane
 - b. The protein accumulates within the cytoplasm or endoplasmic reticulum
 - c. The abnormal aggregates decrease protein translation, activate protein degradation and may induce apoptosis

Mechanism 2

1. MPZ mutation
 - a. Protein reaches the plasma membrane but fails to adhere to adjacent MPZ molecules

Mechanism 3

1. The mutated protein reaches the plasma membrane, adheres to adjacent molecules but fails to maintain normal Schwann cell-axon interactive

CMT2K*General Characteristics*

1. Mutations in ganglioside-induced differentiation associated protein 1 (GDAP1)
2. It is allelic to CMT4A
3. Most often causes autosomal recessive demyelinating, axonal and intermediate forms
4. There is a rare AD form

Clinical Manifestations

1. Usually manifests in childhood
2. May have vocal cord paralysis; the AD form has a milder phenotype, and this sign is usually absent
3. Nerve conduction velocities may be axonal or demyelinating

Neuropathology (CMT2K)

1. A generalized decrease in myelinated fibers more evident in large myelinated fibers
2. Wallerian degeneration and signs of regeneration (small clusters of thinly myelinated fibers) are seen
3. Onion bulb formation is not prominent
4. Electron microscopy of CMT2A may have an abnormal accumulation of mitochondria
5. CMT2E has giant axons packed with disorganized neurofilament

Laboratory Evaluation

1. EMG:
 - a. Sensory NCS have reduced or absent SNAP amplitudes in both upper and lower extremities
 - b. Conduction velocities are normal or only slightly slow; greater than 38 m/sec
 - c. Distal sensory latencies may be slightly prolonged

- d. Distal extremity muscles may show fasciculation and fibrillation potentials
- e. Rare patients with CMT2 have continuous motor unit action potential firing that is abolished by neuromuscular blockade
- f. Recruitment is decreased in weak muscles

Dominant Intermediate CMT**Overview**

There are subgroups of CMT in which NCVs (nerve conduction velocities) overlap the axonal and demyelinating range of 25–45 m/s; axonal neuropathies > 38 m/sec. There are axonal and demyelinating characteristics on nerve biopsies.

The three intermediate types of CMT that have been identified are:

1. CMTA on chromosome 10q24.1-25.1
2. D1-CMTB (19p 12-p13.2)
3. D1-CMTC (1p34-p35), CMT1X, CMT2E, late onset CMT1B and CMT4A have patients that may qualify for this category
 - a. Clinical features are similar to those described in CMT1 and CMT2

DI-CMTB*General Characteristics*

- a. Mutations in the DNM2 gene lead to dynamin 2 protein alterations that cause AD centronuclear myopathy and dominant intermediate CMT type B
- b. Dynamin 2 is a large GTPase whose best-known function is related to membrane scission during vesicle budding from plasma or Golgi membranes
- c. Pleiotropic functions include:
 - i. Synaptic vesicle recycling
 - ii. Postsynaptic receptor internalization, neurosecretion, actin assembly and centrosome cohesion
- d. The major function of dynamin 2 in peripheral neuropathy has been proposed to be clathrin-mediated endocytosis which may be pivotal in myelination

DI-CMTC*General Characteristics*

1. DI-CMTC is caused by mutations in tyrosyl and glycyl-tRNA synthetase (YARs and GARs)
 - a. Aminoacyl-tRNAs are ubiquitously expressed and charge tRNAs with their cognate amino acids
2. They are localized in axon terminals
3. Mutations do not impact charging function and thus may not be primary in disease mechanisms

Congenital Hypomyelinating Neuropathy, Dejerine-Sottas Disease*General Characteristics*

1. CMT3 is genetically heterogeneous with most patients having PMP22, MPZ or ERG2 gene point mutations

2. Loss of function mutations in periaxin has recently been linked to autosomal recessive Dejerine-Sottas disease
3. There is a wide spectrum of clinical phenotypes, electrophysiological characteristics and neuropathology with these gene mutations

Clinical Manifestations (CMT3)

1. Presentation is at birth or in early childhood
2. Infantile form:
 - a. Have hypotonia and distal contractures (arthrogryposis multiplex)
 - b. Severe patients suffer respiratory distress, poor suck and swallow reflexes; many die in several months
 - c. In children that are ambulant:
 - i. Distal muscles are more affected than proximal; weakness may progress to patients becoming wheelchair-bound
 - d. Peripheral nerves are palpably enlarged
 - e. There is sensory loss in all sensory modalities most severe in vibration and proprioceptive domains
 - f. There is generalized areflexia
 - g. Unusual features are sensorineural hearing loss and pupillary abnormalities
 - h. Patients often have pes cavus and kyphoscoliosis

Neuropathology

1. Patients may have hypomyelination with basal lamina
2. Classic onion bulbs or amyelination
3. The nerve fasciculi are enlarged in the face of reduced myelinated fibers. There is less involvement of unmyelinated fibers
4. Hypomyelination with basal lamina onion bulbs is the most common pathology
5. Onion bulbs are composed of layers of basement membranes with minimal Schwann cell lamella in the outer ring
6. Congenital amyelinating neuropathies have few nerve fibers and minimal myelin

Laboratory Evaluation

1. EMG:
 - a. Motor NCV are typically 5–10 m/s
 - b. Distal motor latencies are markedly increased with low amplitudes
 - c. Sensory responses are not obtainable
 - d. There is increased insertional activity, positive sharp waves, and fibrillation potentials; there is decreased recruitment of MUAP (motor unit action potentials)
 - e. If there is some reinnervation there are large amplitude, long duration and polyphasic MUAPs; in severe patients with minimal reinnervation, MUAPs are small
 - f. CSF protein is often moderately elevated

CMT Disease Type 4

General Characteristics

1. Less than 10% of CMT patients in Europe and North America have autosomal recessive CMT

2. In areas with a high percentage of consanguineous marriages such as the Mediterranean basin and parts of the Middle East ARCTM may comprise 30 to 50% of patients with CMT

Clinical Manifestations

1. Childhood onset
2. Usually more severe than the classic CMT phenotype
3. They are most often demyelinating

CMT4A

General Characteristics

1. Caused by mutations in the GDAP1 (ganglioside induced differentiation protein) that is located on chromosome 8q13-q21
2. Expressed in both Schwann cells and neurons
3. Is located in the mitochondrial outer membrane
4. A component of the mitochondrial network
5. The autosomal dominant mutation causes CMT2K

Clinical Manifestations

1. Distal extremity weakness usually occurs before age two; there is developmental delay, and proximal weakness supervenes by the end of the first decade
2. A subgroup of patients is wheelchair bound by the third decade
3. Vocal cord paralysis and diaphragm weakness may occur
4. Mild sensory loss
5. Areflexia
6. Scoliosis and pes cavus occur
7. Autosomal dominant (CMT2K)
 - a. May begin late even at the 6th decade
 - b. Mild clinical course (axonal neuropathy)

CMT4B

General Characteristics

1. CMT4B is caused by mutations in the genes that encode:
 - a. The lipid phosphatase myotubularin-related protein 2 CMTMR2; CMT4B1
2. MTMR13 (CMT4B2); chromosome 11p15
 - a. Phosphoinositides (PI) 3-phosphatases that dephosphorylate phosphatidylinositol 3-phosphate
 - i. Lipids that regulate endolysosomal membrane traffic
 - ii. MTMR2 is catalytically active and associates with inactive MTMR13
 - iii. MTMR13 loss causes axonal degeneration and is associated with myelin outfoldings
 - iv. MTMR2 and MTMR13 are localized to punctuate compartments in Schwann cell cytoplasm
 - v. MTMRs and MTMR13 are physically codependent for normal protein expression

Clinical Manifestations

1. Distal greater than proximal weakness; legs more than arms

2. Weakness occurs at birth or the first year of life; rarely it may be initiated in the third decade
3. Motor milestones are delayed
4. There is primarily large fiber sensory loss
5. Weakness is slowly progressive which may lead to loss of ambulation
6. Reflexes are absent
7. Scoliosis occurs

Neuropathology

1. Focally folded myelin sheaths are noted on nerve biopsy

CMT4C

General Characteristics

1. CMT4C is due to mutations in the SH3TC2 gene
2. The gene maps to chromosome 5q23-q33 and is AR
3. Most patients are from families around the Mediterranean basin but also has been described in a European Gypsy kindred
4. There is significant clinical variation between families

Clinical Manifestations

1. The mean age of onset was in the 4th decade
2. Scoliosis may be the presenting manifestation
3. The early onset form may be characterized by delayed walking, foot deformities and scoliosis by age 5; distal greater than proximal extremity weakness
4. Sensory impairment is primarily in large fiber myelinated afferents and is often manifest in those patients with severe weakness
5. Reflexes are reduced or absent
6. Enlarged nerves may be apparent
7. Cranial VIII involvement with severe vestibular deficits may be prominent; cranial nerve VII and XII may be involved in isolation, or there may be combined involvement of cranial nerves IX and X
8. A subgroup of patients may have proximal muscle weakness

Neuropathology

1. Demyelinating fibers surrounded by excess Schwann cell lamellae that form basal lamina onion bulbs
2. Abnormally long and attenuated Schwann cell processes

Laboratory Evaluation

1. A subgroup of patients demonstrates conduction block and temporal dispersion

CMT4D

General Characteristics

1. An autosomal recessive demyelinating neuropathy
2. Due to R148 X mutations in the N-myc downstream-regulated gene 1 (NDRG1)
3. Probably allelic to hereditary motor and sensory neuropathy with deafness-Lom (HSMNL)

Clinical Manifestations

1. Exclusively found in gypsies kindred's
2. An early demyelinating phenotype with deafness
3. A subgroup of patients with copy number variation (3 Turkish patients)
 - a. Severe distal and mild proximal weakness
 - b. Distal extremity loss of light touch, vibration, and proprioceptive loss
 - c. Kyphoscoliosis, pes cavus, hammer toes and claw hands

Laboratory Evaluation

1. EMG:
 - a. Absence of sensory nerve action potentials
 - b. CMAPs are unobtainable in some patients
2. Moderate sensorineural hearing loss primarily in low frequencies

Neuroimaging

1. White matter hyperintensities (primarily subcortical) seen in a subgroup of patients

CMT4E

General Characteristics

1. Also known as congenital hypomyelination neuropathy
2. Mutations are in PMP22, MPZ or ERG2 genes

Clinical Manifestations

1. CMT3 phenotype

CMT4F

General Characteristics

1. Associated with periaxin (PRX) mutations; chromosome 19q 13.13-q13.2:
 - a. Periaxin protein forms tight junctions between myelin loops and the axon
 - b. Maintenance of normal myelin structure

Clinical Manifestations

1. In general, starts in early childhood but late onset patients have been described
2. Walking is usually late (>3 years); patients may become wheelchair bound in their mid-twenties
3. Associated signs include:
 - a. Restrictive respiratory syndrome due to severe scoliosis (after age 12)
 - b. Strabismus, glaucoma, and myopia
 - c. Pes cavus

Neuropathology

1. Demyelinating neuropathy

Laboratory Evaluation

1. EMG:

- a. Motor conduction velocities are slow; prolonged motor latencies

CMT4G

General Characteristics

1. Mutations that are primarily in the European Roma population are CMT4C, CMT4D, and CMT4G
2. The gene mutations in NDRG1 causes CMT4D
3. HK1 gene mutation causes CMT4G:
 - a. A > C change in a novel alternative untranslated exon in the HK1 gene causes CMT4G/HMSN-Russe
 - b. Hexokinase 1 blocks apoptotic signals at the mitochondria

Clinical Manifestations

1. Severe weakness and sensory loss in a CMT phenotype of the distal extremities
2. A dominant mutation in HK1 causes retinitis pigmentosa

Laboratory Evaluation

1. EMG:
 - a. Motor nerve conduction velocities are in the demyelinating or intermediate range

CMT4H

General Characteristics

1. CMT4H is caused by mutations in the FGD4 gene/Frabin located on chromosome 12p11.21-q13.11
 - a. Encodes a small RHO GTPases with guanine nucleotide-exchange factor Frabin
 - b. Experimental evidence (genetically altered mice) support a role for the protein both in nerve development and myelin maintenance
 - c. Frabin/FGD4 regulates Schwann cell endocytosis

Clinical Manifestations

1. A demyelinating phenotype

CMT4J

General Characteristics

1. Mutations in FIG4 cause the Yunis-Varon syndrome and CMT4J
2. The FIG4 phospholipid phosphatase controls the generation and level of phosphatidylinositol (3,5) P2 phosphoinositide
 - a. Phosphatidylinositol (3,5) P2 regulates membrane and protein trafficking in the endosome-lysosome pathway
 - b. Deficits from FIG4
 - c. Losses cause enlargement of late endosome-lysosomes and cytosolic vacuolization

Clinical Manifestations

1. The Yunis-Varon syndrome

- a. Autosomal recessive inheritance
- b. Skeletal and structural brain abnormalities
- c. Facial dysmorphism
- d. Seizures
2. FIG4 mutations in the syndromes are missense or nonsense that abolish FIG4 enzyme activity
3. CMT4J
 - a. Demyelinating phenotype with AR inheritance
 - b. Late-onset patients may initially have a predominantly motor asymmetric neuropathy with rapid progression

Neuropathology

1. Severe demyelination with axonal loss
2. Onion bulb formation
3. Polymicrogyria

Laboratory Evaluation

1. Both early-onset and late-onset CMT4J demonstrate decreased nerve conduction velocities

HINT1

General Characteristics

1. HINT1 (histidine triad nucleotide binding protein 1)

Clinical Manifestations

1. Progressive distal muscular atrophy and weakness
2. Clinical myotonia

Laboratory Evaluation

1. EMG:
 - a. Neuromyotonia associated with severe predominantly axonal neuropathy

Summary of Neuropathology in CMT Type 4

1. CMT4A:
 - a. Decreased myelinated fibers with hypomyelination
 - b. Basal lamina onion bulbs
2. CMT4B:
 - a. Hypomyelination
 - b. Loss of myelinated fibers
 - c. Basal lamina onion bulbs
 - d. Fibers with excessively folded myelin sheaths (tomacula)
3. CMT4C:
 - a. Decreased large diameter myelinated fibers with less involvement of small and intermediate fibers
 - b. Axons are thinly myelinated and are surrounded by Schwann cells that form classic onion bulbs
4. CMT4F:
 - a. Severe axonal loss; remaining axons are hypomyelinated and associated with onion bulbs
 - b. Tomacula with focal myelin thickening
 - c. Alterations in paranodal myelin loops
 - d. Absence of paranodal septate-like junctions between the terminal loops and the axon

X-Linked CMT Disease**Genes Associated with ARCMT1 (Demyelinating Form)**

1. GDAP1
2. MTMR2
3. SBF2
4. NDRG1
5. EGR2
6. SH3TC2
7. PRX
8. FGD4
9. FIGA

Genes Associated with ARCMT2 (Axonal Form)

1. LMNA
2. MED25
3. HINT1
4. GDAP1
5. LRSAM1
6. NEFL
7. HSPB1
8. MFN2
9. PLEKHG5

CMT1X*General Characteristics*

1. CMT1X is the second most common form of CMT
2. CMT1X is caused by mutations in the GJB1 gene that encodes Cx32
3. Autosomal dominant and maps to chromosome xq13

Clinical Manifestations

1. Motor and sensory neuropathy in affected males
2. No symptoms in carrier females
3. Sensorineural hearing loss and central symptoms in some families
4. Men with CMT1X
 - a. Present in the first two decades of life; usually, male patients present by age 10
 - b. Initial symptoms may include difficulty running and sprained ankles
 - c. Distal weakness of the extremities progresses and involve the gastrocnemius and soleus muscles
 - d. Weakness in the hands is clear in intrinsic muscles, with particular involvement of the thenar eminence
 - e. Pes cavus, hammer toes, and claw hand deformities are common

Sensory loss to all modalities is demonstrated on examination but is usually not a patient complaint. It is more prominent than in CMT1A.

1. Obligate women carriers:
 - a. Females are less affected due to X inactivation, whereby only a fraction of their myelinating Schwann cells expresses the mutant GJB1 allele

- b. Women may be asymptomatic
- c. In those that are affected, the onset of the neuropathy is often in the second decade and has a milder phenotype
- d. Rarely patients may have transient CNS symptoms

Neuropathology

1. Cx32 is expressed by Schwann cells
2. Forms gap junction (GJ) through which there is diffusion of ions and small molecules that include second messengers
3. The diffusion across apposed cell membranes directly connects Schwann cell perinuclear cytoplasm with the adjacent cell compartment inside the myelin sheath
4. Gap junctions (GJs) formed by Cx32 are pivotal in homeostasis of myelinated axons
5. Most Cx32 mutations cause loss of function due to inability to form functional gap junctions (intercellular channels)
6. More than 400 mutations have been described to date; it accounts for approximately 12% of CMT
7. Sensory nerve biopsy:
 - a. Demonstrates a loss of myelinated nerve fibers, primarily of large diameter
 - b. Axonal degeneration and atrophy occur
 - c. Clusters of thinly myelinated regenerated fibers; occasional Schwann cell proliferation with onion bulbs may surround remaining thinly myelinated fibers
 - d. There is a mixture of demyelination and remyelination

Laboratory Evaluation

1. EMG:
 - a. NCS demonstrate characteristics of demyelinating and axonal degeneration that are more severe in affected men than affected women
 - b. SNAPs are absent most often (or reduced) but if obtainable have prolonged distal latencies
 - c. Men usually have intermediate slowing of nerve conduction velocities with mildly prolonged distal motor and F-wave latencies
 - d. Forearm motor NCV are 30–40 m/s in affected males and 30–50 m/s in affected females
 - e. Conduction slowing is less uniform among different nerves, and dispersion is more pronounced than with CMT1A
 - f. There is electrophysiological evidence of distal axonal loss
 - g. Reduction of motor units correlates with clinical severity

CMT2X*General Characteristics*

1. Associated with mutations in Xq24-Xq25; X-linked recessive

Clinical Manifestations

1. Early childhood initiation
2. Distal limb weakness, atrophy, and sensory loss
3. Males have sensorineural hearing loss; some develop cognitive dysfunction
4. Female carriers are asymptomatic

Neuropathology

1. Axonal motor and sensory neuropathy

LRSAM1*General Characteristics*

1. LRSAM1 (leucine-rich repeat and sterile alpha motif-containing protein D is a ubiquitin protein)
2. Mutations in LRSAM1 cause an autosomal dominant axonal CMT (3 families studied)
3. The protein functions in sorting internalized cell-surface receptor proteins and endocytosis
4. The mutation causes the loss of a splice donor site that results in the inclusion of 63 additional base pairs of intronic DNA into the aberrant transcript
5. The gene maps to chromosome 9q33-q34

Clinical Manifestations

1. Distal weakness and atrophy of the lower extremities are the initial manifestations
2. Loss of sensory modalities primarily of large fiber function; areflexia
3. Pes cavus and hammer toes
4. May have late occurrence in adulthood

Neuropathology

1. Sural nerve biopsy
 - a. Severe axonal degeneration

Laboratory Evaluation

1. Severe axonal neuropathy
2. Absent sural nerve sensory action potentials
3. Mildly reduced motor NCVs
4. Severe distal neurogenic features by needle EMG

PLEKHG5*General Characteristics*

1. Mutations in the Pleckstrin homology domain-containing family G member 5 (PLEKHG5) cause an autosomal recessive intermediate CMT
2. PLEKHG5 is expressed in the peripheral nervous system
3. Suggested to have a role in the activation of the RHOA exchange factor and NF-KB signaling pathways that are important in neuronal cell differentiation
4. Loss of function in the NF-KB transduction pathway and aggregate formation of mutant PLEKHG5 may be pathogenic

Clinical Manifestations

1. Onset in childhood
2. Weakness of the distal lower extremities with atrophy
3. Pes cavus and steppage gait
4. Loss of sensation to all modalities, but more large fiber deficits
5. Reflexes are absent in the lower extremities

Neuropathology

1. Loss of large and medium-sized myelinated fibers
2. Electron microscopy reveals that small myelinated fibers have occasional focal folding of myelin with minimal regeneration
3. Unmyelinated fibers demonstrate clustering and atrophy
4. Endoneurial fibroblast proliferation with collagen deposition

Neuroimaging

1. MRI:
 - a. T1-weighted sequences revealed severe muscle atrophy and fatty replacement of the lower leg
 - i. Selective involvement of the anterior and lateral compartment
 - ii. A pattern of length-dependent axonal degeneration

Laboratory Evaluation

1. EMG:
 - a. Median nerve conduction velocities ranged from 24.7 m/s to 29.3 m/s; prolonged motor latencies
 - b. Absent SNAP
 - c. Needle EMG demonstrated severe degeneration
 - d. CPK is modestly elevated

Differential Diagnosis of CMT

1. Autosomal dominant demyelinating neuropathy:
 - a. CMT1A:
 - i. Classic CMT phenotype
 - ii. EMG NCVs are uniformly slowed (20 m/s)
 - iii. Demyelination with onion bulbs
 - iv. Duplication on chromosome 17p11.2 affecting PMP22
 - b. CMT1B:
 - i. Mutations in myelin protein zero (MPZ)
 - ii. Severe early onset form (NCV less than 10 m/s) and a late onset axonal neuropathy
 - iii. Mutations in EGR2 and LITAF/SIMPLE are less than 1% of these patients
2. Hereditary neuropathy with liability to pressure palsies (HNPP):
 - a. Gene deletion in chromosome 17p11.2 that includes PMP22
 - b. Recurrent episodes of focal compression of nerves or plexi with focal motor and sensory deficits
 - c. Tomacula on nerve biopsy
3. X-linked CMT1:

- a. Mutations in the gap junction protein beta; the gene is GJB1 on the X-chromosome
- b. Encoded protein is connexin (CX32)
- c. NCVs are in the intermediate range (25–40 m/s)
- d. Males have greater impairment than females
- e. Mild deafness
- 4. CMT2X:
 - a. The gene has not been identified; mutations are in Xq24-Xq25
 - b. CMT phenotype with cognitive impairment
 - c. Axonal motor and sensory neuropathy
- 2. ARCMT possibly 30–50% of all CMT patients
- 3. Polymorphisms are frequent
- 4. ARCMTs are usually demyelinating and are usually severe:
 - a. CMT4B1 (MTMR2) and CMT4B2
 - i. Focally misfolded myelin
 - b. CMT4D and CCFDN:
 - i. Congenital cataracts
 - ii. Facial dysmorphism
 - iii. Neuropathy
 - iv. Primarily in the Balkan Roma population
 - c. CMT4C (SH3TC2 mutations):
 - i. Most common in European and North American patients
 - ii. Pivotal for myelination and maintenance of the node of Ranvier
 - iii. Severe early scoliosis
 - d. LMNA mutations
 - i. Associated with cardiomyopathy muscular dystrophies, mandibuloacral dysplasia, and restrictive dermopathy
 - e. GDAP1
 - i. Maps to chromosome 8q21.11
 - ii. It is an integral membrane protein of the outer mitochondrial membrane
 - iii. Most often autosomal recessive inheritance but less severe autosomal dominant form has been described

CMT2 Autosomal Dominant Axonal Neuropathies

General Characteristics

- 1. Most present with the classic phenotype of CMT
- 2. Greater range of onset than CMT1A
- 3. NCVs in the upper extremities are greater than 38 m/s with decreased CMAPs (unobtainable in severely affected patients)
- 4. CMT2A:
 - a. Mutations in the mitofusin 2 gene in chromosome 1p36
 - b. Severe early-onset axonal neuropathy; may comprise >90% of severely affected CMT2 patients
 - c. Associated optic atrophy, pyramidal tract, and other CNS deficits
 - d. Approximately 3–4% of genetically defined patients in North America
- 5. CMT2B:
 - a. Mutations in the RAB7 gene or SPTLC1 gene
 - b. Profound sensory loss with ulceration and amputations of toes in the lower extremities
 - c. Minimal weakness
- 6. CMT2D:
 - a. Mutations in the glycyl-tRNA synthetase gene (GARs)
 - b. Weakness with no or minimal sensory loss
 - c. Silver syndrome patients may have a similar presentation (mutation in the BSCL2 gene)
 - d. Severe hand weakness prior to leg weakness
- 7. CMT2C:
 - a. Mutations in the TRPV4 gene that maps to chromosome 12q24.11:
 - i. Great phenotypic variability
 - ii. Scapuloperoneal dystrophy to sensorimotor neuropathy
- 8. CMT2 mutations that present with the classic phenotype include:
 - a. CMT2E (NEFL mutation)
 - b. CMT2F (HSP27 mutation)
 - c. CMT2G and CMT2L (HSP22 mutations)
 - d. CMT2I (MP2 mutations)

Autosomal Recessive CMT4 (ARCMT)

- 1. Most frequently seen in populations with a high percentage of consanguineous marriages

Differential Diagnosis of Intermediate CMT

These are CMT neuropathies whose NCVs overlap the axonal and demyelinating range (25–45 m/s) and whose pathogenesis may affect both Schwann cells and axons.

- 1. Linkage to chromosome 10q24.1-25.1 (DI-CMTA)
- 2. Dynamin 2 (DI-CMTB)
- 3. YARS (DI-CMTC)
- 4. PLEKHG5 (autosomal recessive)

Differential Diagnosis by Pathologic Mechanism

- 1. Gene dosage:
 - a. Duplication of the 11.4-mb region on chromosome 17 that contains the PMP22 gene CMT1A
 - b. HNPP is caused by deletion of the same gene region
- 2. Schwann cell-axonal interaction. Axonal degeneration is seen in all forms of demyelinating CMT and may have a major role in the demyelinating process. Mutations in GJB1 and GDAP1 cause both demyelinating and axonal types of CMT which suggest that primary Schwann cell pathology disrupts myelin-axon interaction to cause axonal degeneration
- 3. Protein misfolding and impaired membrane trafficking:
 - a. Mutant MPZ accumulates in the endoplasmic reticulum to induce apoptosis (cell-based studies)
 - b. Defects of lysosomal transport or degradation:
 - i. CMT1C (LITAF/SIMPLE) mutations

- ii. CMT2B (Rab7) mutations
- c. Disruption of phosphoinositide-mediated trafficking within the cell
 - i. Mutations of myotubularin-related proteins (MTMR2 and 13 and FIGA mutations cause:
 1. CMT4B1
 2. CMT4B2
 3. CMT4J

Impaired Mitochondrial Physiology

Mitochondrial transport is pivotal for the energy supply of distal axons. They undergo fission and fusion that is partially regulated by mitofusin 1 and 2, which are nuclear encoded outer mitochondrial membrane proteins.

1. Suspected defects in mitochondrial function may be involved in CMT2A (MFN2) and CMT4A
2. Defects in PNS-specific proteins:
 - a. PMP22
 - b. MPZ
 - c. Periaxin
3. Defects in widely expressed proteins:
 - a. GARS
 - b. HSP27
 - c. CX32
4. Disruption of protein synthesis with predominant motor neuropathy:
 - a. GARS
 - b. YARS
5. Stress response:
 - a. HSP22 and HSP27
6. Axonal transport:
 - a. HSP27
7. Primarily sensory neuropathy:
 - a. RAB7
 - b. HSP27

Other Hereditary Motor and Sensory Neuropathies

Proximal Hereditary Motor and Sensory Neuropathy/Neuronopathy

General Characteristics

1. Linked to chromosome 3p14.1-q13; autosomal dominant
2. Primarily described early from Okinawa, Japan, but now in many other countries

Clinical Manifestations

1. Resembles Kennedy's disease
2. Muscle cramps are early symptoms, followed by proximal muscle weakness, atrophy, and fasciculation in the legs greater than the arms
3. Facial muscles are slightly weak, but neck flexors and extensors are only slightly involved

4. Dysphasia and dysarthria are rare although the tongue may be slightly weak
5. Bulbar and respiratory weakness may be late signs
6. Patients may be wheelchair bound 5 to 20 years after onset
7. Loss of all sensory modalities with a large fiber predominance occurs in the extremities
8. Reflexes are diminished or absent
9. Neurogenic tremor is common

Neuropathology

1. Loss of large and small myelinated fibers with preserved unmyelinated fibers
2. Loss of anterior horn cells
3. Loss of neurons in the dorsal root ganglia

Laboratory Evaluation

1. Serum creatine kinase levels are mildly elevated
2. EMG:
 - a. SNAPs are unobtainable or are reduced in amplitude
 - b. CMAP amplitudes are reduced with minimal prolongation of distal latencies and NCVs
 - c. Needle EMG reveals diffuse fasciculation and fibrillation potentials
 - d. Decreased recruitment of large amplitude, long duration polyphasic MUAPs

Hereditary Neurologic Amyotrophy

General Characteristics

1. HNA is caused by mutations in the SEPT9 gene located on chromosome 17q25; AD
2. Putative functions involve formation of the neuronal cytoskeleton and cell division

Clinical Manifestations

1. Initiated in childhood
2. Attacks are similar to those that occur with the Parsonage-Turner syndrome (idiopathic brachial neuritis)
3. Usually of sudden onset
4. Recurrent attacks of pain, weakness, and sensory loss in brachial plexus distributions
5. There is usually complete or partial recovery over weeks or months
6. Associated neurologic manifestations include:
 - a. Hypotelorism
 - b. Epicanthal folds
 - c. Cleft palate and uvula (bifid)
 - d. Syndactyly
 - e. Micrognathia
 - f. Facial asymmetry
 - g. Short stature
7. Distinguished from HNPP because of severe pain and no history of nerve compression
8. Episodes are triggered by:
 - a. Infections
 - b. Immunization
 - c. Puerperium
 - d. Stress

Neuropathology

1. There is a founder haplotype in some kindreds with SEPT9; others have heterogeneous tandem duplications; the duplicated regions contain a conserved 645 bp exon within SEPT9 where missense mutations have been shown
2. Axonal degeneration in nerves distal to the plexus injury

Neuroimaging

1. MRI:
 - a. In some instances, there is gadolinium enhancement on T1-weighted sequences in affected components of the brachial plexus

Laboratory Evaluation

1. EMG:
 - a. Reduced amplitudes of SNAPs and CMAPs in all affected components of the plexus (trunks, cords, division and nerves)
 - b. Decreased recruitment of MUAPs
 - c. Positive sharp waves and fibrillation potentials in affected muscle groups associated with decreased recruitment of MUAP
 - d. An axonal process localized to the brachial plexus
 - e. HNPP is demyelinating and is generalized

Scapuloperoneal Neuropathy*General Characteristics*

1. The genetic basis of scapuloperoneal atrophy is heterogeneous
 - a. Inheritance may be autosomal dominant or recessive
2. Alterations in the ankyrin domain of the TRPV4 gene may cause:
 - a. Congenital distal SMA
 - b. Scapuloperoneal SMA
 - c. HMSN2C
3. One family with AD inheritance of scapuloperoneal SMA has been linked to chromosome 12q24.1-q24.31
4. One patient has been linked to a 17p11.2 deletion (Davidenkow phenotype)

Clinical Manifestations

1. Heterogeneous manifestations depending on the genetic background
2. Scapuloperoneal pattern of weakness may be seen in:
 - a. Myofibrillar myopathy
 - b. Scapuloperoneal neuropathy (Davidenkow's syndrome)
 - c. Spinal muscular atrophy
3. Scapuloperoneal neuropathy:
 - a. The disease starts in the second or third decade
 - b. Insidious onset of foot drop with tripping and recurrent ankle sprains
 - c. Gradual onset of proximal hip and shoulder girdle weakness becomes apparent; the involved muscles include:

- i. Pectoralis, serratus anterior, rhomboids, supra- and infraspinatus, trapezius, deltoid and brachioradialis
- ii. Peroneal innervated muscles of the lower extremity are atrophic and weak
- iii. Distal arm muscles are spared
- iv. The distinguishing clinical pattern of weakness in the scapuloperoneal syndromes is upper extremity proximal weakness and lower extremity distal weakness
- v. Sensation may be normal or decreased primarily in large fiber afferents
- vi. Reduced muscle stretch reflexes
- vii. Pes cavus and hammertoes are common

Neuropathology

1. Sural and superficial peroneal nerve biopsy:
 - a. Axonal degeneration
2. Anterior horn cell loss (atrophy)
3. Muscle biopsy reveals signs of denervation with small angulated fibers, type grouping, and atrophy

Laboratory Evaluation

1. Normal median and ulnar nerve CMAPs and NCS; peroneal CMAPs are reduced in amplitude with normal distal latency and CV
2. Reduced SNAPs in the arms and legs but with otherwise normal sensory studies
3. Weak muscle group demonstrates reduced recruitment of large amplitude, long duration polyphasic MUAPs

Hereditary Sensory and Autonomic Neuropathies**Overview**

The hereditary sensory autonomic neuropathies (HSAN) are characterized by sensory and autonomic dysfunction to a greater degree than weakness.

Hereditary Sensory Autonomic Neuropathy 1 (HSAN1)*General Characteristics*

1. HSAN1 is the most common HSAN and has AD inheritance
2. The illness presents in the second through fourth decades, which distinguishes it from other HSANs whose onset is in infancy or childhood
3. HSAN1 is caused by mutations in serine palmitoylation transferase long chain subunit C1 (SPTLC1 gene) located on chromosome 9q22.31
4. Serine palmitoylation transferase is pivotal in the biosynthesis of sphingolipids
5. There may be genetic heterogeneity:
 - a. Both an AR inheritance form and an X-linked form have been described with a similar phenotype
 - b. HSAN1B

- i. Linked to chromosome 3p22-p24
 1. Clinical manifestations are cough, gastroesophageal reflux, and length-dependent neuropathy

Clinical Manifestations of HSN1

1. Late onset presentation in the second through fourth decades
2. Insidious loss of pain and temperature sensation in the feet and hands
3. Severe dystrophic features supervene:
 - a. Dermal ulcerations that become infected
 - b. Osteomyelitis of affected extremities
 - c. Charcot joints
 - d. Severe foot and hand deformities
 - e. Amputated digits
4. Burning, aching and lancinating pain in the extremities
5. Bladder dysfunction and hyperhidrosis of the lower extremities
6. Reduced sensation to all modalities primarily C-fiber and A-delta fibers (slow burning pain C-fibers, A-delta, cold appreciation and lancinating pain)
7. Distal arm and leg weakness progressively develop over time, although a subgroup of patients may have early distal weakness
8. Absent ankle stretch reflexes, but reflexes may be normal in the upper extremities
9. Pes cavus and hammer toes are common

Neuropathology

1. Predominant loss of thinly myelinated fibers (A-delta fibers) and unmyelinated fibers (C-fibers)
2. Reduced density of all fiber sizes
3. Muscle biopsy demonstrates denervation
4. Degeneration of dorsal root ganglion cells and posterior columns
5. Transmission electron microscopy demonstrates:
 - a. Swollen mitochondria with abnormal crystal clustered around the nucleus
 - b. Some mitochondria are wrapped in rough endoplasmic reticulum (ER) membranes
 - c. Observations support a mechanism in which SPTLC1 mutations cause mitochondrial abnormalities and ER stress in HSN1 sensory neurons

Laboratory Evaluation

1. EMG:
 - a. Sensory NCS are normal or demonstrate mildly decreased amplitudes, normal distal latencies and conduction velocities
 - b. Near-nerve recordings demonstrate decreased A-delta and C potentials
 - c. Slightly reduced amplitudes and slowing of conduction velocities develop over time in motor NCS
 - d. Needle EMG supports chronic reinnervation with large MUAPs in addition to positive sharp waves and fibrillation potentials

2. Sympathetic skin responses may be lost
3. CSF examination is normal
4. Serum IgA levels may be elevated

Hereditary Sensory Autonomic Neuropathy Type 2A (HSAN2A)

General Characteristics

1. HSAN2A is autosomal recessively inherited and is caused by mutations in the WNK1 gene on chromosome 12p13.3:
 - a. The mutations are confined to exon "HSN2" of the WNK1 (with-no-lysine kinase 1) serine-threonine kinase gene
 - b. These are truncating mutations in the neuron-specific exon of HSN2 gene that lead to a loss of function of the WNK1 kinase
 - i. A loss-of-function mutation in WNK1 induces an overexpression of neuronal potassium chloride co-transporter KCC2, which putatively is important for peripheral sensory nerve development

Clinical Manifestations

1. Manifests at birth or early childhood
2. Severe sensory loss to all modalities; there is lancinating pain which differentiates it from HSN1
3. Impaired sweating, bladder dysfunction, and impotence; rare to manifest postural hypotension
4. Slightly impaired distal motor strength
5. Scoliosis
6. Sensory loss, most severe to touch-pressure/vibration, which causes:
 - a. Pressure ulcers
 - b. Charcot joints
 - c. Osteomyelitis
 - d. Bone reabsorption
 - e. Amputation of extremity digits

Neuropathology

1. Almost complete absence of myelinated fibers
 - a. Mild loss of small myelinated fibers

Laboratory Evaluation

1. Absent SNAPs
2. Normal to mildly decreased CMAPs amplitude
3. Quantitative sensory thresholds
 - a. Severely abnormal vibratory thresholds
4. Needle EMG:
 - a. Positive sharp waves and fibrillation potentials
 - b. Reduced recruitment of large polyphasic MUAPs, most severe in the distal legs

Hereditary Sensory Autonomic Neuropathy Type 2B (HSAN2B)

General Characteristics

1. HSAN2B is AR and is caused by a homozygous mutation in the FAM134B gene that maps to chromosome 5p15.1

Clinical Manifestations

1. Early childhood onset
2. Distal sensory impairment
3. Hyperhidrosis
4. Urinary incontinence
5. Gait impairment (some patients)
6. Mutilating ulcerations of the hands and feet

Neuropathology

1. Sural nerve biopsy:
 - a. Loss of myelinated fibers

Laboratory Evaluation

1. Sensorimotor axonal neuropathy

Hereditary Sensory Autonomic Neuropathy Type 3 (HSAN3 or Riley-Day Syndrome)*General Characteristics*

1. HSAN3, also known as familial dysautonomia or Riley-Day syndrome, is caused by:
 - a. Mis-splicing of exon 20 from an intrinsic mutation in the inhibitor of kappa light chain polypeptide gene enhancer in B-cells, kinase complex-associated protein (IKBKAP), that maps to chromosome 9q31.3
 - b. That encodes IKK complex-associated protein (IKAP)/elongator protein (LIPI)
 - c. Mis-splicing of IKBKAP causes decreased tRNA modification
2. AR inheritance; most patients are of Ashkenazi Jewish ethnicity

Clinical Manifestations

1. HSAN3 starts in infancy
2. Infants have:
 - a. Poor suck and cry
 - b. Cry without tears
 - c. Livedo reticularis of the skin
 - d. Fluctuations in body temperature and blood pressure
 - e. Vomiting
3. Specific autonomic features:
 - a. Esophageal and gastrointestinal dysmotility
 - b. Hyperhidrosis
 - c. Tonic pupils
 - d. Postural hypotension
4. Recurrent pulmonary infections
5. Developmental delay
6. Seizures may occur
7. Cognitive function is normal
8. Decreased pain and temperature sensation > proprioception and vibration loss
9. Absence of fungiform papillae of the tongue
10. Decreased taste
11. Muscle strength is normal
12. Reduced or absent muscle stretch reflexes; often absent corneal reflexes
13. Occasional Charcot joints occur

Neuropathology

1. Loss of neurons in the cervical and thoracic sympathetic ganglia as well as the Vth nerve nucleus
2. Decreased unmyelinated fibers in sural nerve biopsies (5–15% of the normal fiber density) and a loss of up to 50% of myelinated fibers
3. Elp1 is a subunit of the heterohexameric transcriptional elongator complex
4. Studies in conditional knockout mice demonstrate:
 - a. No impairment in migration, proliferation or survival of sympathetic and sensory neural crest cells
 - b. Ablation of Elp1 in post-migratory sympathetic neurons causes:
 - i. Abnormal target tissue innervations
 - ii. Abnormal neurite outgrowth and branching
 - iii. Alteration of soluble tyrosinated tubulin
 - c. Defects in Elp1 cause:
 - i. Failed target tissue innervations
 - ii. Alteration of cytoskeletal regulation

Laboratory Evaluation

1. EMG:
 - a. SNAPs have slightly reduced amplitude and slow CVs
 - b. CMAPs are normal
2. Sympathetic skin responses are obtainable
3. Quantitative sensory testing (QST) demonstrates altered thresholds to heat, cold and vibration modalities

Hereditary Sensory Autonomic Neuropathy Type 4 (HSAN4)*General Characteristics*

1. HSAN4 is caused by loss of function mutations in the NTRK1 gene (tyrosine kinase A/nerve growth factor TrkA/NGF) gene that is located on chromosome 3q; AR inheritance
2. NGF is a trophic factor essential for the survival of nociceptive neurons and postganglionic sympathetic neurons

Clinical Manifestations

1. Is initiated in infancy or childhood
2. Insensitivity to pain
3. Anhidrosis
4. Self-mutilation
5. Cognitive impairment
6. Severe loss of pain and temperature sensation, and loss of large myelinated proprioceptive and vibratory fibers
7. Preserved strength and muscle stretch reflexes

Neuropathology

1. Sural nerve biopsy:
 - a. Absence of A-delta (1–4 μ) and C fibers (1 μ unmyelinated fibers)
 - b. Reduction of large myelinated fibers to approximately 50% of normal fiber density

2. Mutations in NTRK1 cause the selective loss of NGF-dependent neurons (nociceptive and sympathetic postganglionic neurons)
3. TrkA-NGF complex is internalized into the nucleus of target neurons and induced genes that are pivotal for maintenance and survival of sensory neurons derived from the neural crest

Laboratory Evaluation

1. EMG:
 - a. Normal or slightly diminished SNAPs, CMAP amplitudes and conduction velocities
2. QST:
 - a. Markedly increased thresholds to heat, cold and pinprick; less involvement of mechano and vibration thresholds

Hereditary Sensory Autonomic Neuropathy Type 5 (HSAN5)

General Characteristics

1. HSAN5 is caused by missense mutations in the NGF gene located on chromosome 1p11.2-p13.2; it is autosomal-recessively inherited

Clinical Manifestations

1. Manifests at birth
2. Self-mutilation involves the teeth, lips, tongue, eyes, nose and fingers
3. Bone fractures may be asymptomatic
4. Patients have an indifference to pain. They do not recognize or react to painful stimuli
5. They have normal sensory thresholds to other modalities
6. Normal strength and muscle stretch reflexes

Neuropathology

1. Subgroups of patients have a small reduction of myelinated and unmyelinated fibers, while other patients have normal sural nerve biopsies

Laboratory Evaluation

1. Motor and sensory NCVs, QST and autonomic testing are normal

Rare Hereditary Neuropathies

Metachromatic Leukodystrophy (MLD)

General Characteristics

1. MLD is caused by mutations in the ARSA gene on chromosome 22q13.31; inheritance is AR
2. ARSA encodes arylsulfatase A, which catalyzes the hydrolysis of sulfatide, the sulfate ester of cerebroside
3. In MLD, arylsulfatase A and prosaposin enzymes metabolize galactosyl sulfatide, a glycolipid of myelin membranes

4. The enzyme deficiencies cause an accumulation of sulfatides in Schwann cells and oligodendrocytes (primarily galactosylceramide)

Clinical Manifestations

1. Disease manifestations are characterized by the age at onset:
 - a. Late infantile onset (18–24 months):
 - i. Onset between 1–2 years of age
 - ii. Progressive weakness
 - iii. Cognitive impairment
 - iv. Dysarthria (bulbar)
 - v. Children become cortically blind, quadriparetic and may have seizures
 - vi. Hypotonia, Babinski sign and loss of reflexes develop
 - b. Juvenile onset (4–10 years):
 - i. Presents in late childhood or adolescence
 - ii. Similar phenotype to the late infantile form
 - iii. Peripheral neuropathy may be present in the early stages of the disease:
 1. Decreased peripheral nerve conduction velocities
 - c. Adult onset (3rd to 4th decade):
 - i. Patients develop a slowly progressive dementia
 - ii. Often a psychosis
 - iii. Spasticity
 - iv. Ataxia
 - v. Extrapyramidal signs
 - vi. Visual loss

Neuropathology

1. Degeneration of myelin (often frontal lobe predominant) in the subcortical white matter
2. Nerve biopsy:
 - a. Decrease of myelinated fibers with evidence of remyelination
 - b. Accumulation of metachromatic inclusions in Schwann cell cytoplasm
 - c. Electron microscopic evaluation:
 - i. Inclusions are laminated bodies within Schwann cells

Neuroimaging

1. Abnormal subcortical white matter may have a pattern of radiating stripes
2. Confluent periventricular white matter (T2-weighted sequences); spares accurate fibers
3. Cranial nerve enhancement occurs; rarely there is enhancement of peripheral nerves

Laboratory Evaluation

1. Decreased arylsulfatase A can be demonstrated in the urine, leukocytes or cultured fibroblasts
2. Cerebrospinal fluid protein is markedly elevated (100–300 mg/dl)

3. EMG:
 - a. Motor nerve conduction studies (NCS) reveal:
 - i. Reduced amplitude and prolonged distal latencies
 - ii. Conduction velocities of 10–20 m/s in the legs and 20–40 m/s in the arms
 - iii. Rare temporal dispersion; no conduction block
 - iv. Usually unobtainable sensory NCS
4. All evoked potentials (visual, brainstem and somatosensory) are delayed

Krabbe's Disease

General Characteristics

1. Krabbe's disease is an autosomal recessive disease caused by mutation in the β -galactosidase gene (GALC) that maps to chromosome 14q 24.3-q 32.1:
 - a. Encodes β -Galactosidase which metabolizes galactocerebroside to ceramide and galactose
 - b. Hydrolyzes psychosine

Clinical Manifestations

1. Presents in early infancy or adulthood
2. Infantile form:
 - a. Usually, presents between 3–8 months; infants appear normal at birth
 - b. Irritability and hypersensitivity evolve with feeding difficulties, vomiting and generalized clonic-tonic seizures
 - c. Progressive weakness, spasticity, blindness and deafness supervene
 - d. Gradual loss of reflexes occurs with a developing neuropathy;
 - i. Babinski sign remains
 - ii. Death supervenes by the age of 2
3. Adult onset:
 - a. Progressive dementia
 - b. Spasticity and paraparesis
 - c. Hemiparesis
 - d. Cerebellar ataxia
 - e. Optic atrophy
 - f. Cortical blindness

Neuropathology

1. Cortical atrophy (may be parietal lobe predominant)
2. Macrophages filled with galactocerebroside (globoid cells) are demonstrated
3. Sural nerve biopsy:
 - a. Segmental demyelination or hypomyelination as well as loss of myelinated fibers
 - b. Globoid cells
 - c. Electron microscopy demonstrates:
 - i. Electron-dense granules and tubular crystalloid inclusions in the cytoplasm of macrophages

Neuroimaging

1. MRI:
 - a. Cortical atrophy (parieto-occipital predominant)
 - b. Peripheral nerves may enhance
 - c. Corticospinal tract demyelination

Laboratory Evaluation

1. Decreased β -galactosidase in leukocytes and cultured fibroblasts
2. 50% of patients have increased CSF protein
3. EMG:
 - a. Motor NCS (nerve conduction studies)
 - i. Mild to moderate decrease of CMAP amplitude
 - ii. Moderately prolonged distal latencies
 - iii. Moderately slow NCVs
 - iv. Delayed or absent F-waves
 - b. Sensory NCS:
 - i. Absent SNAPs or severely reduced amplitudes and distal latencies and slow CV if obtained

Fabry's Disease

General Characteristics

1. Fabry's disease (angiokeratoma corporis diffusum):
 - a. Caused by mutations in the galactosidase gene that maps to chromosome Xq21-22
 - b. A multisystemic lysosomal storage disorder that presents with phenotypic and genotypic variability among affected male and female patients
 - c. Globotriaosylceramide (Gb3) and galactosylceramide (Ga2) isoforms and analogs have been identified by mass spectroscopy in the urine of Fabry's disease patients

Clinical Manifestations

1. Most prominently affects males in childhood or adolescence
2. Affected individuals often present with neuropathic extremity pain
3. Angiokeratomas (reddish purple maculopapular lesions) are seen in a bathing suit distribution; angioectasias may be seen in the nail beds mucosa and conjunctiva
4. Systemic manifestations:
 - a. Hypertension
 - b. Myocardial infarction
 - c. Renal failure
 - d. Small vessel CNS disease
 - e. Heat intolerance
 - f. Severe atherosclerotic changes
 - g. Women most often suffer the neuropathy

Neuropathology

1. Sural nerve biopsy:
 - a. Reduction of thinly myelinated and unmyelinated nerve fibers
 - b. Glycolipid granules are found in ganglion cells of the peripheral and sympathetic nervous system as well as perineural cells
 - c. Skin biopsy:
 - i. Decreased epidermal fiber density
 - ii. Globotriaosylceramide (Gb3) and analogs, as well as galactosylceramide (Ga2) isoforms/analogues

are demonstrated in the vascular endothelium, nerve, cardiomyocytes, renal glomerular and tubular epithelial cells

- iii. Gb3 isoforms that contain saturated fatty acids are the most abundant

Neuroimaging

1. Ischemic stroke
2. White matter hyperintensities
3. Vertebrobasilar dolichoectasia
4. Pulvinar sign

Laboratory Evaluation

1. Low galactosidase activity in leukocytes and cultured fibroblasts
2. Ga2 and Gb3 and respective isoforms and analogs can be found in the urine
3. EMG:
 - a. Mildly decreased amplitudes of motor and sensory NCS
4. QST:
 - a. Small fiber deficits

Adrenoleukodystrophy/Adrenomyeloneuropathy

General Characteristics

1. Adrenoleukodystrophy and adrenomyeloneuropathy are allelic linked dominant diseases
 - a. Caused by mutations in the peroxisomal transmembrane adenosine triphosphate binding cassette ABCD1 transporter gene that is located on chromosome q28
2. ABC transporter protein:
 - a. Is a member of the peroxin family of proteins
 - b. Peroxin proteins are involved in the transport, biogenesis and proliferation of peroxisomes:
 - i. In brain capillary endothelial cells, they also function as ATP-driven efflux pumps for xenobiotics and metabolites
 - ii. Mutations in the ABC transporter gene cause:
 1. Impaired transport of very long chain fatty acids (VLCFA) as well as VLCFA CoA synthetase into peroxisomes that cause decreased beta oxidation of VLCFA

Clinical Manifestations

1. Onset between 4 to 8 years of age in X-linked dominant ALD
2. Male patients have progressive:
 - a. Dementia
 - b. Optic atrophy
 - c. Cortical blindness
 - d. Hearing loss
 - e. Seizures
 - f. Spasticity
 - g. Adrenal insufficiency

Clinical Manifestations of Late Onset

1. Onset in adolescence or adulthood
2. Phenotype is similar but with a much slower progression
3. Late-onset patients may present with symptoms suggestive of schizophrenia

Clinical Manifestations of Adrenomyeloneuropathy (AMN)

1. Occurs in approximately 30% of patients with adrenoleukodystrophy
2. Onset is in the third to fifth decade
3. Progressive spastic paraplegia develops with a mild to moderate peripheral neuropathy
4. The degree of muscle stretch reflex sensitivity depends on the neuropathy (normal to reduced)
5. A subgroup of patients may develop dementia in the later course of the disease
6. Adrenal insufficiency occurs in approximately 2/3 of patients
7. Rarely patients may present with an adult onset spinocerebellar phenotype or with isolated adrenal insufficiency
8. Women may develop a myelopathy in their thirties

Neuropathology

1. In the CNS:
 - a. Demyelination and perivascular inflammation occur predominantly in the parietal and occipital lobes
 - b. The spinal cord shows bilaterally symmetric long tract degeneration in a drying back pattern
2. Sural nerve biopsy:
 - a. Loss of all myelinated fiber sizes as well as unmyelinated fibers
 - b. Electron microscopy reveals:
 - i. Lamellar inclusions in the cytoplasm of Schwann cells

Neuroimaging

1. MRI:
 - a. Adrenoleukodystrophy demonstrates an elevated diffusion pattern
 - i. An apparent diffusion coefficient (ADC) maps in ADL
 - b. Subcortical white matter confluent demyelination occurs in ADL
 - c. Similar MRI patterns of demyelination occur in approximately 50% of AMN patients late in the course of the disease

Laboratory Evaluation

1. Elevated very long chain fatty acids (C24, C25, C26), are demonstrated in the urine
2. Approximately 85% of obligate female carriers have elevated urinary VLCFA levels
3. Many patients have laboratory evidence of adrenal insufficiency
4. EMG:

- a. ALD has normal nerve conduction studies
- b. AMN demonstrates:
 - i. Sensory and motor slightly reduced amplitudes, prolonged distal latencies, and slightly slow CVs
 - 1. Most compatible with a primary axonopathy with secondary demyelination
 - 2. Rarely some patients have electrophysiological features of a primary demyelinating process
- 5. Somatosensory evoked potentials
 - a. Evidence of central slowing

Refsum's Disease

General Characteristics

- 1. Refsum's disease is an autosomal recessive peroxisomal disorder
- 2. Classic Refsum's disease is caused by mutations in PAHX that is located on chromosome 10p13:
 - a. Encodes phytanoyl-CoA hydroxylase that catalyzes the oxidation of phytanic acid
- 3. Less commonly mutations in the PRX7 gene located on chromosome 6q22-24 cause the disease
 - a. Encodes peroxin7 receptor protein

Clinical Manifestations

- 1. May manifest in infancy to adulthood; usually in late childhood
- 2. Classic tetrad:
 - a. Retinitis pigmentosa (often the earliest sign)
 - b. Peripheral neuropathy
 - c. Cerebellar ataxia
 - d. Elevated CSF protein
- 3. Other signs and symptoms include:
 - a. Anemia
 - b. Ichthyosis
 - c. Cardiac arrhythmia (conduction defects)
 - d. Deafness
 - e. Very late-onset cognitive decline and leukoencephalopathy
- 4. Over time patients develop:
 - a. Distal numbness and paresthesias in the legs (in their early twenties)
 - b. Atrophic, weak distal leg musculature and foot drop
 - c. Proximal shoulder and pelvic girdle weakness evolve
 - d. Sensory loss is primarily in a length-dependent manner with large myelinated fiber predominance
 - e. Generalized absence of muscle stretch reflexes
 - f. The neuropathy may fluctuate
 - g. Nerves become hypertrophic

Neuropathology

- 1. Phytanic acid is branched chain fatty acid that accumulates in many tissues
 - a. When it exceeds a millimolar range, it leads to severe symptoms

- 2. Degradation of phytanic acid is accomplished by alpha-oxidation inside of peroxisomes. A decrease in its breakdown results from:
 - a. General peroxisomal dysfunction
 - b. A defect in one of the enzymes involved in alpha-oxidation
- 3. Phytanic acid reduces histone acetylation, which induces cell death in an experimental cell culture system
- 4. Sural nerve biopsy:
 - a. Demonstrates loss of myelinated nerve fibers; remaining axons are thinly myelinated and are associated with onion bulb formation

Laboratory Evaluation

- 1. Elevated serum phytanic acid levels
- 2. Elevated CSF protein
- 3. EMG:
 - a. Sensory nerve conduction studies (NCS):
 - i. Reduced amplitudes, prolonged latencies, and slow CVs
 - ii. Motor NCS
 - 1. Normal or moderately reduced amplitudes, prolonged distal latencies and slowing of CV (10–30 m/s)

Tangier Disease

General Characteristics

- 1. Tangier disease is an autoimmune disorder caused by mutations in the ABCA1 gene that maps chromosome 9q22-31
- 2. ABCA1 is pivotal in the secretion of cellular free cholesterol and phospholipids to an intracellular acceptor apolipoprotein A1 which forms nascent high-density lipoprotein (HDL)
- 3. ABCA1 is pleiotropic and is important for:
 - a. Plasma membrane remodeling
 - b. ApoA1 binding to the cell surface
 - c. Unfolding of the N-terminal of ApoA1 on the cell surface which is followed by lipidation of ApoA1 and the release of nascent HDL

Clinical Manifestations

- 1. It may present as:
 - a. An asymmetric mononeuropathy multiplex
 - b. A slowly progressive, symmetric polyneuropathy that is more severe in the legs than the arms
 - c. A pseudosyringomyelia phenotype in the arms in which there is dissociation between loss of pain and temperature with retained position and vibration sense
- 2. Swollen yellowish orange enlarged tonsils
- 3. Splenomegaly and lymphadenopathy occur

Neuropathology

- 1. Extremely low levels of plasma high-density lipoprotein cholesterol

2. Accelerated atherosclerosis
3. Accumulation of cholesterol in many body tissues
4. Impaired cholesterol efflux from affected tissues
5. Sural nerve biopsy:
 - a. Axonal degeneration with demyelination and remyelination
 - b. Electron microscopy:
 - i. Abnormal accumulation of lipid in Schwann cells predominately those associated with thinly myelinated fibers

Laboratory Evaluation

1. Severe reduction of serum high-density lipoprotein cholesterol
2. Increased levels of triacylglycerol levels
3. EMG:
 - a. Some patients have moderately reduced amplitudes, prolonged distal latencies and slow CV in motor and sensory nerves

Cerebrotendinous Xanthomatosis (Cholestanolosis) CTX

General Characteristics

1. A rare autosomal recessive lipid storage disease
2. CTX is caused by mutations in the CYP27A1 gene:
 - a. Encodes the mitochondrial enzyme sterol 27-hydroxylase
 - b. The CYP27A1 gene maps to chromosome 2q333-qter
 - c. The mutations lead to decreased synthesis of bile acid, an excess production of cholesterol with its accumulation in tissues

Clinical Manifestations

1. The onset of CTX is usually after the second decade
 - a. Average age at diagnosis is 35 years of age
2. Adult onset of:
 - a. Ataxia
 - b. Dementia
 - c. Seizures
 - d. Psychiatric disorders
 - e. Spasticity
 - f. Mild sensory neuropathy
 - g. Mild myopathy
3. Non-neurologic manifestations:
 - a. Tendon xanthomas
 - b. Childhood-onset cataracts
 - c. Infantile onset diarrhea
 - d. Premature atherosclerosis
 - e. Osteoporosis
 - f. Respiratory insufficiency

Neuropathology

1. Premature atherosclerosis
2. Multiple dispersed lipid crystal clefts
3. Perivascular accumulation of foamy macrophages

4. Sural nerve biopsy:
 - a. Loss of myelinated nerve fibers with evidence of demyelination and onion bulb formation
 - b. Lipid inclusions are seen in Schwann cells

Neuroimaging

1. MRI:
 - a. A generalized decrease of both gray and white matter
 - b. Bilateral symmetric hyperdense lesions in the dentate nuclei on both T1- and T2-weighted images
2. PET imaging:
 - a. Decreased metabolic activity in both the frontal and temporal lobes

Laboratory Evaluation

1. Increased serum levels of cholesterol
2. EMG: (depends on degree of neuropathy)
 - a. Motor and sensory NCS may reveal absent amplitudes with slightly prolonged distal latencies and decreased CVs
 - b. Compatible with a sensorimotor axonal polyneuropathy

Hereditary Ataxias with Neuropathy

Overview

The hereditary ataxias are progressive neurodegenerative disorders with involvement of:

1. The cerebral cortex
2. Basal ganglia
3. Cerebellum
4. Brainstem
5. Spinocerebellar and corticospinal tracts
6. Motor neurons
7. Peripheral nerves

The CNS manifestations predominate, although, in Friedreich's ataxia and inherited vitamin E deficiency, peripheral nerve manifestations may be significant.

Friedreich's Ataxia

General Characteristics

1. An autosomal recessive disease caused by a GAA trinucleotide repeat of the first intron of the frataxin gene located in chromosome 9q13
2. Ninety-seven percent of patients have an expanded GAA triplet repeat in both alleles (100 to 1700 repeats; normal 40 or less triplet repeats); the remaining 3% have an expanded GAA repeat in one allele and a point mutation in the other:
 - a. The gene encodes the mitochondrial protein frataxin
 - b. Dysregulation of iron metabolism is a pivotal component of the disease, which is characterized by:
 - i. Mitochondrial iron accumulation

- ii. Decreased activity of iron-sulfur cluster enzymes
- iii. Frataxin has a primary role in iron-sulfur cluster biogenesis

Clinical Manifestations

1. Usually presents between 2–16 years of age; late onset cases occur
2. Gait ataxia and clumsiness are often the presenting signs
3. Progressive neurologic manifestations include:
 - a. Dysarthria
 - b. Optic atrophy
 - c. Nystagmus
 - d. Hearing loss
 - e. Pyramidal signs
 - f. Motor neuronal loss
 - g. Distal extremity atrophy
 - h. Prominent loss of proprioception and vibration sensitivity
 - i. Pes cavus
 - j. Loss of muscle stretch reflexes
 - k. Rare dementia
 - l. Babinski sign

Non-Neurologic Manifestations

1. Pigmentary retinal degeneration
2. Cardiomyopathy
3. Scoliosis
4. Diabetes mellitus

Neuropathology

1. Role in protection against free radical damage and mitochondrial DNA replication
2. Marked atrophy of the posterior columns and dorsal roots
3. Sural nerve biopsy:
 - a. Loss of large myelinated fibers

Neuroimaging

1. MRI:
 - a. MRI of the brain is usually normal
 - b. Atrophy of the cervical spinal cord

Laboratory Evaluation

1. Genetic testing for the gene mutations
2. Electrocardiogram:
 - a. Low voltage QRS complexes
 - b. Non-specific ST and T-wave changes
 - c. Deep Q waves
 - d. Conduction defects
3. EMG:
 - a. Sensory nerve conduction studies (NCS):
 - i. Absent or reduced amplitudes
 - ii. H-reflexes are unobtainable
 - b. Motor NCS:
 - i. Moderately affected
 - c. Magnetic stimulation studies:
 - i. Slow central motor conduction
 - d. Somatosensory evoked potentials:
 - i. Slow central motor conduction

Vitamin E Deficiency

General Characteristics

1. Rare autosomal recessive disease due to mutations in the tocopherol transfer protein gene (TTPA gene) that is located in chromosome 8q13:
 - a. The gene encodes alpha-TTP, a cytosolic liver protein that putatively functions in the intracellular transfer of alpha-tocopherol
 - b. Defects in the transfer protein cause reduced incorporation of vitamin E into serum very low-density lipoproteins (VLDL) which in turn causes its rapid elimination and consequent low levels in the CNS and PNS

Clinical Manifestations

1. Onset in hereditary patients is between 5 and 10 years of age
2. Slowly progressive ataxia, dysarthria, decreased vibration, and proprioceptive sensitivity occur
3. Pes cavus, Babinski sign, generalized weakness with decreased or absent muscle stretch reflexes are common signs
4. Acquired vitamin E deficiency may have:
 - a. Ophthalmoplegia
 - b. Optic neuropathy
 - c. Retinitis pigmentosa
 - d. Above are not seen in the hereditary patients

Neuropathology

1. Severe loss of dorsal root ganglion cells
2. Degeneration of the posterior column
3. Loss of cells in the cuneate and gracile nuclei
4. Myelin sheath vacuoles and disrupted Schmidt-Lanterman incisures occur in the peripheral nerve

Laboratory Evaluation

1. Isolated low vitamin E serum levels
 - a. Patients who have malabsorption deficits (acquired vitamin E deficiency) have concomitant:
 - i. Low serum cholesterol
 - ii. VLDL
 - iii. Vitamin A
 - iv. Vitamin C levels
2. EMG:
 - a. Sensory NCS:
 - i. Absent or slowed with low amplitudes
 - b. Motor conduction velocities are usually normal although some patients demonstrate slightly prolonged conduction velocities

Homozygous Hypobetalipoproteinemia (HHBL)

General Characteristics

1. HHBL is caused by mutations in the APOB gene (both alleles) that causes homozygous hypobetalipoproteinemia that maps to chromosome 2p

Clinical Manifestations

1. Malabsorption of lipid-soluble vitamins in the disease that causes:
 - a. Retinal degeneration
 - b. Coagulopathy
 - c. Peripheral neuropathy

Laboratory Evaluation

1. Increased distal latencies and slowed NCVs

Abetalipoproteinemia (ABL) (Bassen-Kornzweig Disease)*General Characteristics*

1. ABL is inherited in an autosomal dominant manner and is caused by mutations in the large subunit of microsomal triglyceride transfer protein (MTP) that maps to chromosome 4q 22-24:
 - a. Encodes the large subunit of MTP (97-KDa subunit)
 - b. This subunit forms a heterodimer with the endoplasmic reticulum enzyme protein disulfide isomerase (PPI)
 - c. MTP is a chaperone that is pivotal in the transfer of lipids into apolipoprotein B (apoB)

Clinical Manifestations

1. Multisystem manifestations include:
 - a. Fat malabsorption
 - b. Acanthocytosis
 - c. Low serum cholesterol
 - d. Deficiency of serum apoB
 - e. Steatorrhea

Neurological Manifestations

1. Presentation within the first two decades is often ataxia and night blindness
2. Ataxia is progressive and leads to loss of ambulation by the fourth or fifth decade
3. Patients have short stature, pes cavus, and hammer toes
4. Severely decreased vibration and proprioception sensibility that also causes sensory ataxia
5. Mild distal extremity atrophy and weakness
6. Muscle stretch reflexes are decreased or absent
7. Rarely there is ophthalmoparesis

Neuropathology

1. Degeneration of the posterior columns and ventral spinocerebellar pathways
2. Sural nerve biopsy:
 - a. Axonal degeneration with a predominant loss of large diameter myelinated fibers; demyelination with remyelination

Laboratory Evaluation

1. Acanthocytes are demonstrated on blood smear
2. Decreased serum of:
 - a. Cholesterol

b. VLDLs

c. Chylomicrons

d. Vitamin A, E, and K

3. EMG:

- a. Sensory SNAPs are absent or if obtainable reveal reduced amplitudes with slowing of conduction velocities with normal or slightly prolonged distal latencies
- b. CMAPs may be slightly reduced with mild reduction of distal latencies and CVs
- c. Brainstem auditory evoked potentials are normal as opposed to reduced in Friedreich's ataxia

Disorders of Defective DNA Repair**Ataxia Telangiectasia***General Characteristics*

1. Ataxia telangiectasia is an autosomal recessive disorder that is caused by mutations in the ataxia telangiectasia mutated gene (ATM gene) that maps to chromosome 11q23:
 - a. The mutated ATM protein functions primarily as a nuclear protein that is involved in the early recognition and response to double-stranded DNA breaks
 - b. It is a high molecular weight phosphoinositol kinase
 - c. Its other roles include:
 - i. Phosphorylation of protein substrates that activate and coordinate signaling pathways for:
 - a. Cell cycle checkpoints
 - b. Nuclear localization
 - c. Gene transcription
 - d. The response to oxidative stress
 - e. Apoptosis
 - ii. Mutations in the ATM gene alter DNA repair

Clinical Manifestations

1. Cutaneous telangiectasia
2. Cerebellar ataxia
3. Conjunctival telangiectasia
4. Oculomotor dyspraxia
5. Sinopulmonary infections
6. Children develop choreoathetosis and dysarthria within the first decade
7. Distal motor weakness
8. Severe loss of proprioception and vibration sensitivity

Neuropathology

1. Sural nerve biopsy:
 - a. Loss of large myelinated fibers
2. High cancer risk (lymphoma and leukemia)
3. Adverse reactions to radiation and chemotherapy
4. Immunodeficiency
5. Glucose transporter aberrations
6. Insulin resistant diabetogenic response
7. Chromatin and chromosomal changes
8. Mitochondrial deficiencies that cause inefficient respiration and cellular metabolism

Laboratory Evaluation

1. Decreased serum levels of IgA and IgG
2. Increased serum alpha-fetoprotein
3. EMG:
 - a. Absent or reduced SNAPs amplitudes
 - b. Mild reduction of NCVs
 - c. Slightly prolonged distal sensory latencies
 - d. Similar but less severe changes are seen on motor NCS

Xeroderma Pigmentosa (XP)*General Characteristics*

1. Xeroderma pigmentosa is a rare autosomal recessive disease
2. It is caused by mutations in seven genes (XPA-XPG) that cause a defect in nucleosides excision repair (NER)
 - a. The eighth gene causes a defect in polymerase activity
3. It causes greater than 1000 fold increase in the frequency of all forms of major skin cancer due to hypersensitivity to (UV) radiation and carcinogenic agents

Clinical Manifestations

1. Intense cutaneous photosensitivity
2. Poikiloderma
3. Actinic keratosis
4. Erythema
5. Hyperpigmented lentiginous macules
6. Malignant lesions in sun-exposed areas

Clinical Manifestations of Gene Mutation of XPA, XPB, XPD, and XPG

1. Onset between 1 and 2 years of age
2. Microcephaly
3. Cognitive impairment
4. Seizures
5. Deafness
6. Cerebellar ataxia
7. Dystonia
8. Choreoathetosis
9. Primary sensory neuropathy

*Neuropathology**Sural nerve biopsy:*

1. Loss of myelinated and unmyelinated fibers
2. Sensory fibers are affected to a greater degree than motor fibers

*Laboratory Evaluation**EMG:*

1. Decreased SNAPs
2. Slowing of motor and sensory NCVs

Cockayne Syndrome*General Characteristics*

1. The majority of patients (approximately 80%) carry mutations in CSB/ERCC6 that maps to chromosome 10q11:

- a. Encodes a SWI/SNF family DNA translocase
 - i. The other major gene, CSA/ER CC8, that is mutated encodes a ubiquitin ligase
2. The major function of these genes is in transcription-completed nucleotide excision repair
3. XPD, XPB, and XPG mutations are described in a small number of patients
4. CSB affects the expression of thousands of genes many of which are neuronal in the absence of DNA damage

Clinical Manifestations

1. Children appear normal at birth but by 12 months they demonstrate slow growth and signs of aging
2. At age between 4 and 10 they show evidence of:
 - a. Progeria-like facial dysmorphism
 - b. Cognitive deficits
 - c. Ataxia
 - d. Sensorineural hearing loss
 - e. Loss of muscle stretch reflexes
 - f. Photosensitivity
 - g. Pigmentary retinopathy
 - h. Dwarfism

Neuropathology

1. There is evidence that the defects seen in Cockayne syndrome (CS) are due to dysregulation of gene regulatory networks rather than from aberrations in DNA repair
2. Sural nerve biopsy:
 - a. Segmental demyelination and Schwann cell inclusions

Laboratory Evaluation

1. EMG:
 - a. Moderate reduction of NCVs and prolonged distal latencies in motor and sensory nerves

Other Hereditary Neuropathies**Giant Axonal Neuropathy***General Characteristics*

1. Recessive mutations in the GAN that maps to chromosome 16q23
 - a. Encodes gigaxonin protein
2. Changes in peripheral nerves that are similar to CMT type 2 (may be a continuum)
3. Evidence supports disorganization of the intermediate filament network

Clinical Manifestations

1. Presents in the first decade of life
2. Children are normal at birth and complete early milestones
3. At approximately two years of age, they become ataxic and by age 4 they have a sensorimotor polyneuropathy
4. Sensory loss is demonstrated in all sensory modalities in a length dependent phenotype

5. Mild distal muscle atrophy and weakness
6. Loss of muscle stretch reflexes in the legs and decreased reflexes in the arms
7. Babinski sign is present
8. Patients have curly or kinky hair

Neuropathology

1. Sural nerve biopsy:
 - a. Segmental demyelination with loss of myelinated axons
 - b. Giant axonal swellings are noted
2. Electron microscopy:
 - a. Axonal swellings are composed of abnormal density packed intermediate neurofilaments which are most prominent distally and in paranodal areas
 - b. Degeneration of central CNS tracts is demonstrated in postmortem pathology

Laboratory Evaluation

1. Gigaxonin is reduced due to both mRNA and protein instability mechanisms
2. EMG:
 - a. Absence or reduced amplitudes of SNAPs and CMAPs
 - b. Mildly slow CVs
 - c. Prolonged distal latencies of motor and sensory nerves

Porphyria

General Characteristics

1. There are three forms of porphyria that are associated with both peripheral neuropathy and CNS signs and symptoms:
 - a. Acute intermittent porphyria
 - b. Variegate porphyria
 - c. Hereditary coproporphyria
2. The porphyrias are autosomal dominant diseases of both the peripheral and central nervous systems

Clinical Manifestations

1. A photosensitive rash is encountered with variegate porphyria and hereditary coproporphyria but not with acute intermittent porphyria
2. The neurologic symptomatically is similar in all three forms of disease
3. Attacks of porphyria are initiated by specific drugs (primarily those metabolized by the p450 cytochrome system)
 - a. Thorazine, penicillin, gabapentin and diazepam are safe
4. Other triggers include:
 - a. Pregnancy
 - b. Luteal phase of the menstrual cycle
 - c. Alcohol
 - d. Fasting
5. Neurologic manifestations include:

- a. Severe abdominal pain (most often without guarding) i.e. a soft abdomen; often associated with prior surgical scars
- b. Agitation, hallucinations and at times psychotic behavior
- c. Major motor seizures occur
- d. Episodes of cortical blindness; some associated with seizures and others due to posterior reversible encephalopathy
- e. A Guillain-Barré phenotype:
 - i. Motor weakness can be asymmetric and proximal
 - ii. Sensory impairment is much less dramatic than motor involvement but occur as radicular pain between attacks
 - iii. Motor involvement may affect arms or legs preferentially
 - iv. Rarely cranial nerves may be affected most commonly VII and XII
 - v. Muscle stretch reflexes are usually absent although ankle jerks may be retained
 - vi. Autonomic dysregulation is common and manifests during an acute attack with:
 1. Hypertension (rarely hypotension) and pupillary dilatation
 2. Tachycardia
 - vii. Between attacks patients may complain of:
 1. Constipation
 2. Urinary retention
 3. Incontinence

Neuropathology

1. Sural nerve biopsy
 - a. Axonal degeneration

Laboratory Evaluation

1. The urine is often brownish due to the high concentration of porphyrin metabolites
2. The diagnosis is made by determining in the urine or stool specific intermediary precursors of heme:
 - a. Acute intermittent porphyria:
 - i. Deficiency of porphobilinogen deaminase
 1. Increased porphobilinogen in the urine or stool
 - b. Variegate porphyria:
 - i. Deficiency of protoporphyrinogen oxidase
 1. Increased protoporphyrinogen IX in the urine or stool
 - c. Hereditary coproporphyria:
 - i. Increased coproporphyrinogen III in the stool or urine
3. X-linked sideroblastic anemia, ALAD deficient porphyria, erythropoietic protoporphyria, and congenital erythropoietic porphyria
 - a. Can cause an axonal neuropathy
4. There is no neuropathy with porphyria cutanea tarda
5. Other laboratory features:
 - a. CSF protein may be normal or slightly elevated

- b. Liver enzymes may be slightly elevated, and there may be slight anemia
- c. Cholesterol levels may be slightly elevated
- d. Inappropriate antidiuretic hormone occurs and produces a low serum sodium
- e. Delta-aminolevulinic acid is often elevated with AIP during exacerbations
- 6. Specific enzyme assays can be obtained from erythrocytes or leukocytes
- 7. EMG:
 - a. Sensory NCS demonstrate normal conduction velocities and distal sensory latencies, but with slightly reduced amplitudes
 - b. CMAPs are reduced (marked)
 - c. Motor NCVs are reduced and distal motor latencies are minimally prolonged
 - d. Needle EMG demonstrates reduced recruitment, positive sharp waves and fibrillation potentials

Neuroimaging

- 1. MRI:
 - a. White matter involvements and cortical involvement
 - b. A subgroup demonstrates predominant involvement of the caudate, putamen and thalamus

Erythromelalgia

General Characteristics

- 1. May occur as an inherited autosomal dominant condition, or it can be acquired
- 2. It is caused by mutations in the SCN9 gene that maps to chromosome 2q24
 - a. Encodes the Nav 1.7 protein
 - b. Missense mutations cause a gain of function that promotes neuronal hyperexcitability
 - c. The channel is expressed in nociceptive neurons of the dorsal root ganglia and in sympathetic neurons
 - d. Mutations alter voltage dependence, the kinetics of deactivation, and steady-state slow inactivation
 - e. Mutations of the Nav 1.7 channel also cause "paroxysmal extreme pain disorder" (PEPD)
 - f. Deficiency of the Nav 1.7 channel causes congenital indifference to pain

Clinical Manifestations

- 1. Episodic erythema with intense burning pain and warmth of the extremities
- 2. The edema and increased blood flow to the extremities is a feature of neurogenic edema produced by the release of vasoactive neuropeptides that include substance P and calcitonin gene-related peptide from unmyelinated C-fibers
- 3. The acquired form occurs from small fiber neuropathies (neurogenic inflammation) chemotherapy, myeloproliferative and autoimmune disease
- 4. Symptoms may begin at any age in the inherited type

- 5. Clinical manifestations of paroxysmal extreme pain disorder (PEPD)
 - a. Severe burning pain in the rectum (most commonly), eye, or jaw regions

Neuropathology

- 1. Electrophysiological studies show that inherited erythromelalgia mutations enhance activation, whereas those that cause paroxysmal extreme pain disorder alter fast inactivation
- 2. The changes in sodium channel gating arise from:
 - a. Alterations in conformation (affects all gating characteristics)
 - b. Voltage sensing charge (affects activation)
 - c. Interaction within the protein (binding to the inactivation links)
 - d. Interaction with other proteins (generation of resurgent sodium currents)
- 3. Skin biopsies:
 - a. May be normal
 - b. Reduced epidermal nerve fiber density
 - c. Rarely observed is perivascular inflammation and thickening of arteriolar basement membrane and smooth muscle hyperplasia

Guillain-Barré Syndrome and Its Variants

Overview

Guillain-Barré syndrome (GBS) is an immune-mediated polyneuropathy mediated by autoreactive leukocyte infiltration of specific components of the peripheral nervous system. The process induces neuroinflammation, demyelination, and an axonal degenerating polyneuropathy (AIDP). A bacterial protein is the epitope presented by a macrophage to a T-cell that after penetrating the blood vessel endothelium (peripheral blood-nerve barrier) recognizes a cross-reactive antigen and releases cytokines that activate endoneurial macrophages. Endoneurial macrophages in turn secrete enzymes and nitric oxide radicals and infiltrate compact myelin concomitantly with activated T-cells.

Mechanisms of demyelination include:

- 1. Release of cytokines
- 2. Activated T-cells interact with B-cells to produce antibodies which cross the damaged blood-nerve barrier
- 3. The antibodies interact with epitopes on Schwann cell and axonal surfaces which fix complement that:
 - a. Destroy and damage Schwann cells
 - b. Produces vesicular dissolution of myelin

In acute motor axonal neuropathy (AMAN):

- 1. The process is antibody-mediated
- 2. There is little or no inflammatory infiltrate
- 3. There is cross-reactivity from an epitope of the infective agent with an epitope of the peripheral nerve. The most likely epitopes of the peripheral nerves in AMAN are:

- a. GM1
- b. GM1b
- c. GD1a
- d. GALNAc-CD1a which is expressed on the motor nerve axolemma

A large component in the pathogenesis of GBS is humeral immunity that is demonstrated by:

1. The demonstration of immunoglobulin and complement on peripheral nerves
2. The therapeutic benefit of plasmapheresis and intravenous immunoglobulin (IVIG)
3. The existence of antibodies against peripheral nerve in GBS sera
4. The experimental demonstration that some patient IgM antibody or serum produces complement-dependent demyelination of peripheral nerve
5. In GBS patients:
 - a. Activated complement components are detected in serum and the cerebral spinal fluid
 - b. Anti-myelin antibodies rise before activated complement that supports an antibody-mediated complement attack on peripheral nerve myelin
6. Several infectious agents have been identified in association with GBS attacks, which include:
 - a. *Campylobacter jejune*
 - b. Cytomegalovirus
 - c. Epstein-Barr virus
 - d. *Mycoplasma*
 - e. *Campylobacter jejune* has been the most intensively studied and appears to be conclusive as a triggering agent
7. The mechanism for GBS with strong support is that of molecular mimicry between lipopolysaccharide of the bacterial wall and ganglioside-like epitopes on nerve cells, which causes cross-reactivity of the immune response following exposure to the infective agent. In the molecular mimicry hypothesis of *C. jejune* antecedent infection and the immunopathogenesis of GBS, several mechanistic aspects remain poorly understood:
 - a. Several *C. jejune* strains that express GM1 ganglioside-like epitopes fail to induce anti-ganglioside antibodies
 - b. Patients develop different GBS variants after exposure to the same epitope
 - c. Susceptibility genes may predispose patients to develop GBS after specific infecting agent exposure (i.e., bacterial vs. viral)
 - d. Host factors that include cytokines and toll-like receptors (TLRs) in addition to molecular mimicry are pivotal in the production of cross-reactive antibodies seen in GBS patients

The Role of Toll-Like Receptors (TLRs) and Cytokines in GBS Pathogenesis

Toll-like receptors are structurally related receptors that recognize specific components of micro-organisms and endogenous ligands that are associated with cell damage. They re-

cognize pathogen-associated molecular patterns (PAMPs). Their activation induces expression of proinflammatory cytokines (IL1, IL6, and TNF) which are a component of T-cell differentiation and the host immune response.

Cytokines are small proteins secreted by a variety of immune cells that are involved in inflammation as well as the recruitment and amplification of leukocyte infiltration into the peripheral nervous system after specific stimulation. They have pleiotrophic functions which include the regulation of cellular replication, differentiation, and activation. Th1 cytokines (IFN-gamma and IL12) induce autoimmune processes, while Th2 cytokines (IL4) are primarily involved in antibody-mediated autoimmune diseases. In GBS, cytokines are produced by infiltrating monocytes and Schwann cells in AIDP and by macrophages in the axonal form of the disease. Cascades of immune-mediated inflammatory responses are initiated by immune recognition receptors that involve lymphocytes, monocytes, and cytokines that cause peripheral nerve demyelination. Cytokines are pivotal in the disruption of the blood-nerve barrier, allowing the infiltration of immune cells to access peripheral myelin and Schwann cells. One cytokine TNF-alpha that is produced by infiltrating Th1 cells is directly myelin toxic and decreases the synthesis of myelin protein and glycolipids.

Interferon-gamma, which is produced by Th1 cells, has pleiotrophic effects that include:

1. Activation of endothelial cells, macrophages and T-cells
2. Increases the expression of major histocompatibility complex II that enhances the antigen presenting capacity of macrophages
3. Induces the differentiation of T-cells to a Th1 phenotype
4. B-cell class switching
5. Apoptosis of T-cells
6. Enhances the production of other inflammatory cytokines such as TNF-alpha, IL1-B and IL5
7. IFN-gamma inhibits Th2 cells

Experimental studies have demonstrated that Th1 cytokines are associated with immune-mediated disease progression early in the course of illness due to their role in neuroinflammation. Th2 mediated immune responses are characteristic of later phases of recovery. IL23 in conjunction with IL6 and TGFB1 stimulate naïve CD4⁺ T-cells to differentiate into Th17 which further enhance the production and secretion of IL1B and IL6 from monocytes which amplifies the inflammatory cascade. IL17 levels in the CSF have been correlated with GBS severity. Toll-like receptors are transmembrane proteins that are pattern recognition receptors (PRRs). They are critical for the initiation of both innate and adaptive responses against microbial organisms by activating the NF-KB inflammatory pathway. Excessive signaling has been implicated in atherosclerosis and autoimmune disease by activating self-reactive T- or B-cells. TLRs have also been shown to activate antigen presenting cells through MyD88 (myeloid differentiation primary-response gene) dependent or independent transduction pathways. TLR2 has been demonstrated

to deliver co-stimulatory signals to antigen-activated T-cells and to enhance T-cell proliferation, survival, effect, or function.

At present, a widely accepted theory for the initiation of GBS in the case of *C. jejune* is that of molecular mimicry between liposaccharides (LPS) on its cell envelope and ganglioside epitopes on peripheral nerves that induce a cross-reactive immune response.

Special Conditions That Cause GBS

1. After seroconversion in HIV (lymphocytosis in the CSF)
2. Vaccinations (swine flu)
3. Lymphoma
4. Bone marrow transplantation
5. Graft-versus-host disease
6. Following the use of immunomodulating drugs (TNF-alpha antagonists)

Acute Inflammatory Demyelinating Polyradiculoneuropathy (AIDP)

General Characteristics

1. AIDP is the most common cause of acute generalized weakness whose annual incidence is 1–4/100,000 persons
2. The peak age of onset is approximately 40 years of age; there may be a slight male predominance
3. Preceding conditions include:
 - a. Infections
 - b. Surgery
 - c. Trauma
 - d. Immune dysfunction
 - e. Systemic illness
4. Infections:
 - a. Approximately 60–70% of patients with AIDP have a history of preceding infection (usually within 10–14 days)
 - b. *Campylobacter jejune* is the most common infection and accounts for approximately 30% of patients
 - c. CMV accounts for approximately 15% of patients:
 - i. Younger patients
 - ii. Severe course
 - iii. Respiratory failure
 - iv. Cranial nerve involvement
 - v. Subgroup of patients with GM2 antibodies
 - d. EBV (10% of patients):
 - i. Mononucleosis
 - ii. Pharyngitis and hepatitis may be associated
 - e. *Mycoplasma* (approximately 5% of patients):
 - i. Fever
 - ii. Headache with a dry cough
 - iii. Cold agglutinin in the serum

Clinical Manifestations

1. Sensory symptoms:
 - a. Early distal numbness and paresthesias

- b. Minimal sensory deficit but large fiber predominant with proprioception and vibratory loss greater than pain and temperature
- c. Severe muscle, back and extremity pain occurs in 50% of patients; over time it may be reported by 80% of patients
- d. Rarely back and radicular pain precedes weakness
- e. Occasionally there is a sensory level on the trunk but no analgesia below the level; there is a variant with transverse myelitis in association with the classic pattern in which there is profound sensory loss
2. Weakness:
 - a. The usual pattern is mild distal weakness that may progress to complete quadriparesis
 - b. The weakness is first noted in the legs, then ascends to include the trunk, arms, head, and neck. This pattern is usually symmetrical
 - c. 10% of patients have upper extremity weakness greater than lower extremity weakness
 - d. In 60% the lower extremities are weaker than the upper extremities
 - e. Approximately 30% upper and lower extremities are equally affected
 - f. Descending weakness occurs in approximately 14% of patients
 - g. Proximal weakness may be greater than distal weakness
 - h. Rarely fasciculation or myokymia is noted

Cranial Nerve Involvement

1. Symmetrical peripheral facial weakness is appreciated in 60–70% of severe patients; rarely it is unilateral in association with asymmetric motor weakness; quadriparesis without facial weakness is rare
2. 10–20% of patients have partial or complete ophthalmoplegia or ptosis
3. Respiratory paralysis occurs in approximately 30% of patients within two weeks

Sphincter Involvement

1. Urinary retention for 1–2 days occurs in approximately 2% of patients; often associated with spinal type paresthesias
2. Fecal incontinence occurs in 1% of patients

Autonomic Dysregulation

1. Common
2. Occurs most commonly with quadriparesis and during ventilator support
3. Manifestations:
 - a. Sinus bradycardia
 - b. Sinus arrest
 - c. Variety of supraventricular arrhythmias
 - d. Paroxysmal hypertension or hypotension
 - e. Vagal episodes:
 - i. Bronchorrhea, bradycardia, and hypotension

- f. Ileus
- g. Peripheral vasomotor instability, cyanosis and livedo reticularis
- 4. Areflexia most often occurs within one week; diminished or absent reflexes in a paretic limb by three days
- 5. Course of the illness:
 - a. Average time to nadir is approximately 17–20 days
 - i. It occurs after the first week in 40% of patients
 - ii. 80% after the second week
 - iii. 90% by the third week

Unusual Features within the Classic Presentation

1. Unilateral paralysis
2. Radicular pain and weakness at onset
3. Severe neck, back and extremity pain; deep ache, mechanical and thermal allodynia; hyperalgesia (the “meningitis variant”)
4. Central features (associated with peripheral manifestations):
 - a. Optic neuritis
 - b. Babinski sign
 - c. Conjugate recovery of ophthalmoplegia:
 - i. Recovery of upgaze earlier than horizontal gaze
 - ii. Preservation of Bell’s phenomenon with impaired voluntary gaze
5. Severe generalized burning pain (peripheral C-fiber mediated)
6. Early and almost pure respiratory failure (often associated with deltoid muscle and flexor and extensor neck muscle weakness)
7. Early severe vibration and position sense loss (sensory ataxia)
8. Preserved triceps reflex
9. Increased intracranial pressure:
 - a. Bilateral papilledema
 - b. Increased CSF protein
 - c. Cytotoxic intracranial edema (Joynt hypothesis)
 - d. Blockage of the Pacchionian granulations (Denny-Brown hypothesis)
 - e. Respiratory paralysis; $PCO_2 > 70$ mm/Hg
10. Severe ataxia (Richter’s variant):
 - a. Primary involvement of large peripheral nerve fibers, A-beta and A-alpha fibers; heavily myelinated afferents that carry proprioception and vibratory sensibility to the dorsal root ganglia (DRG)
 - b. Severe ataxia of the upper and lower extremities
 - i. The ataxia is evident through all components of the movement rather than the terminal 1/3 which is characteristic of cerebellar disease
 - c. In Richter’s variant there is less loss of proprioceptive position sense than expected; it is hypothesized that the primary defect is abnormal spindle afference to the cerebellum
11. Transverse myelitis (concomitant with the peripheral demyelination):

- a. Occurs concomitantly with the onset of the peripheral neuropathy
- b. A clear sensory level (usually at T4–T6)
- c. Bowel and bladder are involved
- d. Reflexes in the arms may be greater or more active than those of the legs
- 12. Miller-Fisher syndrome:
 - a. Ophthalmoplegia
 - b. Ataxia
 - c. Areflexia
 - d. Anti-GQ1b antibody
 - e. May present with only two components of the triad
 - f. Excellent prognosis
- 13. Bickerstaff’s brainstem encephalitis:
 - a. Acute ophthalmoplegia and ataxia
 - b. Alterations in mental status
 - c. Babinski sign
 - d. Hemisensory loss
 - e. Most likely on a continuum of Miller-Fisher syndrome
 - f. A significant proportion of patients demonstrates anti-GQ1b IgG

Designated GBS Variants

1. Miller-Fisher syndrome
2. Bickerstaff’s encephalitis
3. Idiopathic cranial neuropathy
4. Pharyngeal-cervical-brachial (descending variant)
5. Transverse myelitis
6. Acute sensory neuropathy/ganglionopathy (Richter’s variant)
7. Acute small fiber neuropathy (C-fiber mediated generalized burning pain)
8. Acute autonomic neuropathy
9. Severe back and neck pain (“meningitis form”)

Neuropathology

1. Perivascular mononuclear cell infiltration of macrophages and lymphocytes; early predisposition for nerve roots in areas of peripheral nerve root entrapment and motor nerve terminals
2. Nodes of Ranvier demonstrate alteration of paranodal myelin and demyelination of internodal segments
3. In severe cases, polymorphonuclear cells may be concomitantly seen with monocytes in areas of axonal degeneration
4. Recovery demonstrates remyelination with reduced myelin to axon ratio associated with an increased number of internodes

Laboratory Evaluation

1. Cardiac arrhythmias:
 - a. Occur in 10–80% of patients:
 - i. Sinus tachycardia (30–60%)
 - ii. Sinus bradycardia (10–30%)
 - iii. Premature atrial and ventricular contractions

- iv. Ventricular tachycardia and asystole are rare except in the autonomic variant
- b. EKG:
 - i. Abnormalities occur in 50–80% of patients
 - ii. Depressed ST segments
 1. Inverted T-waves: varying QT intervals
 - iii. Mild or asymptomatic glomerulonephritis
 - iv. Inappropriate ADH occurs in 7–25% of patients (the usual serum sodium is between 120–130 meq/dl)
 - v. Diabetes insipidus is very rare
 - vi. Ileus and gastric retention occur in >40% of patients
 - vii. Compression mononeuropathy is seen primarily in the peroneal and ulnar nerves
 - viii. Pseudotumor cerebri occurs in 1–3% of patients
 - ix. Pulmonary emboli (dramatically decreased incidence with the use of compression boots)
- c. EMG evaluation:
 - i. Prolonged distal motor latencies early in the course of the disease
 - ii. Conduction block with >20% progressive reduction of CMAP (30% of patients)
 - iii. Slowing of motor nerve conduction with dispersion of the alpha waveform; conduction velocities may decrease during recovery due to remyelination (some patients)
 - iv. Slowed sensory nerve conduction velocities occur by three weeks of illness in 75% of patients; decreased sensory amplitudes
 - v. Median and ulnar sensory potentials are decreased when the sural nerve may be normal
 - vi. Positive sharp waves and fibrillation potentials are usually demonstrated within the first four weeks in approximately 20–60% of patients
 - vii. Fisher variant:
 1. Reduced or absent sensory potentials with normal motor studies
 - viii. Abnormal spontaneous activity is noted in affected muscles in 2 to 4 months
 - ix. Myokymia may be seen in the face and extremities early in the course of the illness
 - x. Approximately 15 to 20% of patients may have normal nerve conduction velocities
 - xi. Conduction velocities may remain normal for several weeks in a small number of patients
2. CSF abnormalities:
 - a. Cytoalbuminologic dissociation occurs in 80–90% of patients
 - b. In general, five lymphocytes or less/mm³ are seen; rarely up to 20 lymphocytes/mm³
 - i. The more cells that are seen, the more likely another problem such as lymphoma, carcinomatosis of the meninges, or leukemia is involving the nerve roots
 - ii. HIV, Lyme's disease, and sarcoidosis are the exception and may demonstrate >40 lymphocytes/mm³
 - c. Protein elevation:
 - i. Starts approximately on day 3 to 10
 - ii. The usual levels that are attained are between 100–180 mg/dl; it is extremely rare to note levels greater than 500 mg/dl (this level suggests a spinal block; Froin's reaction)
 - d. Autoimmune antigenic targets at the node of Ranvier:
 - i. Approximately 30% of patients with acute or chronic inflammatory demyelinating polyneuropathy have autoantibodies that are demyelinating
 - ii. Specific antigens are identified in approximately 13% of patients
 - iii. Autoantibodies identified at the node of Ranvier include:
 1. Neurofascin 186
 2. Gliomedin and moesin in the nodal domain
 3. Paranodal domain:
 - a. Contactin-1
 - b. Caspr-1
 - c. Neurofascin 155

Axonal GBS (AMASN)

General Characteristics

1. Clinically and early EMG findings are similar to AIDP

Clinical Manifestations

1. There is sensory loss early in the hands and feet to all modalities
2. Patients have a more rapid course over days, rather than 1–2 weeks as is more typical of AIDP
3. Ophthalmoplegia, dysphagia, and respiratory muscle weakness can occur
4. Autonomic dysregulation with blood pressure variation and cardiac arrhythmias occur
5. There is loss of segmental motor stretch reflexes
6. Recovery is less complete than in AIDP

Neuropathology

1. Sensory and motor nerve biopsies have demonstrated demyelination rather than a primary axonopathy in patients with inexcitable motor and sensory electrodiagnostic studies
2. A subgroup of patients appears to have a primary axonopathy
3. Demyelination and lymphocytes are absent or minimal on nerve biopsy
4. Axonal degeneration affects the dorsal and ventral roots as well as peripheral nerves
5. Three autopsied patients who succumbed early in the course of the illness demonstrated macrophages in the periaxonal space of myelinated internodes as well as rare intra-axonal macrophages; these changes are seen in AMAN but rarely in AIDP

6. AMSAN may follow *C. jejune* infection; there is some support for “molecular mimicry” between GM1 or GM1a on the nodal axolemma and pathogens in the immune response

Laboratory Evaluation

1. CSF cytoalbuminologic dissociation is usual
2. GM1 antibodies concordant with *C. jejune* infection is common
3. EMG:
 - a. Decreased amplitudes or absent CMAPs are demonstrated within 7–10 days
 - b. Distal latencies of the CMAP and nerve conduction velocities, if obtainable, are minimally affected
 - c. Decreased recruitment
 - d. In time (weeks) needle EMG demonstrates fibrillation potentials and positive sharp waves most marked in distal regions of affected muscles

Acute Motor Axonal Neuropathy (AMAN)

General Characteristics

1. Identified in patients with seasonal acute flaccid paralysis in Northern China; has now been identified worldwide
2. An antecedent infection (most often gastrointestinal) occurs in 30 to 85% of patients
3. 67% to 92% of patients have serological evidence of *C. jejune* infection associated with the illness
4. Not uncommon in both Asians and Central and South Americans

Clinical Manifestations

1. Occurs in both children and adults, and presents as a sudden onset of generalized weakness
2. Distal muscles are more severely affected than proximal muscles
3. Approximately 1/3 of patients have cranial nerve deficits and respiratory failure
4. There are no sensory signs or symptoms
5. Cardiac arrhythmias, hyperhidrosis, and blood pressure fluctuations occur
6. Muscle stretch reflexes may be normal or absent and occasionally are exaggerated during the recovery phase
7. AMAN progresses more rapidly and has an earlier peak than demyelinating forms; recovery time is similar to AIDP

Neuropathology

1. Lengthening of nodal gaps occurs early in the illness
2. Deposition of IgG and complement activation factors (C3d and C5,6–9) occurs in nodal and internodal axolemma of motor fibers
3. Macrophages are noted in the affected nodes of Ranvier and periaxonal space
4. Axon retracts from the Schwann cell due to macrophage migration through the Schwann cell basal lamina

and dissects beneath the myelin sheath to the periaxonal space

5. If axons degenerate, the innermost myelin sheath (adaxonal lamina) may remain intact
6. Degeneration of large myelinated intramuscular nerve fibers is noted
7. Pathogenesis:
 - a. Lymphocytes and autoantibodies that link to GM1 or GD1 gangliosides located at the nodes of Ranvier activate complement which alters sodium channel clusters and axonal junctions

Laboratory Evaluation

1. Cytoalbuminologic dissociation in the CSF is seen. Lack of pleocytosis is a distinguishing point from poliomyelitis
2. Serological evidence of recent *C. jejune* infection is seen in the majority of patients
3. Elevation of GM1 and GD1a antibodies occurs commonly
4. EMG:
 - a. Nerve conduction studies reveal low amplitude CMAPs with normal SNAPs when obtainable
 - b. CMAP distal latencies and conduction velocities are slow, as are F-waves
 - c. Rarely, conduction block without other features of demyelination occurs
 - d. Sural sparing occurs
 - e. Needle EMG reveals positive sharp waves, fibrillation potentials, and decreased recruitment of MUAPs
 - f. Autonomic studies are less impaired than in AIDP

GBS Variants

Miller-Fisher Syndromes

General Characteristics

1. There is a spectrum between Miller-Fisher syndrome and Bickerstaff's encephalitis which includes alterations in consciousness and hemisensory loss as well as ophthalmoplegia, ataxia, and areflexia
2. There is a 2:1 male predominance and it occurs in children
3. In more than 2/3 of patients, there is a preceding infection

Clinical Manifestations

1. The mean age of onset is in the fourth decade
2. Diplopia is usually the first symptom followed by:
 - a. Sensory ataxia and incoordination
 - b. Complete ophthalmoplegia with ptosis; pupillary involvement is rare
 - c. Facial weakness, dysarthria, and dysphagia occur in a significant proportion of patients
 - d. Limb weakness occurs in approximately 1/3 of patients
 - e. Paresthesia of the face and distal extremities in approximately 50% of patients; delayed facial weakness
 - f. Generalized weakness may supervene
3. Patients start to recover in approximately two weeks, and a full recovery may be seen by six months

Neuropathology

1. Demyelination and inflammatory infiltrates in cranial nerve III, IV, VI
2. Inflammation in the sensory ganglia of peripheral nerves
3. GQ1b antibodies directed against oculomotor nerves and sensory ganglia

Laboratory Evaluation

1. Cytoalbuminologic dissociation is seen in the CSF (in approximately 60% of patients)
2. Serologic evidence of recent infection with *C. jejune*
3. Anti-GQ1b antibodies are noted in a significant number of patients (approximately 80%); they peak in the first week. The profile is similar in Bickerstaff's variant
4. EMG:
 - a. NCS reveal decreased amplitudes of SNAPs that is out of proportion to prolongation of distal latencies or sensory conduction velocities
 - b. CMAPs in the extremities are usually normal
 - c. In >50% of patients, there is mild to moderate decrease of facial CMAPs
 - d. Sural nerve sparing

Idiopathic Sensory Neuropathy*General Characteristics*

1. Proposed to be an autoimmune process directed against the dorsal root ganglia (DRG)
2. Known diseases with prominent DRG pathology include:
 - a. Paraneoplastic syndromes (anti-Hu antibodies)
 - b. Sjögren's syndrome
 - c. Toxins
 - d. Infections (Herpes Zoster and simplex)

Clinical Manifestations

1. Age of onset is between 18 and 81 years
2. There may be an abrupt onset, or symptoms may evolve over days and even years; the course can be chronically progressive or relapsing as well as monophasic
3. Rare antecedent infections are reported (Epstein-Barr virus)
4. Presentation is numbness and tingling of the extremities, face, and trunk
5. Symptoms begin asymmetrically in the upper extremities in more than 50% of patients; most often the sensory symptoms are generalized, but they can remain localized
6. Radicular symptoms may occur and are often painful
7. Decreased large myelinated fiber afference; vibration and proprioception are affected to a greater degree than pain and temperature
8. Sensory ataxia is prominent
9. Pseudoathetosis of the outstretched upper extremities may be evident
10. Positive Romberg sign
11. Muscle stretch reflexes are decreased or unobtainable:

- a. There may be proximal progression of sensory loss over days to months; the face is frequently affected early with paresthesias around the mouth
 - b. There is no weakness or respiratory failure
12. Most often there is improvement of sensory parameters within 1–2 months after onset

Neuropathology

1. Sensory nerve biopsy:
 - a. Preferential loss of large myelinated fibers (12–22 μ) as opposed to small thinly myelinated (1–4 μ A-delta fibers) or unmyelinated 1 μ fibers
 - b. Mild perivascular inflammation
 - c. No segmental demyelination
2. One autopsy (five weeks after onset of the illness) revealed:
 - a. Inflammation of sensory and autonomic ganglia with loss of neurons and Wallerian degeneration
 - b. Normal motor roots and neurons
 - c. Consistent with a CD8⁺ T-cell mediated process directed against DRG neurons

Laboratory Evaluation

1. Most often the CSF protein is normal or only slightly elevated; high proteins have been reported
2. Rare pleocytosis
3. A subgroup of patients has an IgM, IgG or IgA monoclonal gammopathy as well as increased GD1b antibodies
4. Antifibroblast growth factor receptor 3 antibodies have been identified in a subgroup of patients in whom an autoimmune pathogenesis was suspected
5. EMG:
 - a. SNAPs are often unobtainable; in those that can be studied, there are normal distal sensory latencies and conduction velocities or slightly prolonged latencies or decreased CVs
 - b. Differential EMG parameters:
 - i. An absent or abnormal blink reflex supports a non-paraneoplastic etiology of sensory neuropathy
 - ii. The masseter reflex is abnormal in patients with a sensory neuropathy but is normal with sensory neuronopathy

Acute Small Fiber Sensory Neuropathy*General Characteristics*

1. Many of these neuropathies are idiopathic. The most common well-described small fiber neuropathies include:
 - a. Diabetes mellitus
 - b. Amyloidosis
 - c. Sjögren's syndrome
 - d. Transthyretin-met 30 gene mutations
 - e. Antisulfatide antibody neuropathy
 - f. Some paraneoplastic antibodies
 - g. Hereditary sensory and autonomic neuropathies

Clinical Manifestations

1. The usual small fiber neuropathies present insidiously with burning pain and autonomic dysregulation in the extremities, with preserved strength and reflexes
2. In autoimmune small fiber neuropathy:
 - a. Presentation may be acute
 - b. The pattern may or may not be length dependent
 - c. An antecedent infection is common
 - d. Pain and temperature modalities are primarily affected
 - e. Normal or brisk muscle stretch reflexes are demonstrated
 - f. Strength is maintained
 - g. Burning and dysesthesia usually abate by four months, but objective sensory loss may last longer

Neuropathology

1. Skin biopsy:
 - a. Reduced intraepidermal nerve fiber density
 - b. Alterations in sweat glands

Laboratory Evaluation

1. CSF evaluation often demonstrates cytoalbuminologic dissociation
2. EMG:
 - a. Motor and sensory conduction velocities are normal
3. Alterations in autonomic nerve testing
4. QST:
 - a. Increased thermal thresholds as well as cold pain thresholds

Autoimmune Autonomic Neuropathy*General Characteristics*

1. Autoimmune autonomic ganglionopathy is a pure autonomic disorder which affects both cholinergic and adrenergic function
2. This is a heterogeneous neuropathy in regards to onset, specific autonomic deficits, and the presence of somatic involvement

Clinical Manifestations

1. The onset may be abrupt, or insidious and chronic
2. Approximately 20% of patients may have selective cholinergic dysfunction, while the vast majority demonstrate widespread sympathetic and parasympathetic dysfunction
3. Approximately 80% of patients have orthostatic signs and symptoms
4. Gastrointestinal dysfunction occurs in approximately 70% of patients
5. Heat intolerance and hypohidrosis is very common
6. Blurred vision
7. Dry mouth and sicca signs
8. Urinary retention or incontinence
9. Approximately 1/3 of patients have numbness, dysesthesia of the distal extremities

10. Impotence may be severe and an early sign
11. The course is most often monophasic, with a plateau phase that is followed by partial recovery

Neuropathology

1. Nerve biopsy:
 - a. Decreased density of small diameter myelinated nerve fibers (1–4 μ)
 - b. Stacks of empty Schwann cell profiles and collagen pockets
 - c. Mild epineural perivascular inflammation
 - d. Autopsy material:
 - i. Neuronal loss in thoracic sympathetic and dorsal root ganglia

Laboratory Evaluation

1. Cytoalbuminologic dissociation (slightly elevated protein)
2. Decreased standing plasma norepinephrine levels
3. Approximately 20% of patients have elevated serum levels of ganglionic acetylcholine receptor autoantibodies
4. EMG:
 - a. Routine motor and sensory nerve conduction studies and needle EMG evaluation are normal
 - b. QST:
 - i. Alteration in thermal thresholds
 - c. Autonomic evaluation:
 - i. In greater than 60% of patients, there is reduced variability of the heart rate with deep breathing
 - ii. Abnormalities in the Valsalva maneuver include:
 1. Exaggerated fall of the blood pressure during early phase II of the response
 2. Absent recovery of the systolic and diastolic blood pressure during late phase II
 3. Reduced or absent overshoot of the systolic and diastolic blood pressures during phase IV
 - iii. Absent sympathetic skin responses
 - iv. Thermoregulatory sweat test:
 1. Areas of anhidrosis are seen between 12 to 97% of patients
 - v. Abnormalities of gastrointestinal motility throughout the GI tract

Pharyngeal-Cervical-Brachial Variant (Munsat's Variant)*General Characteristics*

1. A regional pattern of involvement; descending paralysis occurs in approximately 10% of patients who develop GBS

Clinical Manifestations

1. Weakness is limited early to pharyngeal and neck muscles that spread to the upper extremities; the legs are spared
2. Ptosis is common
3. Severe swallowing and respiratory compromise may occur
4. Approximately 30% of patients have an antecedent infection caused by C. jejune
5. AIDP, Miller-Fisher syndrome, and Bickerstaff's encephalitis overlap

Neuropathology

1. Axonal neuropathy

Laboratory Evaluation

1. Anti-GT1a IgG antibodies are positive in approximately 50% of patients; anti-GQ1b IgG antibodies are positive in approximately 40% of patients; IgG antibodies to GM1, GM1b, GD1a and GalNAC-GD1a1 serological markers for axonal GBS are detected in 27% of patients
2. 5% of descending GBS (pharyngeal cervical brachial variant) have anti-GT1a IgG antibodies which may cross react with GQ1b antibodies; the IgG GQ1b antibodies seen in Fisher syndrome almost always cross react with GT1a
3. EMG:
 - a. NCV are normal early; demyelinating features may be noted later in the upper extremities
 - b. Slightly elevated CSF protein

Paraparetic Variant*General Characteristics*

1. In one large study (492 patients) 8% had paraparesis

Clinical Manifestations

1. Presentation with paraparesis without arm or hand weakness; normal upper extremity strength was maintained throughout period of illness in 77% of patients
2. These patients have a milder phenotype than those with quadriparesis:
 - a. Less cranial nerve involvement
 - b. Milder leg weakness
3. 50% of patients have arm sensory deficits
4. 73% have absent arm reflexes

Neuropathology

1. Not determined

Laboratory Evaluation

1. MRI:
 - a. Lumbar spinal roots may demonstrate gadolinium enhancement
2. EMG:
 - a. Demyelinating features
 - b. NCV studies include arm as well as leg involvement in approximately 80% of patients who have cauda equina or spinal cord involvement

The Differential Diagnosis of AIDP**Overview**

In general, the differential diagnosis of AIDP is very straightforward, although subtypes and variants form a spectrum with overlapping features. The basic pathophysiology is autoimmune, and in most instances there is a history of upper

respiratory or gastrointestinal illness (particularly *C. jejune*), a monophasic disease course, and symmetrical extremity and cranial nerve weakness. Delayed facial weakness occurs in AIDP and the Miller-Fisher variants. There are pure motor and sensory axonal forms, and there is overlap between the Fisher and Bickerstaff variants. Rarely the process is descending with severe cranial-pharyngeal weakness. Several studies have demonstrated white matter hyperintensities on MRI with variable signs during the course of AIDP. Spinal cord involvement with both long and short segment MRI documented myelitis is seen. The Miller-Fisher variant and Bickerstaff's brainstem encephalitis (now primarily thought to be a spectrum) may be misdiagnosed as a brainstem stroke, botulism, or myasthenia gravis. Bickerstaff's encephalitis may appear similar to Wernicke's encephalitis due to its alteration in consciousness. The reflexes in AIDP may remain normal or are increased in approximately 10% of patients. Experimental studies suggest that there are inhibitory fibers in the ventral roots that when affected primarily may increase reflexes. Alternatively, demyelination of the cortical spinal tracts anywhere in their course would disinhibit muscle stretch reflexes below the level of the lesion. The paraparetic form may be misdiagnosed as a CMV infection in a patient with HIV. Chronic inflammatory demyelination polyneuropathy and a severe aggressive episode of multiple sclerosis have clinical signs that resemble AIDP. Complicating the diagnosis, however, are patients who present without an obvious history of prior infection, or with associated neurological or medical problems that alter their mental status.

A high cervical spinal cord injury causes flaccid quadriplegia, loss of bowel and bladder control, hypothermia (97° Fahrenheit) and hypotension. If it is acute and severe, males may ejaculate or have an erection. Acute inflammatory myopathy may be associated with sore muscles, rare diaphragmatic weakness, depressed but not absent muscle stretch reflexes, and no bowel or bladder dysfunction. Metabolic muscle disease, periodic paralysis, hypophosphatemia and hypercalcemic states spare the cranial nerves and bowel and bladder. Myasthenia gravis usually affects the extraocular muscles more than extremity musculature, but both can be affected concomitantly during exacerbations. There is no sensory loss, muscle stretch reflexes are maintained, and the pupils are clinically normal. Hyperkalemic periodic paralysis may present with generalized weakness, normal mentation, some myotonic features, no bowel or bladder dysfunction, and absent myotatic and muscle stretch reflexes. Toxic neuropathies that cause acute paralysis often have concomitant CNS involvement.

Acute Peripheral Neuropathies**Toxic Neuropathies***General Characteristics*

1. History of exposure
2. Involvement of other organ systems

Clinical Manifestations

1. Thallium (hair loss, distal extremity pain)
2. Arsenic (hyperkeratosis, GI symptoms)
3. Lead (encephalopathy, hypertension, abdominal pain)
4. N-hexane (encephalopathy; industrial exposure)

Acute Demyelinating Neuropathies

1. Amiodarone (painful; skin changes)
2. Perhexiline (lumbosacral roots)
3. Gold (rash; wasting of intrinsic hand muscles)
4. Alcohol (painful, associated with neuropathy from pan-tothenic acid deficiency and concomitant B12 deficiency)

Drugs

1. Vincristine/vinblastine
2. Cisplatin
3. Paclitaxel
4. Gold
5. Chloroquine (concomitant muscle involvement)
6. Mervacor (all cholesterol lowering agents) usually a painful symmetrical distal neuropathy but rarely a GBS presentation
7. Disulfiram
8. Nitrofurantoin
9. Isoniazid
10. Emetine

Infections

1. Diphtheria (pharyngeal muscles)
2. Tick paralysis (ataxia is often more prominent than weakness)
3. Poliomyelitis
4. Enteric viruses
5. Lyme's disease
6. HIV
7. CMV

Metabolic

1. Porphyria (AIP, variegate and coproporphyria)
2. Hypermagnesemia
3. Hypophosphatemia (concomitant muscle involvement; proximal > distal)
4. Hyperkalemia, potassium level > 6 mg/dl
5. Renal tubular acidosis
6. Secondary hypokalemic periodic paralysis
7. Hyperaldosteronism

Toxins

1. Organophosphate insecticides
2. Hydrocarbons
3. Buckthorn
4. Toluene
5. Solvents

Autoimmune Diseases

1. Demyelinating disease (MS, ADEM, acute hemorrhagic leukoencephalitis)
2. CIDP
3. Vasculitis (SLE, Sjögren's, Periarteritis nodosa)

Acute Quadriparesis

1. Hypokalemic periodic paralysis (severe hypokalemia with fewer EKG changes than the very low potassium produces in other circumstances; lid retraction; no myotatic reflexes)
2. Tick paralysis:
 - a. Ataxia precedes weakness and low muscle stretch reflexes
3. Organophosphate poisoning:
 - a. Miosis
 - b. Hyperhidrosis
4. Botulism:
 - a. Ptosis
 - b. Pupillary dilatation
 - c. Pharyngeal paralysis
 - d. GI symptoms
5. Myasthenia gravis:
 - a. Cranial nerve involvement
 - b. Muscle stretch reflexes are spared
6. Polymyositis:
 - a. Painful swollen muscles (particularly with severe rhabdomyolysis)
 - b. Retained reflexes
7. Critical care neuropathy:
 - a. Usually at least 2 to 3 weeks in the ICU
 - b. Concomitant large fiber myopathy
 - c. Multi-organ involvement
 - d. Concomitant sepsis
 - e. Difficulty in weaning off a respirator

Acute Quadriparesis with Severe Pain

1. Acute intermittent porphyria:
 - a. Acute severe abdominal pain that is accompanied by a soft abdomen
 - b. Autonomic dysregulation (arrhythmia, paroxysmal hypo- and hypertension)
 - c. Non-dermatomal patchy sensory loss
 - d. Retained ankle muscle stretch reflexes
2. Arsenic poisoning:
 - a. Distal extremity weakness
 - b. Painful extremities
 - c. Hyperkeratosis of palms and soles
 - d. Mees lines in the fingernails
3. Vasculitic neuropathy:
 - a. Distal extremity weakness and sensory loss
 - b. Associated underlying medical conditions (SLE, PAN, Sjögren's syndrome)
 - c. Asymmetric extremity involvement
 - d. Asthma
 - e. Eosinophilia

4. Mononeuritis multiplex:
 - a. Underlying autoimmune cause; quadriceps pain with femoral nerve infarction

Acute Neuropathy with Prominent Sensory Abnormalities

1. Autoimmune:
 - a. Functional loss of the dorsal columns; large myelinated fiber modalities affected
2. Rabies:
 - a. Simulates the pharyngeal-cervical-brachial GBS variant
 - b. Pharyngeal spasms
 - c. Severe muscle pain
 - d. A motor neuropathy upon examination
3. Vasculitic neuropathies:
 - a. Mononeuritis multiplex
 - b. Approximately 15% of patients have distal symmetrical involvement; often not symmetrical by EMG evaluation
4. Ciguatera toxin:
 - a. Generalized burning pain
 - b. Large joint arthritic pain
 - c. The mouth is often involved
 - d. Paradoxical temperature perception (cold is felt as hot)
5. Thallium:
 - a. Distal pain
 - b. Alopecia
6. Arsenic poisoning:
 - a. Burning distal extremity pain
 - b. Hyperkeratosis of palms and soles
 - c. Vascular collapse
7. Perhexiline
 - a. Lumbosacral root involvement
8. Paralytic shellfish ingestion:
 - a. Domoic acid
 - b. Small fiber neuropathy
 - c. GI Symptoms

Increased CSF Protein and Acute Neuropathy

1. Carcinomatous meningitis
2. Leukemic and lymphomatous meningitis
3. Arsenic
4. Lead
5. Vincristine
6. Perhexiline
7. Thallium

Disorders of the Neuromuscular Junction Simulating AIDP

1. Myasthenia gravis:
 - a. Severe cranial nerve involvement, particularly the extraocular muscles with pupillary sparing
 - b. Muscle stretch reflexes are retained
2. Botulism:
 - a. Internal ophthalmoplegia (pupils are involved); nasopharyngeal weakness > ophthalmoplegia
3. Snake envenomation (neurotoxic):

- a. Pain at the site of envenomation
 - b. Perioral numbness
 - c. Pharyngeal paralysis
 - d. Toxin may be mixed; if hemotoxic component disseminated intravascular coagulation can be initiated
4. Hypermagnesemia:
 - a. No myotatic reflexes
 - b. Cranial nerves are spared
 - c. Usually occurs during the treatment of toxemia
 5. Aminoglycosides:
 - a. In the setting of gram-negative sepsis
 - b. Less cranial nerve involvement
 6. Tetanus:
 - a. Opisthotonus
 - b. Pharyngeal and masseter spasm
 - c. Extreme sensitivity to startle and sound
 7. Succinylcholine:
 - a. Prolonged exposure
 - b. Failure to move after surgery
 - c. May occur in an undiagnosed myasthenia patient (during surgery)

Acute Myopathy Simulating AIDP

1. Polymyositis:
 - a. No VIIth nerve involvement
 - b. Reflexes are relatively preserved
2. Acute rhabdomyolysis:
 - a. Severe edema of affected muscles
 - b. Tight, thin-appearing skin, often with blisters
 - c. Lumbar quadratus may be the first large muscle involved
 - d. Severe pain (mechanical hyperalgesia)
3. Critical care myopathy:
 - a. Associated with axonal neuropathy
 - b. May have diaphragmatic involvement
 - c. Usually patients have had a prolonged ICU stay associated with multiple medical complications

CNS Abnormalities Simulating AIDP

1. Acute transverse myelitis
 - a. Simulating the paraparetic variant
2. Cervical cord intrinsic pathologies:
 - a. Cavernous hemangioma bleed
 - b. Acute MS or ADEM
 - c. Metastasis
3. Rhombencephalitis:
 - a. Simulates the spectrum of Fisher syndrome and Bickerstaff's encephalitis
 - b. Herpes simplex (in HIV-infected patients)
 - c. CMV (lumbosacral root involvement in a terminally ill AIDS patient; CD4 T-cells < 50/mm³)
 - d. Listeria brainstem infection:
 - i. Dorsal pons involvement
 - ii. Occurs in pregnancy, immune suppression, and after ENT procedures

4. Locked-in syndrome:
 - a. Quadriplegia or -plegia
 - b. Vertical gaze and consciousness intact
 - c. No horizontal eye movements
5. Basilar artery infarction:
 - a. Pinpoint pupils (<0.5 mm)
 - b. Herald hemiparesis
 - c. May have prominent sensory loss
 - d. Pharyngeal muscle and horizontal gaze center involvement
2. There are four major patterns of progression:
 - a. Chronic monophasic (15%)
 - b. Fluctuating over weeks or months (approximately 30% of patients)
 - c. Stepwise (>30%)
 - d. Chronically progressive (15%)
3. The relapsing form presents in the second to third decade
4. Increased prevalence in men
5. Triggers include:
 - a. Infection
 - b. Vaccination
 - c. Surgery
 - d. Trauma

Distinguishing Acute-Onset CIDP from Fluctuating Guillain-Barré Syndrome

1. Treatment-related fluctuations of GBS
 - a. Occur within eight weeks
2. Chronic inflammatory polyneuropathy with acute onset:
 - a. Less severely affected than patients with AIDP and treatment-related fluctuations
 - b. Do not require mechanical ventilation
 - c. Rare cranial nerve involvement
 - d. CIDP EMG evaluation
 - e. Acute-onset CIDP is a high differential when a patient thought to have AIDP deteriorates after eight weeks from onset, as there are usually three or more episodes of neurologic deterioration

Chronic Inflammatory Demyelinating Polyneuropathy and Related Autoimmune Neuropathies

CIDP

General Characteristics

1. These are a heterogeneous group of inflammatory neuropathies that have overlapping clinical pathologic and electrodiagnostic features but a distinct pathogenesis
2. The entities include:
 - a. Chronic inflammatory demyelinating polyneuropathy (CIDP)
 - b. Distal acquired demyelinating sensorimotor neuropathy (DADS)
 - c. Multifocal acquired demyelinating sensory and motor neuropathy (MADSAM)
 - d. Multifocal motor neuropathy (MMN)
 - e. Multifocal acquired motor axonopathy (MAMA)
3. CIDP represent approximately 10 to 30% of undiagnosed peripheral neuropathy in referral centers
4. The course must be progressive for at least eight weeks which distinguishes it from AIDP; a variant, subacute demyelinating polyneuropathy, may have an onset over 4–8 weeks which can remit and thus would be AIDP or, if progressive, CIDP

Clinical Manifestations

1. The peak incidence is between 40 to 60 years of age

6. Infection has been identified as antecedent to relapse or exacerbation in 20–30% of patients; pregnancy may also trigger a relapse
7. Progressive symmetrical proximal and distal weakness of the extremities is most common; early distal extremity numbness and weakness may be prominent
8. 80% of patients manifest both motor and sensory involvement
 - a. Approximately 10% have a pure motor or sensory (5–10%) presentation
9. Numbness in the extremities occurs in 70–80% of patients; painful paresthesias occur in 15–50%
10. Large fiber modality deficits (vibration and proprioception) are found primarily on examination, and when severe, may cause sensory ataxia
11. There is loss or depression of muscle stretch reflexes
12. Facial muscles are rarely affected but can be, causing ophthalmoparesis, dysarthria, dysphagia, and sensorineural hearing loss; neck extensor weakness can cause a dropped head syndrome
13. Autonomic involvement is uncommon
14. Papilledema has been described in a subgroup of patients with a POEMS phenotype (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes)
15. Intercostal and diaphragmatic involvement is uncommon in classic CIDP
16. Approximately 3% of patients demonstrate CNS demyelination

Associated Medical Conditions

1. HIV
2. Inflammatory bowel disease
3. SLE
4. Diabetes mellitus
5. Monoclonal gammopathy
6. Paraneoplastic syndromes
7. Graft-versus-host or rejection following bone marrow transplantation
8. Neurotoxins

Neuropathology

1. Nerve biopsy:

- a. Segmental demyelination and remyelination
2. Proliferation of Schwann processes that form “onion bulbs” and nerve hypertrophy
3. Demyelination patterns include:
 - a. Segmental with remyelination (20–40%)
 - b. Axonal degeneration (20–40%)
 - c. Mixed demyelination and axonal degeneration (12%)
 - d. Normal evaluation (20–40%)
4. Endoneurial and perineurial edema
5. Inflammatory cell infiltrates in the epineurium, perineurium or endoneurium; most often is perivascular
6. Inflammatory cells include:
 - a. Macrophages
 - b. CD3⁺ activated T-cells (CD8⁺ and CD4⁺ lymphocytes)
 - c. Dendritic cells
7. Overexpression of matrix metalloproteinases by T-cells
8. Electron microscopy:
 - a. Cellular infiltrates:
 - i. Penetrate the basement membrane
 - ii. Lyse the superficial myelin lamellae
 - iii. Penetrate along intraperiod line
 - iv. Endocytosis disrupts myelin
 - v. Recruited Schwann cells remyelinate the demyelinated internodes
 - vi. Failure of regulatory T-cells mechanisms may be causative

Laboratory Evaluation

1. An elevated CSF protein is documented in 80–95% of patients; mean protein is 135 mg/dl but levels >1000 mg/dl often occur with POEMS
2. The cell count is most often normal, but approximately 10% of patients have >5 lymphocytes/mm³. High cell counts in the CIDP setting suggest:
 - a. HIV
 - b. Lyme’s disease
 - c. Neurosarcoidosis
 - d. Carcinomatosis of the meninges
 - e. Lymphoma/leukemia
3. CSF oligoclonal bands are found in approximately 65% of patients
4. IgA, IgM or IgG monoclonal gammopathy occurs in 25% of patients
5. A subgroup of patients has demonstrated antibodies against GM1, P0, and P2 myelin proteins

Neuroimaging

1. MRI:
 - a. Demonstrates hypertrophy and enhancement of nerve roots and peripheral nerves
2. EMG:
 - a. Reduction in conduction velocity in two or more nerves
 - b. Partial conduction block or abnormal temporal dispersion in one or more motor nerves
 - c. Prolonged distal latencies in two or more nerves

- d. Absent F-waves or prolonged minimum F-wave latencies

Differential Diagnosis

1. If weakness is distal throughout the course:
 - a. Rule out hereditary demyelinating neuropathies
2. Sensory signs out of proportion to muscle weakness:
 - a. Rule out IgM monoclonal gammopathy with or without antibodies against myelin-associated glycoprotein (MAG)
 - b. Pure sensory neuropathy:
 - i. A small group of CIDP patients with “chronic sensory demyelinating neuropathy”
 - ii. Sjögren’s syndrome
 - iii. Sensory ganglionitis of paraneoplastic origin
3. Differential points between chronic demyelinating sensory polyradiculopathy versus sensory ganglionitis and anti-MAG induced neuropathies include:
 - a. Decreased or absent reflexes
 - b. Normal sensory SNAPs
 - c. Abnormal H-reflexes and somatosensory evoked potentials (proximal demyelination of sensory roots)
 - d. Papilledema and respiratory insufficiency:
 - i. Occurs most often in the setting of CIDP POEMS
 - ii. Rule out underlying plasmacytoma or lymphoma
 - e. Approximately 3% of CIDP patients have clinical, MRI or electrodiagnostic features of CNS demyelination
 - i. CIDP can precede or follow attacks of central demyelination
 - f. Rare diabetic patients have:
 - i. Asymmetric proximal and distal arm and leg weakness
 - ii. An elevated CSF protein
 - iii. Characteristic demyelination on electrodiagnostic studies
 - g. CIDP phenotype may be produced by toxins which include:
 - i. Cyclosporine
 - ii. Tacrolimus
 - iii. Tumor necrosis factor alpha (TNF-alpha) blockers
 - h. The most common malignancies associated with CIDP include:
 - i. Melanoma
 - ii. POEMS syndrome (Plasmacytoma)
 - iii. Lymphoma
 - iv. Castleman’s disease
 - v. Waldenström’s macroglobulinemia
 - vi. Carcinoma of the lung, pancreas, colon, and choriocarcinoma

Distal Acquired Demyelinating Symmetric Polyneuropathy (DADS)

General Characteristics

1. The phenotype is based on the pattern of weakness in patients with features of CIDP
2. DADS patients have only distal signs and symptoms

Clinical Manifestations

1. Mild symmetric distal weakness
2. Distal and symmetric sensory loss
3. Decreased or absent muscle stretch reflexes

Neuropathology

1. Elevated IgM (primarily anti-MAG); rare GM1 antibodies
2. Demyelinating and remyelinating characteristic on nerve biopsy; IgM deposition in paranodal areas
3. Decreased claudin-5 protein levels in microvascular endothelial cells

Laboratory Evaluation

1. Monoclonal proteins are detected in more than 50% of patients
2. In those patients with IgM-DADS neuropathy, 2/3 have MAG antibodies
 - a. These patients are older than those with idiopathic DADS neuropathy or CIDP; their mean age is 62 years
3. EMG:
 - a. CMAPs:
 - i. Demyelinating features with no conduction block
 - ii. Abnormal SNAPs
4. CSF protein: elevated

Multifocal Motor Neuropathy (MMN)*General Characteristics*

1. Prevalence range from 0.3–3 patients in 100,000 people
2. Males > females at 3:1
3. Is associated with the use of tumor necrosis factor blockers
4. The weakness is in the distribution of peripheral nerves whereas in ALS it is in the distribution of myotome

Clinical Manifestations

1. In 80% of patients, the onset is less than 50 years of age (mean age 40 with range between 20 and 70 years)
2. The onset is asymmetric and often in the upper extremity
3. The ulnar, median, and radial nerves are most commonly affected
4. There may be differences in the severity of involvement of different muscles supplied by the same nerve
5. In approximately 66% of patients, weakness starts in the distal upper limb with wrist and finger extension involvement
 - a. In approximately 25% of patients symptoms occur in the lower extremity initially; rarely it may start in the proximal muscles of an upper extremity
6. The onset is insidious as weakness progresses over years
7. Weakness is associated with cramps and fasciculations
8. Early in its course the weakness is not accompanied by muscle atrophy; rarely affected muscle groups are hypertrophied (possibly due to myokymia)
9. There may be vague sensory symptoms, numbness
10. Rare cranial nerve involvement

11. Muscle stretch reflexes are variable in unaffected muscles; weak and atrophic muscles have depressed reflexes
12. There are no corticospinal signs
13. There is usual involvement of two or more nerves, but monofocal motor neuropathy may be an early presentation

Neuropathology

1. MMN is characteristically associated with increased levels of IgM antibodies against ganglioside GM1
2. The association of GM1 antibody and a motor phenotype is also seen in acute motor axonal neuropathy (AMAN)
3. Autopsied patients reveal:
 - a. Immunoglobulin deposition and inflammatory demyelination in motor roots
 - b. There is more GM1 ganglioside in motor than sensory roots
 - c. Treatment with infliximab may cause a similar phenotype but with more rapid progression
4. GM1 is localized to both the axolemma and myelin of peripheral nerves:
 - a. Primarily at the nodes of Ranvier and adjacent paranodes
 - b. GM1 concentrates in the cholesterol enriched domains of the plasma membrane which stabilizes the paranodal area and modulates ion channel clustering by maintenance of tight junctions
5. Experimental studies support an autoimmune attack with complement activation that is effected by membrane attack complexes (MAC) that compromise the plasma membrane and nodal regions. The result is nodal disruption and sodium channel dispersion as well as axonal damage
6. Autoantibodies to neurofascin-186 and gliomedin may be found in MMN and may contribute to conduction block and motor weakness

Laboratory Evaluation

1. CSF is usually normal (differential point from CIDP and MADSAM)
2. Approximately 20 to 80% of patients have IgM serum antibodies against GM1 ganglioside; antibodies are also noted against asialo-GM1 and GM2; monoclonal proteins are rare
3. EMG:
 - a. Demyelinating features
 - b. Prominent conduction block
 - c. Normal SNAPs
 - d. Reduction in CMAP may occur in chronic patients due to secondary axonal degeneration
 - e. Motor NCS also demonstrate
 - i. Prolonged distal latencies
 - ii. Prolonged or absent F-waves
 - iii. Demyelinating features are more often found in the arms
 - iv. Electrophysiological deficits may occur in nerves that innervate normal muscles

Differential Diagnosis

1. Diagnostic points in favor of MMN versus amyotrophic lateral sclerosis:
 - a. MMN is predominant in the upper extremities
 - b. Lacks bulbar and respiratory muscle involvement
 - c. Less atrophy in weak muscles (at least early in the illness)
 - d. Cramps and fasciculations are less prominent than in motor neuron disease (occurs in approximately 50% of patients with MMN)
 - e. No upper motor neuron signs
 - f. Characteristic conduction block on EMG
 - g. MMN can have brisk reflexes in 8% of patients, or they can be normal in approximately 20% of patients
 - h. Rarely the phrenic nerve can be involved with associated respiratory embarrassment:
 - i. MMN is more asymmetric than CIDP and does not evolve into generalized weakness as rapidly
 - ii. Multifocal acquired demyelinating sensory and motor neuropathy (MADSAM may affect single nerves but has both clinical and electrodiagnostic features of sensory involvement)
2. Multifocal motor acquired motor axonopathy (MAMA)
 - a. A subgroup of rare patients has the clinical phenotype of MMN:
 - i. Only axonal features on electrodiagnostic studies
 - ii. Most patients lack GM1 antibodies
 - iii. May respond to immune therapies

MADSMA (Lewis-Sumner Syndrome)*General Characteristics*

1. A multifocal demyelinating neuropathy with persistent conduction block

Clinical Manifestations

1. A male predominance
2. A mononeuritis multiplex clinical picture
3. Weakness in the distribution of individual peripheral nerves
4. Mild wasting
5. Cramps and fasciculations
6. Partial loss of muscle stretch reflexes
7. Stepwise course
8. Lower limb involvement at onset is frequent but spread to the upper extremities is common in later stages of the disease
9. Cranial nerve involvement occurs with MNN
10. Mixed sensory and motor involvement occurs in approximately 50% of patients
11. Pain is seen in 20% of patients; oculomotor, facial and trigeminal are reported

Neuropathology

1. Sensory nerve biopsy:
 - a. Thinly myelinated nerve fibers are involved

- b. Endoneurial edema
- c. Occasional perivascular inflammatory infiltrates
- d. Asymmetric loss of large myelinated nerve fibers between and within fascicles
- e. Demyelinating and remyelinating feature

Laboratory Evaluation

1. CSF protein is usually increased
2. Rare monoclonal protein
3. GM1 antibodies are rare
4. EMG:
 - a. Demyelinating features
 - b. Conduction block
 - c. Abnormal SNAPs

Chronic Immune Sensory Polyradiculopathy (CISP)*General Characteristics*

1. Most probably a restricted variant of CIDP

Clinical Manifestations

1. Insidious onset of progressive numbness and paresthesias
2. Sensory ataxia
3. Presentation may be asymmetric; modalities of sensation that are affected are proprioception and vibration
4. Normal muscle strength
5. Absent or reduced muscle stretch reflexes

Neuropathology

1. Biopsy of lumbar sensory rootlets demonstrates:
 - a. Decreased density of large myelinated fibers
 - b. Demyelinated axons
 - c. Endoneurial edema
 - d. Onion bulb formation

Laboratory Evaluation

1. CSF has elevated protein with a normal cell count
2. No GM1, GD1b, GQ1b, Ro, or anti-La serum antibodies
3. EMG:
 - a. Routine motor and sensory NCS, as well as needle EMG, is normal
 - b. Reflexes are abnormal
4. Somatosensory evoked potential interpeak latencies show decreased conduction in proximal nerve segments
5. MRI:
 - a. Thickening and enhancement of nerve roots

Idiopathic Perineuritis*General Characteristics*

1. A non-specific inflammation and thickening of the perineurium most often associated with:
 - a. Diabetes mellitus
 - b. Ulcerative colitis
 - c. Connective tissue disease
 - d. Vasculitis

- e. Cryoglobulinemia
 - f. Lymphoma
 - g. Malignancies
2. It is idiopathic if it occurs without an underlying disease

Clinical Manifestations

1. Variable presentation:
 - a. A subgroup of patients develops sensory loss, hyperpathia, dysesthesia in a multiple nerve distribution
 - b. A group that is indistinguishable from AIDP or CIDP with generalized symmetric motor and sensory loss
 - c. Some patients complain of migratory sensory loss
 - d. May have a remitting and relapsing course
 - e. Examination may reveal positive Tinel's sign over peripheral nerves as well as hyperesthesia or hyperpathia in affected areas
 - f. Large fiber sensory modalities are less affected than small fiber modalities of pain and temperature
 - g. Usually, muscle strength is preserved, but generalized weakness has been noted
 - h. Normal muscle stretch reflexes

Neuropathology

1. Nerve biopsy:
 - a. Thickening and fibrosis of the perineurium with macrophage and lymphocyte infiltration
 - b. Axonal degeneration with loss of myelinated fibers
 - c. Mild perivascular inflammation

Laboratory Evaluation

1. Normal CSF, ANA, liver function profile, serum protein and electrophoresis
 - a. Abnormal laboratory profile suggests a specific underlying disease
2. EMG:
 - a. NCS demonstrate multifocal or generalized decrease in SNAP amplitudes or they are unobtainable
 - b. Normal motor nerve EMG and NCS

Vasculitic Neuropathy

General Characteristics

There are several different classifications of vasculitis that are based on:

1. The size of the affected blood vessel
2. Whether it is primary or secondary to a systemic disease or if it is systemic or isolated to the peripheral nervous system
 - a. All are immune-mediated pathologies; the attack being directed to blood vessels

Nomenclature Based on the 2012 Revised International Chapel Hill Consensus Conference

Large Vessel Vasculitis (LVV)

This is a vasculitis that affects the aorta and its major branches, although any size artery may be affected. The two major LVVs are Takayasu's arteritis and giant cell arteritis (GCA).

Medium Vessel Vasculitis (MVV)

This vasculitis predominantly affects medium-sized arteries, the main visceral arteries, and their branches. Any sized artery may be affected concomitantly. The two major diseases in this category are periarteritis nodosa (PAN) and Kawasaki disease (KD).

Small Vessel Vasculitis (SVV)

This vasculitis group of is divided into anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis and immune complex SVV. ANCA-associated vasculitis is necrotizing with minimal immune deposits that predominantly affects small vessels. The prefix indicates ANCA reactivity, i.e., MPO-ANCA (myeloperoxidase), or PR3-ANCA (anti-proteinase 3). The ANCA specificity identifies distinct disease categories.

ANCA-associated vasculitis is divided into:

1. Microscopic polyangiitis (MPS)
2. Granulomatosis with polyangiitis (Wegener's)
3. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)

Immune Complex Small Vessel Vasculitis

Immune complex SVV is a vasculitis in which there is moderate or extensive immunoglobulin deposition and complement factors that predominately affect small vessels. Glomerulonephritis is the most frequent pathology.

This category includes:

1. Anti-glomerular basement membrane disease (anti-GBM)
2. Cryoglobulinemia vasculitis (CV)
3. IgA Vasculitis (Henoch-Schönlein)
4. Hypocomplementemic intracranial vasculitis (HVV) (anti-Clq vasculitis)

Variable Vessel Vasculitis (VVV)

In this vasculitis, there is no predominant vessel size or type (arteries, veins, capillaries) that are affected. Behçet's disease and Cogan's syndrome comprise this category.

Single Organ Vasculitis (SOV)

This is a vasculitis in a single organ that is not an expression of a systemic vasculitis. The involved vessel type includes cutaneous small vessel vasculitis, testicular arteritis, and central nervous system vasculitis.

Clinical Manifestations

Peripheral nervous system vasculitis presents in 3 basic patterns:

1. A mononeuropathy or mononeuropathy multiplex
2. Overlapping mononeuropathies
3. Distal symmetric polyneuropathy

The mononeuropathy pattern usually evolves asymmetrically and affects multiple nerves. In overlapping mononeuropathies, different nerves on both sides of the body are affected to varying degrees, which leads to generalized but

asymmetric involvement. In progressive involvement of peripheral nerves, a generalized pattern of involvement develops that mimics a distal symmetric polyneuropathy. Between 6 to 70% of patients present with mononeuropathy or mononeuropathy multiplex. Approximately 30 to 40% of patients present with an asymmetric distal peripheral neuropathy. Patients with mononeuropathy or multiple mononeuropathies usually complain of burning or paresthesias in the affected nerve distribution. Examination reveals appropriate weakness and sensory loss. Rarely patients may have pure sensory loss. Muscle stretch reflexes are variable depending on the degree of nerve involvement.

Neuropathology

1. The most commonly biopsied sensory nerves are:
 - a. The sural
 - b. The superficial sensory branches of the peroneal
 - c. The radial sensory nerves
2. The diagnostic yield is improved if both muscle and nerve can be examined. This combination is most commonly obtained with superficial peroneal nerve and peroneus brevis biopsy
3. Transmural inflammatory cell infiltration is seen
4. Necrosis of the vessel wall occurs
5. Immunocytochemistry may reveal:
 - a. IgM and/or IgG
 - b. Complement
 - c. Membrane attack complex deposition on the affected vessel walls
6. Fiber loss between and within nerve fascicles
7. Axonal degeneration
8. Immunostaining of the epi- and endoneurial vessels, the perineum and monocytes may demonstrate:
 - a. Receptor for advanced glycosylation end products (RAGE)
 - b. Nuclear factor-kappa B
 - c. Interleukin 6 expressed by CD4⁺, CD8⁺ and CD68⁺ cells that invade peripheral nerves and strongly support the autoimmune mechanisms hypothesized as the cause of these illnesses
 - d. Skin biopsies may demonstrate a loss of epidermal nerve fibers in some patients

Systemic Vasculitis That Affect Large and Medium-Sized Vessels

Giant Cell Vasculitis

General Characteristics

1. Giant cell arteritis and Takayasu's disease are the two categories of large vessel arteritis. There is no peripheral neuropathy with Takayasu's disease
2. Affects large and medium-sized vessels primary of the aortic arch, internal and external carotid arteritis; rarely the vertebral arteries are affected

Clinical Manifestations

1. General neurological signs and symptoms:
 - a. Headache; often a burning scalp with associated mechanical allodynia is seen
 - b. Jaw and tongue claudication
 - c. Rarely palpable nodules are noted in the temporal artery
 - d. Tongue lesions (resembling squamous cell cancer) and a perforated nasal septum are noted
 - e. Ischemic optic neuropathy
 - f. Stroke
- g. Peripheral nervous system manifestations:
 - i. 10 to 15% of patients develop:
 1. Multiple mononeuropathies
 2. Radiculopathies
 3. Brachial plexopathies
 4. Generalized sensorimotor peripheral neuropathy

Neuropathology

1. Thrombosis of the ophthalmic and posterior ciliary arteries
2. Intense granulomatous or "giant cell" arteritis is seen in approximately 2/3 of patients

Neuroimaging

1. Ultrasound of the artery may reveal thickening
2. Contrast material enhanced magnetic resonance imaging (MRI) of superficial cranial arteries has a sensitivity of 78% and a specificity of 90%

Polyarteritis Nodosa

General Characteristics

1. The most common form of the necrotizing vasculitis
2. Primarily involves small and medium-sized blood vessels in multiple organs
 - a. The incidence is 2–9/million of the population

Clinical Manifestations

1. Presents between 40 to 60 years of age
2. Involved organs:
 - a. Long medullary arteries of the kidney
 - b. Bowel, skin and testes
 - c. Lobar liver infarction
 - d. Weight loss
 - e. Fever similar to that which occurs with lymphoproliferative disease
3. Multiple mononeuropathies
4. The sciatic nerve (peroneal or tibial branches) are the most commonly involved peripheral nerves
5. In less than 2% of patients, the cranial nerves or CNS is involved
6. Myalgias and arthralgias are seen in 30 to 70% of patients
7. Skin involvement is manifest by petechiae, livedo reticularis, subcutaneous painful nodules, and distal gangrene
8. Severe hypertension (occasional ICH) occurs with renal involvement

Neuropathology

1. Involvement of small nutrient arteries of peripheral nerves occurs in approximately 75% of patients (autopsy series)
2. A necrotizing arteritis primarily affecting medium-sized vessels
3. Fibrinoid necrosis of all 3 coats of the vessel wall; infiltrating eosinophils may be prominent
4. Muscle biopsy:
 - a. Perivascular inflammation and necrosis
5. Spared pulmonary circulation
6. Nerve biopsy:
 - a. Transmural infiltration of CD8⁺ T-cells, macrophages, and polymorphonuclear cells
7. Blood vessels may demonstrate IgM, IgG, complement components and membrane attack complexes
8. Aneurysms of the long medullary arteries of the kidney occur

Laboratory Evaluation

1. Approximately 1/3 of patients have evidence of Hepatitis B infection; may also be associated with hepatitis C and HIV
2. ESR is elevated in most patients

Churg-Strauss Syndrome (CSS)*General Characteristics*

1. Rarest subtype of anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis
2. Has the lowest frequency of ANCA-positivity (approximately 30%)
3. HLA-DRB4 association has been documented
4. Approximately 1/3 the incidence of PAN

Clinical Manifestations

1. A clinical overlap occurs between PAN, Churg-Strauss syndrome, and Hypereosinophilic syndrome
2. Rhinitis and asthma may be longstanding prior to onset
3. Later in the course of asthma there may be marked eosinophilia and an eosinophilic pneumonitis
4. The neuropathy is usually preceded by fever and weight loss
 - a. Acute painful mononeuropathy multiplex
5. Signs of systemic vasculitis usually are seen by three years after the onset of asthma. Late onset asthma in patients older than 35 years of age is a seminal feature
6. Approximately 20 to 50% of patients may develop a necrotizing glomerulonephritis (ischemic nephropathy occurs with PAN)
7. Several patients have used leukotriene antagonists after being weaned from corticosteroids. A few patients have been associated with macrolide antibiotic use

Neuropathology

1. Nerve biopsy: Necrotizing vasculitis similar to PAN; CD8⁺ T-cytotoxic lymphocytes, CD4⁺ cells, and eosinophilic infiltrates in the nerve are demonstrated

2. Intravascular and extravascular granulomas are rarely seen around affected blood vessels
3. Although the disease is usually considered Th2 mediated, recent evidence supports roles for Th1 and Th17 responses
4. HLA-DRB4 association has been described; CD4⁺ T-cells secrete IL4, IL5 and IL13 which are involved in allergic and eosinophilic processes
5. Eotaxin-3 and CCL17 that are secreted by endothelial and epithelial cells may amplify the immune response. FL5 is of particular interest as a mediator of eosinophilia
6. End organ damage may be caused by vasculitis or eosinophilic infiltration

Laboratory Evaluation

1. Eosinophilia, leukocytosis and elevated ESR
2. Increased C-reactive protein, rheumatoid factor and serum IgG and IgE levels are commonly detected
3. Approximately 2/3 of patients have positive anti-neutrophil antibodies primarily myeloperoxidase or p-ANCA
4. Approximately 50% of patients have pulmonary infiltrates by chest x-ray

Wegener's Granulomatosis (Granulomatosis with Polyangiitis)*General Characteristics*

1. The new designation is granulomatosis with polyangiitis
2. Necrotizing vasculitis which primarily affects medium- to small-sized blood vessels
3. Prevalence is 3/100,000 persons in the USA
4. More common in Caucasian ethnicity and slightly more common in men in European population

Clinical Manifestations

1. Granulomatous vasculitis of the upper and lower respiratory tract
2. Glomerulonephritis
3. Pulmonary involvement occurs in greater than 75% of patients
4. Orbital vasculitis occurs in approximately 50% of patients:
 - a. Inflammation of ocular structures include:
 - i. The globe
 - ii. Orbital fat
 - iii. Orbital nerves
 - iv. Extraocular muscles
 - v. Lacrimal gland
 - vi. Optic nerve
 - b. Signs and symptoms of orbital involvement:
 - i. Ocular pain
 - ii. Erythema and edema of the eyelids
 - iii. Conjunctival injection
 - iv. Nasolacrimal duct obstruction
 - v. Epiphora

- vi. Limitation of extraocular muscle movement
 - vii. Afferent pupillary defect
 - viii. Proptosis
 - ix. Diplopia
 - x. Loss of vision
5. Dermatologic involvement occurs in approximately 50% of patients
 6. Asymmetrical multiple mononeuropathies
 7. Mononeuropathies of the lower cranial nerves as they exit the skull and pass through the retropharyngeal tissue
 8. The peroneal nerve may be the most commonly affected nerve
 9. Symmetrical distal polyneuropathy occurs in 10–20% of patients;
 - a. Neuropathy may be more common in patients with severe renal involvement
 10. The frequency of peripheral nerve involvement is less than in the other vasculitides
 - c. Sinus metastatic breast cancer (although the eye may be retracted with scirrhous breast cancer)

4. Orbital Inflammatory Diseases:
 - a. Idiopathic sclerosing orbital inflammation (CD3⁺ T-cells)
 - b. Thyroid orbitopathy:
 - i. Inferior rectus may be preferentially involved whereas the superior rectus muscle may be primarily involved with lymphoma
 - ii. Most often, all muscles are involved
 - c. Sarcoidosis (usually affects the meninges surrounding the optic nerve)
 - d. Temporal arteritis (primarily affects the ophthalmic and posterior ciliary arteries)
 - e. IgG4-related disease
 - f. Rarely polyarteritis nodosa and Kawasaki disease, as well as Churg-Strauss syndrome, may involve orbital tissues

Neuropathology

1. A primary necrotizing vasculitis of small to medium-sized vessels
2. Large vessel involvement has been described with luminal stenosis, occlusion or wall thickening; the abdominal aorta is the most commonly affected vessel
3. Classic triad is vasculitis, tissue necrosis, and granulomatous inflammation
4. Granulomas consist of collections of epithelioid histiocytes; lung, kidney, and sinuses are involved

Laboratory Evaluation

1. The majority of patients have ANCA directed against proteinase-3 in the serum with a specificity of 98% and 95% sensitivity
2. Absence of peripheral eosinophilia distinguishes it from Churg-Strauss disease

Neuroimaging

1. An orbital mass from GPA is suggested by:
 - a. Sinus involvement
 - b. Paranasal bone erosion

Differential Diagnosis of Orbital Granulomatous Polyangiitis

1. The basic conditions to be differentiated are infectious, neoplastic and other orbital inflammatory conditions
2. Infections:
 - a. Mycobacterial
 - b. Invasive fungus infection (aspergillus and mucormycosis)
 - i. Primarily in immune suppressed patients
 - ii. Diabetes
3. Primary and Secondary Neoplasms
 - a. Extranodal marginal zone B-cell lymphoma
 - b. Non-Hodgkin's and Hodgkin's lymphoma

Microscopic Polyangiitis

General Characteristics

1. The incidence is approximately 1/3 that of PAN which it resembles clinically
2. Primarily a disease of small blood vessels, the absence of granulomas and minimal or no immune deposits on blood vessels

Clinical Manifestations

1. Average age of onset in 50 years
2. Glomerulonephritis is common
3. There is involvement of the lungs and GI tract in approximately 50% of patients
4. There may be eye vascular involvement
5. The spleen and muscle are involved in 20–30% of patients
6. Polyneuropathy occurs in approximately 15–35% of patients

Neuropathology

1. A necrotizing vasculitis with minimum immune complex deposition in the vasculature
2. Capillaries, vessels, and arterioles are primarily involved; there may be some involvement of small- and medium-sized arteries
3. Pulmonary capillaritis is common
4. Necrotizing glomerulonephritis is seen in a majority of patients

Laboratory Evaluation

1. ANCA are directed primarily against myeloperoxidase (MPO-ANCA) but in a minority of patients there is an antibody response directed toward proteinase 3 (PR3-ANCA)
2. Rheumatoid factor is noted in approximately 50% of patients
3. Rarely there is decreased complement
4. Hepatitis B, C antibodies may be detected

Behçet's Disease*General Characteristics*

1. The illness is primarily seen in the Middle East, India, and Japan
2. Men are slightly more affected than women
3. Small to medium-sized vessels are involved

Clinical Manifestations

1. Oral and genital ulcers (well circumscribed and often painful)
2. Painful oral aphthous ulcers are more common than genital ulcers
3. Anterior or posterior uveitis
4. Retinal vasculitis; iridocyclitis
5. Associated erythema nodosa
6. Thrombophlebitis
7. CNS manifestations:
 - a. Sinus thrombosis
 - b. Aseptic meningitis
 - c. Stroke (ischemic)
 - d. Dementia/psychosis
 - e. Brainstem presentation
 - f. Purely ocular presentation
 - g. Meningoencephalitis
8. Peripheral nervous system manifestations:
 - a. Sensorimotor neuropathy (distal demyelination)
 - b. Mononeuropathy multiplex
 - c. Motor predominant polyradiculoneuropathy
 - d. Lumbosacral polyradiculitis
 - e. Neurologic signs and symptoms may clear over weeks

Neuropathology

1. Anti-Th1 and lymphocytes and IL-6 as well as TNF
2. The gut microbiota has a specific signature:
 - a. Decreased genera Roseburia and Subdoligranulum
 - b. A significant decrease in butyrate production has been noted:
 - i. Butyrate promotes the differentiation of T-regulatory cells
3. Perivascular and meningeal infiltrates of lymphocytes
4. Sinus thrombosis
5. Vasculitic arterial lesions

Laboratory Evaluation

1. CSF:
 - a. Lymphocytic pleocytosis
 - b. Moderately elevated protein
 - c. Normal glucose

Secondary Systemic Vasculitides***Vasculitis Associated with Connective Tissue Disease****General Characteristics*

1. Incidence varies by disease

2. The major entities include:

- a. SLE
- b. Rheumatoid arthritis
- c. Mixed collagen vascular disease
- d. Scleroderma (systemic sclerosis)
- e. Sjögren's syndrome

Clinical Manifestations

1. Fever, weight loss
2. Anorexia
3. Skin rash, renal, lung, gastrointestinal involvement depending upon the illness
4. Specific neurologic features dependent upon the disease

Neuropathology

1. Similar to PAN

Laboratory Evaluation

1. Disease specific
2. In general, an increase of biomarkers of autoimmune disease

Vasculitis Associated with Infection*General Characteristics*

1. The most common infections associated with vasculitic neuropathy are:
 - a. HIV
 - b. Hepatitis B and C
 - c. Cytomegalovirus
 - d. Epstein-Barr virus

Clinical Manifestations

1. Disease specific
2. Directly related to treatment

Neuropathology

1. Disease specific

Laboratory Evaluation

1. Disease specific

Malignancy Related Vasculitis*General Characteristics*

1. Various cancers are associated with vasculitic neuropathies
2. The most common malignancies associated with various vasculitic neuropathies are:
 - a. Small cell carcinoma of the lung
 - b. Lymphoma
 - c. Leukemia/myeloproliferative disorders
3. Rarely carcinoma of the kidney, prostate, bile duct and stomach are associated with vasculitic neuropathy

Clinical Manifestations

1. Symmetric distal neuropathy

2. Mononeuropathy multiplex
3. Lymphoma and leukemia may directly infiltrate nerves

Neuropathology

1. Non-specific transmural or perivascular inflammation of small blood vessels is seen rather than a necrotizing vasculitis
2. Lymphoma may induce vasculitic neuropathy

Laboratory Evaluation

1. Disease specific

Drug-Induced Hypersensitivity Vasculitis

General Characteristics

1. Cutaneous manifestations are predominant

Clinical Manifestations

1. Internal organs may be involved that includes:
 - a. Glomerulonephritis
 - b. Gastrointestinal and myocardial involvement
2. Distal symmetric polyneuropathy
3. Self-limited

Neuropathology

1. Capillaries, arterioles, and venules are involved
2. Leukocytoclastic mechanism
3. Amphetamines, cocaine, and opioids have been reported as causing both CNS and PNS vasculitis

Laboratory Evaluation

1. Increased ESR > 50% of patients
2. Rheumatoid factor in approximately 100% of patients
3. ANA positivity in approximately 15% of patients

Vasculitis Associated with Essential Mixed Cryoglobulinemia

General Characteristics

1. Cryoglobulins:
 - a. Are circulating immune complexes
 - b. They are immunoglobulins directed against immunoglobulins
 - c. They are categorized as:
 - i. Type I cryoglobulins:
 1. IgM monoclonal immunoglobulins directed against polyclonal IgG
 - a. Occur with plasma cell dysplasia
 - ii. Type II cryoglobulins:
 1. A combination of monoclonal IgM and polyclonal immunoglobins directed against polyclonal IgG
 - iii. Type III cryoglobulins:
 1. A mixture of polyclonal IgM, IgG, and IgA immunoglobulins
 2. Directed against polyclonal IgG

- iv. Type II and Type III cryoglobulins:

1. Occur in patients with mixed cryoglobulinemia and are detected in connective tissue diseases as well as hepatitis B and C
2. Essential mixed cryoglobulinemia is designated when mixed cryoglobulinemia is detected without an underlying disease. It may occur with viral hepatitis:
 - a. Most patients with essential mixed cryoglobulinemia have hepatitis C antigen in the serum

Clinical Manifestations

1. Raynaud's phenomena
2. Bleeding diathesis (platelet dysfunction)
3. Retinal hemorrhage
4. Arthralgias
5. Malaise
6. Weakness
7. Skin ulcers
8. Blue cyanotic extremities (primarily fingers and toes)
9. Peripheral neurologic manifestations:
 - a. Painful distal symmetric sensory or sensorimotor polyneuropathy
 - b. Mononeuropathy multiplex
 - c. Rare small fiber neuropathy

Neuropathology

1. Cooling precipitates IgG and IgM immunoglobulins that redissolve on heating
2. Necrotizing vasculitis; occlusive microangiopathy
3. Involvement of small arteries, arterioles, capillaries and venules
4. Nerve biopsy:
 - a. Wallerian degeneration:
 - i. Perivascular mononuclear cell infiltration
 - ii. Center of the nerve fascicle may be more involved than the periphery
 - iii. Perivascular mononuclear cell infiltration
 - iv. Lack of local HCV replication in the biopsied nerve:
 1. Putative mechanism of the neuropathy is a virus-triggered immune-mediated process
 2. Ischemia from hyperviscosity
 3. Immune complex deposition in the vasa vasorum that occludes the nutrient blood supply of the nerve

Laboratory Evaluation

1. Hepatitis C is detected in greater than 80% of patients
2. Rheumatoid factor is increased in 80% of patients
3. Decreased complement is detected in greater than 75% of patients
4. ANA is elevated in approximately 20% of patients
5. ANCA detected in approximately 5% of patients
6. EMG:
 - a. Similar to PAN

Isolated PNS Vasculitis (Non-Systemic)

General Characteristics

1. Necrotizing vasculitis is restricted to the peripheral nervous system
2. Inflammatory and connective tissue biomarkers are absent; a few patients demonstrate anti-neutrophil cytoplasmic antibodies (ANCA)
3. 60% of vasculitic neuropathies are restricted solely to peripheral nerves
4. Incidence: 5/million of the population/year
5. Primarily a disease of adults, but childhood patients are well documented

Clinical Manifestations

1. Usually, presents as a subacute symmetrical or asymmetrical polyneuropathy (45% of patients)
2. Overlapping episodes of mononeuropathy multiplex (40% of patients)
3. Solely mononeuropathy multiplex is detected in approximately 40% of patients

Neuropathology

1. Involvement of the small- and medium-sized arteries of the epineurium and perineurium
2. Immune complex deposition occurs in affected vessels
3. Up-regulation of metalloproteinase-2 and -9 in affected nerves
4. Vasculitis may be demonstrated on muscle biopsy

Laboratory Evaluation

1. ESR may be mildly elevated as are ANA titers
2. EMG may demonstrate conduction block early in the course
3. Positive sharp waves and fibrillation potentials are detected in affected muscle

Differential Diagnosis of Vasculitic Neuropathy by Signs and Symptoms

Overview

The suspicion of a systemic vasculitic neuropathy occurring in the face of a known systemic vasculitis is raised with the onset of an asymmetric neuropathy that may evolve over time into a symmetric distal motor sensory neuropathy due to overlapping mononeuropathies (nerve infarctions) of specific peripheral nerves. Early trigeminal nerve involvement and mononeuropathy multiplex are seminal features of these diseases (Sjögren's disease, systemic sclerosis). The specific features of each entity identify the underlying cause of the vasculitis.

In SLE, the neuropathy usually occurs in the face of established disease. Central nervous features usually predominant with stroke, seizure, psychosis as major signs. A trans-

verse myelitis usually at T4–T6 (or from a dropped cervical level) in many instances may be confused with neuropathy if bladder involvement is not prominent. Serosal surface involvement, arthralgia, malar skin rash are usually evident when the sensorimotor or sequential mononeuropathies begin. The major differential considerations at this stage are toxic, metabolic, or nutritional causes and often immune suppressive drugs and biologic anticytokine agents. Proximal myopathy is common, which may further complicate the clinical picture. A GBS picture that may evolve in patients with systemic signs of weight loss, anorexia, and slight anemia is more suggestive of PAN. The important considerations if the process presents a GBS pattern of weakness are cervical spinal cord inflammation, cavernous hemangioma, compression, mitosis, or infection (SBE is often at the T4–T6 level in IV drug addiction). In later stages of a GBS presentation from systemic autoimmune processes, a CIDP pattern may be noted which must be differentiated from lymphoma, HIV, Castleman's disease, graft-versus-host disease, osteosclerotic myeloma (POEMS) and monoclonal gammopathies. The DADs, MADSAM (Lewis-Sumner variant) and multiple motor nerve with conduction block are readily differentiated on clinical and EMG parameters. A vasculitic sensorimotor neuropathy is suggested by an asymmetric onset, stuttering course, and significant motor involvement.

The major differential features that are problematic for making the diagnosis of Sjögren's syndrome are distinguishing it from other processes associated with the SICCA complex. These disorders are sarcoid, graft-versus-host disease, amyloidosis, hepatitis C, HIV, and HTLV-1 disease. In sarcoid, bilateral VIIth nerve involvement rather than Vth nerve involvement is classic (Heerfordt's disease). Dural enhancement associated with intracranial lesions in the posterior hypothalamus and pituitary regions are diagnostic. Severe mucous ulcerative inflammation is characteristic of graft-versus-host disease whereas Sjögren's is primarily glossitis and has conjunctival symptomatology. Dissociated sensory loss (small fiber modality loss), autonomic neuropathy in association with a primary loss of reflexes, cardiac and renal disease, supports a diagnosis of amyloid neuropathy. HTLV-1 is a long-standing myelopathy with severe spasticity and bladder involvement. Hepatitis C and cryoglobulinemic neuropathy is suspected in patients with severe Raynaud's phenomenon, livedo reticularis and, rarely, gangrene and cyanosis of the fingers and toes. HIV most commonly is associated with a distal symmetrical neuropathy (with or without treatment with highly effective retroviral agents) parotid hypertrophy (cyst formation on MRI) and severe periventricular demyelination with global atrophy on MRI. Paraneoplastic sensory neuropathy can present with a severe sensory ataxia. Prominent dorsal column large fiber proprioceptive and vibratory deficits are common. It may also present with the burning pain of a small fiber (C-fiber) neuropathy with associated autonomic features. Idiopathic chronic ataxic neuropathy does not have autonomic involvement that is common in both Sjögren's and

paraneoplastic syndromes. Anti-Hu antibodies are found in the majority of paraneoplastic syndromes.

Other immune-mediated ataxic sensory polyneuropathies include:

1. Miller-Fisher variant of GBS
2. Myelin-associated glycoprotein neuropathy (MAG)
3. Pure sensory CIDP
4. Immunoglobulin associated paraproteinemias (particularly IgM)
5. Neuropathy with anti-sulfatide antibodies
6. SICCA complex
7. Syphilis (may cause proliferative endarteritis at the dorsal root entry zone or possible immune dysfunction at the level of the DRG with consequent death of large myelinated afferents that comprise the posterior column)
8. Herpes zoster (most often causes proprioceptive neuronal destruction by direct invasion in the DRG; the virus is activated during immune suppression)

The hypersensitivity vasculitides are diagnosed by their characteristic leukocytoclastic skin reactions. These skin reactions may occur with cryoglobulinemic neuropathies which are most often secondary to hepatitis C and rarely to hepatitis B infection. Henoch-Schönlein purpura occurs primarily in children in association with GI pain and arthralgias as well as the seminal purpura. The sensorimotor neuropathy is a minor part of the symptom complex. Hypersensitivity vasculitis most often occurs from an autoimmune reaction to drugs that contain sulfa or penicillin and may present with dramatic swelling and burning of the fingers and toes. Temporal arteritis usually presents in elderly patients with systemic signs of weight loss, anorexia, and proximal muscle pain as well as a low-grade headache and tender scalp. It most often involves the external carotid vascular system that affects the watershed between the posterior ciliary arteries and the central retinal artery with concomitant ischemia of the optic nerve head and visual loss. Rarely, the arch of the aorta, carotid, and subclavian arteries are affected. Sensorimotor peripheral neuropathy and neuropathy multiplex occur.

Polyarteritis nodosa is overwhelmingly a disease of the peripheral nervous system. It should always be suspected in a middle-aged man who has developed late onset asthma, eosinophilia, liver, kidney or testicular infarction. Microaneurysms of the long medullary arteries of the kidney are diagnostic. In this setting, overlapping mononeuropathies and an asymmetrical peripheral neuropathy may present as GBS. Raised palpable nodules from infarction of skin arterioles often in the quadriceps muscle should be sought. Mononeuropathy and asymmetrical peripheral neuropathy is common. CNS stroke is rare. Microscopic polyangiitis (MPA) primarily affects the kidney, but vasculitis may also be seen in the eyes, lung, muscle and, rarely, the brain. ANCA antibodies are detected in the serum of >90% of patients. A sensorimotor neuropathy in the setting of severe renal involvement should suggest this diagnosis. Decreased complement and increased rheumatoid factor are supportive. The lungs are in-

involved in approximately 50% of patients, and the neuropathy does not cause burning feet which helps to separate it from uremic neuropathy.

Churg-Strauss sensorimotor neuropathy is suggested in patients with eosinophilia and interstitial lung disease. The pituitary is occasionally involved. The IgE is increased in the serum in 75% of patients and ANCA antibodies are present in 50–75% of patients.

Wegener's granulomatosis (renamed granulomatous polyangiitis) invariably attacks the sinuses (greater than 90% of patients). It is also associated with granulomatous lung disease. Orbital and Vth cranial nerve involvement are caused by direct extension of the granulomatous process. Mononeuropathies are more common than an asymmetric, stuttering, slowly progressive distal predominant sensorimotor neuropathy.

The idiopathic eosinophilic syndrome is a heterogeneous group of disorders in which there is a persistent and extreme degree of eosinophilia (often > 20,000/mm³). There is eosinophilic infiltration of many organ systems. Neuropathy occurs in approximately 50% of patients, may concomitantly affect cranial nerves and is usually a diffuse painful sensorimotor axonal neuropathy. Mononeuropathy multiplex may also occur. Diffuse eosinophilic involvement of the nerves rather than a vasculitic process is thought to be its mechanism.

Rheumatoid arthritis often involves the carpal tunnels symmetrically and less commonly the tarsal tunnels. In patients with severe longstanding disease, (ulnar deviation of the hands; forward flexed frozen neck) hand paresthesias may occur from subluxation of C1–C2 (pannus destruction of the cruciate and transverse ligaments). Severe intrinsic hand muscle atrophy out of proportion to the arthropathy may also be a presentation. A high sediment rate (ESR) and increased levels of rheumatoid factor are seen in greater than 90% of patients. Low-level eosinophilia, and ANA and ANCA antibody response with decreased complement are supportive. Rarely, mononeuropathy and an asymmetric peripheral neuropathy occur.

Scleroderma is easily diagnosed from its distinctive physical findings. Often not appreciated is its penchant for trigeminal or mental nerve involvement ("numb chin" syndrome; also seen with sickle cell disease and breast cancer). Carpal tunnel syndrome is common in its early inflammatory stage. Later in its course, a sensorimotor neuropathy may develop. It should always be suspected in patients with early severe Raynaud's phenomena. The CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) is associated with a sensorimotor neuropathy. Raynaud's phenomena is often severe in SLE and rheumatoid arthritis. Scleroderma presents no difficulty in differentiation from other connective tissue diseases or vasculitic neuropathies. Realizing that the Vth nerve, carpal and tarsal tunnel and a vasculitic neuropathy may occur is what is overlooked.

Mixed connective tissue disease has features of scleroderma, SLE, and polymyositis. It frequently presents with trigeminal neuropathy. Rarely a sensorimotor neuropathy is present. High antibody titers of ANA antibodies to extractable nuclear RNP ribonuclease-VI are detected in the serum.

Behçet's disease primarily affects the CNS with anterior and posterior uveitis, optic neuritis, a brainstem syndrome or vasculitic stroke. Its seminal feature is aphthous ulceration of the mouth and genitals. Occasionally patients have a well demarcated extragenital, erythematous ulcer on the body that is extremely painful. Large joint and GI involvement occur. Venous thrombosis of the cortical veins and sinuses is increasingly recognized. Rarely patients have a concomitant distal predominant sensorimotor polyneuropathy.

Relapsing polychondritis may present with erythematous, sudden painful ears. Ochronosis (homogentisic aciduria) and uremia may also involve the pinna. This inflammatory autoimmune disease of cartilage causes tracheal stenosis, saddle nose deformity and heart valve inflammation. Optic neuritis, vestibulopathy, and conductive hearing loss from eustachian tube involvement are the seminal central features. Rarely, patients have a concomitant distal predominant sensorimotor polyneuropathy.

The major differential diagnostic problem occurring in the diagnosis of vasculitic neuropathy lies not in differentiating one connective disease from another in which it may occur, but rather diagnosing in the absence of systemic features.

Differential Diagnosis of Vasculitic Peripheral Neuropathy

Secondary Vasculitis

1. Connective tissue disease
2. Malignancy
3. Infection
4. Cryoglobulinemia
5. Hypersensitivity reactions

Primary Vasculitis

1. Giant cell (temporal arteritis)
2. Takayasu's (extremely rare)
3. Polyarteritis nodosa
4. Churg-Strauss syndrome
5. Wegner's granulomatosis (granulomatous polyarteritis; GPA)
6. Microscopic polyarteritis (MPS)
7. Idiopathic eosinophilic syndrome (possibly vasculitic)
8. Isolated peripheral nerve vasculitis

Differential Diagnosis of Mononeuropathy Multiplex

1. Traumatic compression neuropathy
2. Compression neuropathy superimposed on peripheral nerve disease
3. Hereditary liability to pressure palsy (HNPP)

4. Multifocal acquired demyelinating sensory and motor neuropathy
5. Multifocal motor neuropathy
6. Chronic inflammatory demyelinating polyneuropathy
7. Sensory perineuritis
8. Isolated peripheral nerve vasculitis
9. Periarthritis nodosa
10. Granulomatous polyarteritis
11. Churg-Strauss syndrome
12. Microscopic polyangiitis
13. Systemic lupus erythematosus
14. Rheumatoid arthritis
15. Relapsing polychondritis
16. Mixed connective tissue disease
17. Sjögren's
18. Cryoglobulinemia
19. Leukemia/lymphoma infiltration
20. Intravascular lymphoma
21. Isolated (non-systemic) vasculitis
22. Paraneoplastic vasculitis
23. Leprosy
24. Herpes zoster
25. Lyme's disease
26. HIV
27. CMV
28. Hepatitis B and C
29. Sarcoid
30. Lymphomatoid granulomatosis
31. Diabetes mellitus
32. Amyloidosis
33. Neoplastic infiltration
34. Atherosclerotic vascular diseases
35. Amphetamines
36. Cocaine
37. Heroin
38. Lumbosacral/brachial plexopathy

Neuropathies of Systemic Disease

Sjögren's Syndrome

General Characteristics

1. A chronic inflammatory process that involves the exocrine glands
2. If it occurs alone it is primary Sjögren's syndrome, or in association with other autoimmune diseases, it is secondary Sjögren's
3. Extra glandular manifestations of the disease are divided into two groups that involve:
 - a. Lung
 - b. Kidney (interstitial nephritis)
 - c. Liver
 - d. Due to lymphocytic invasion of epithelial tissue
4. Skin vasculitis, peripheral neuropathy, CNS manifestations, glomerulonephritis

- a. Due to immune complex deposition
- b. Low C4 levels
- c. High lymphoma risk

Clinical Manifestations

1. The sicca complex is a seminal feature and comprises:
 - a. Xerophthalmia (dry eyes)
 - b. Xerostomia (dry mouth)
 - c. Dryness of mucous membranes
2. More common in females than males
3. Age of onset is in middle years
4. CNS complications include:
 - a. Transverse myelitis or dorsal column spinal cord degeneration
 - b. Diffuse white matter hyperintensities simulating demyelinating disease (CNS; rare)

Peripheral Neuropathy

General Characteristics

1. Evident in 10 to 20% of patients
2. May be the presenting sign of the disease and may be evident without signs of the sicca complex
3. Patterns of peripheral neuropathy:
 - a. Length-dependent axonal sensorimotor neuropathy
 - b. Small fiber neuropathy
 - c. Autonomic involvement
 - d. Vasculitic pattern with multiple mononeuropathy multiplex
- e. Trigeminal nerve involvement is prominent
- f. Sensory neuropathy/ganglionopathy manifest by:
 - i. Progressive numbness and paresthesias of the extremities, trunk and face in a non-length dependent manner
 - ii. Signs and symptoms may be asymmetric, and the arms may be more involved than the legs
 - iii. Severe large myelinated fiber involvement with proprioceptive and vibratory loss that may cause pseudoathetosis; Romberg sign is prominent in patients with lower limb involvement
 - iv. Autonomic involvement is seen by:
 1. Orthostatic hypotension
 2. Adie's pupil
 3. Anhidrosis
 4. Fixed tachycardia
 5. Strength may be maintained
 6. Reduced or absent muscle stretch reflexes

Neuropathology

1. Nerve biopsy (sensorimotor neuropathy):
 - a. Axonal degeneration with some segmental demyelination
 - b. Rare perivascular inflammation of perineural and endoneurial blood vessels
 - c. Rare necrotizing vasculitis

2. Biopsy of patients with sensory neuropathy/ganglionopathy:
 - a. Loss of large myelinated fibers (dorsal column spinal cord degeneration)
 - b. CD8⁺ T-cell perivascular inflammation and degeneration of large sensory neurons of the dorsal root ganglia
3. Skin biopsy (patients with small fiber neuropathy)
 - a. Decreased nerve fiber density
4. Growing evidence supports a mechanism of disease involving B-cells, cytotoxic T-cells, and T-helper cells in chronic inflammation which alters the expression of proinflammatory cytokines
5. Dysfunction of co-inhibitory and co-stimulatory immune checkpoint inhibitors that regulate T-cell activation has been postulated as a pivotal mechanism

Laboratory Evaluation

1. Serum antibodies to SS-A/Ro, SS-B/LA, and anti-nuclear (ANA) antibodies may be detected
2. CSF is most often normal
3. Salivary gland, lip, and parotid biopsy may reveal lymphocytic infiltration
4. Schirmer's test is positive for keratoconjunctivitis
5. EMG:
 - a. Decreased or absent SNAPs in patients with the sensory neuropathy phenotype
 - b. Motor nerve conduction velocities and needle EMG are usually normal

Rheumatoid Arthritis

General Characteristics

1. Peripheral neuropathy occurs in approximately 50% of patients; 50% of the neuropathies are vasculitic
2. Systemic features of anemia and weight loss occur in severely affected patients; adenopathy, pericarditis, interstitial lung disease, glomerulonephritis and serosal surfaces may be involved in severely involved patients; small joint involvement is the seminal feature

Clinical Manifestations

1. Entrapment neuropathies that may be bilateral: median nerve in the carpal tunnel; digital, ulnar, anterior and posterior interosseous nerves; ulnar entrapment in the cubital tunnel or Guyon's canal; sciatic nerve entrapment in the posterior popliteal fossa; tarsal tunnel syndrome
2. Distal symmetric polyneuropathy:
 - a. Insidious onset of paresthesias and decreased sensibility in both upper and lower extremities
 - b. Minimal motor deficits
 - c. Hands are often severely wasted
3. Mononeuropathy or mononeuropathy multiplex:
 - a. May have an acute or subacute onset that evolves into a severe distal sensorimotor neuropathy
 - b. Cranial nerve involvement is rare

Neuropathology

1. Arteritis primarily of small vessels of the fibrinoid type
2. Immune globulins may be detected on the vessel walls
3. Rare transmural inflammatory cell infiltrate
4. Vasculitis may be initiated by anti-TNF-alpha or biological agents

Laboratory Evaluation

1. Elevated ESR, rheumatoid factor, and anti-nuclear antibodies are seen in the serum
2. A few patients develop ANCA antibodies
3. EMG:
 - a. Absent or reduced amplitudes of SNAPs
 - b. Usually normal nerve conduction velocities

Systemic Lupus Erythematosus*General Characteristics*

1. Prevalence of 1/2000 in the population
 - a. More common in women than men
 - b. Possibly more prevalent in black than Caucasian patients
2. Multiple organ system involvement
3. Approximately 2–27% of patients develop a peripheral neuropathy
 - a. CNS involvement is much more common than that of the peripheral nervous system

Clinical Manifestations

1. Concomitantly with nervous system involvement, the joints, serosal surfaces, heart, lung, kidney, skin, and muscles are affected
2. Patterns of neuropathy:
 - a. Slowly progressive sensory loss starting in the feet
 - b. Pure small fiber phenotype
 - c. Multiple mononeuropathies that may fuse with long-standing disease that causes a symmetric generalized axonal sensorimotor polyneuropathy
 - d. AIDP or CIDP pattern
3. Cranial neuropathy:
 - a. Occurs in 5 to 10% of patients
 - b. Involves cranial nerves II, III, V, VI, and X (laryngeal component)
4. Rare neuropathies:
 - a. CTS
 - b. Acute sensory ataxic neuropathy
 - c. Neuromyotonia

Neuropathology

1. Nerve biopsy:
 - a. Endoneurial mononuclear inflammatory infiltrate
 - b. Increased expression of class II antigens within nerve fascicles and on endothelial cells
 - c. Upregulation of metalloproteinases-3 and -9 within blood vessel walls

d. Skin biopsy:

- i. Decreased density of intra-epidermal C-fibers
2. Mounting evidence supports dysregulated microRNA network from interference with the miRNA expression profile
 - a. MicroRNAs regulate the differentiation and function of immune cells that leads to autoimmune disease. MicroRNA-1246 that regulates B-cell activation may be particularly relevant in the pathogenesis of SLE
 3. Small- and medium-sized vessels are primarily involved with a necrotizing vasculitis
 4. Vasculopathy > true vasculitis occurs in cerebral vessels; scattered perivascular inflammatory cells are noted
 5. Dorsal root ganglion (autopsy material):
 - a. Cytotoxic/suppressor CD8⁺ T-cells surround neurons
 - b. Arterioles, capillaries, and venules may be involved

Laboratory Evaluation

1. ANA positive antibodies occur in >95% of patients
2. Double-stranded DNA positive antibodies are seen in approximately 70% of patients
3. Anti-Ro and La antibodies are detected in >25% of patients
4. ANCA antibodies are detected in approximately 10% of patients
5. Rheumatoid factor (RF) is positive in >75% of patients
6. Cryoglobulins are found in approximately 15% of patients
7. EMG:
 - a. Overlapping mononeuropathies (later stages of the illness)
 - b. NCS most commonly show a length dependent axonal sensory neuropathy

Scleroderma*General Characteristics*

1. Fibrosis of the skin and visceral organs from the deposition of extracellular matrix proteins that consist of interstitial collagens (type I and III), cellular fibronectin, basement membrane proteins (laminins and others) and cellular fibronectin
2. Activation of myofibroblasts, which include actin (ACTA2), express smooth muscle proteins, are contractile which contributes to the distortion of parenchymal architecture
3. Scleroderma limited to the skin rarely causes neuropathy (linear scleroderma, morphea, diffuse cutaneous scleroderma)
4. The incidence is 10–15/million of the population; there are important ethnic differences
5. Peak incidence is in the third to fifth decades
6. The ratio of women to men is 3:1
7. The CREST variant includes:
 - a. Calcinosis
 - b. Raynaud's phenomenon

- c. Esophageal dysmotility
- d. Sclerodactyly
- e. Telangiectasia
- f. CREST may be associated with a vasculitic neuropathy

Clinical Manifestations

1. Raynaud's phenomenon is seen in 95% of patients
2. Slowly progressive skin and systemic organ involvement occur over years; visceral involvement primarily occurs in the GI tract, kidney, and lung
3. Sensorimotor neuropathy:
 - a. Complicates 5 to 67% of long standing patients
 - b. Asymmetric at onset
 - c. Later stages become symmetrical
 - d. Motor greater than sensory involvement occurs in <10% of patients
4. Entrapment neuropathies:
 - a. Carpal tunnel syndrome is seen in 10% of patients, most prominent in the early inflammatory stages of the illness
 - b. May have pressure palsies of other major nerves
5. Trigeminal inflammatory ganglionitis:
 - a. Affects 3% of scleroderma patients
 - b. Bilateral and asymmetrical in 60% of patients
 - c. Rare involvement of the VIIth and IXth nerve; mental nerve involvement causes the "numb chin" syndrome
6. Multiple mononeuropathies have been described in rare patients with CREST

Neuropathology

1. Fibroblasts and myofibroblasts are key fibrosis effectors in many organs; synthesize extracellular matrix proteins
2. TGF-1B cascade plays a major role in fibrosis
3. Nerve biopsy:
 - a. Axonal sensory > motor polyneuropathy
 - b. Increased endoneurial and perineural tissue
 - c. Rare vasculitis
4. Microvascular alterations:
 - a. Perturbation of endothelial cells
 - b. Neointimal formation
 - c. Pericyte activation
 - d. Perivascular inflammation
 - e. Capillary dilation and capillary atrophy are noted in the nail-fold
5. Small arteries and arterioles (50–500 μ m) demonstrate concentric fibrous intimal lesions that obliterate the lumen

Laboratory Evaluation

1. Positive anti-Scl-70 and anti-centromere antibodies are detected in greater than 60% of patients
2. Anti-nucleolar anti-RNA polymerase I, II and III antibodies; anti-ribonucleoprotein (RNP) antibodies are increased in some patients
3. Elevations of VEGF, PDGF, FGF-2 and DIGF in the plasma

Mixed Connective Tissue Disease (MCTD)

General Characteristics

1. A disease with a clinical overlap of SLE, scleroderma, and polymyositis
2. Presence of antibodies against the U1 small nuclear ribonucleoprotein autoantigen (U1-snRNP)
3. Women are affected more than men
4. Severe pulmonary hypertension a cause of death in some patients

Clinical Manifestations

1. Mild distal axonal sensorimotor polyneuropathy occurs in approximately 10% of patients
2. Trigeminal neuropathy
3. CTS (carpal tunnel syndrome)
4. Autonomic features

Neuropathology

1. Axonal neuropathy

Laboratory Evaluation

1. Elevated ESR
2. Hypergammaglobulinemia
3. Anti U1-snRNP antibodies
4. EMG:
 - a. Axonal features; some patients with mixed axonal-demyelinating characteristics
 - b. Rare polyradiculopathy presentation
5. MRI:
 - a. Patients have been described with cauda equina enhancement

Relapsing Polychondritis

General Characteristics

1. Inflammation of cartilaginous and proteoglycan rich structures
2. Peak incidence is in the fifth decade
3. Involved structures include:
 - a. Ear, nose, articular and tracheobronchial tree
 - b. Less frequently involvement of:
 - i. Cardiac valves
 - ii. Eye (episcleritis, conjunctivitis, uveitis, keratitis)

Clinical Manifestations

1. Optic neuritis (rare)
2. Sensorineural hearing loss in greater than 30% of patients
3. Vestibular involvement
4. Rare involvement of cranial nerves III, IV, V, and VI
5. Rare sensorimotor neuropathy and mononeuropathy
6. May have a coexistent autoimmune disorder

Neuropathology

1. Development of autoimmunity against cartilage that includes type II, IV, and XI collagen and constituent proteins such as matrilin-1

2. Interferon-gamma, interleukin 12 and IL-2 increase during disease activity, suggesting Th1 dysregulation
3. There may be an increased risk of myelodysplastic disease
4. Coincidence with Behçet's disease is designated MAGIC syndrome (mouth and genital ulcers with inflamed cartilage)
5. Renal disease and parenchymal lung involvement occur

Laboratory Evaluation

1. Increased interferon-gamma, IL-2 and IL-12
2. Rare ANCA-associated vasculitis

Sarcoidosis

General Characteristics

1. A granulomatous multisystem disease of unknown etiology
2. Neurosarcoidosis is usually seen with other forms of the disease but may be isolated in 1% of patients
3. Adult onset is usually between 30 to 40 years of age
4. Most frequently seen in Northern Europe, Japan and the east coast of the USA
5. African-American patients have an incidence 4× greater than Caucasian patients
6. Possible incidence is 10/100,000 in the population

Clinical Manifestations

1. The presenting symptoms are often fever, weight loss, arthralgias and fatigue
2. Erythema nodosa and enlarged lymph nodes may occur
3. Mucosal lesions of the nose and sinuses are common
4. Uveitis is often severe
5. The disease most often affects the lungs and mediastinal lymph nodes, but the heart (conduction defects) and the kidney are frequently affected
6. The peripheral and central nervous systems are affected in approximately 5% of patients
 - a. The most common cranial nerve that is involved is VII. The second cranial nerve may be compressed by meningeal infiltration. Any cranial nerve may be involved but the VIIth, VIIIth, and II are primary
 - b. Meningeal involvement
 - c. The posterior hypothalamus and pituitary are often involved, but infiltrates may be seen anywhere in the cortex

Peripheral Nervous System Involvement

1. Radiculopathy or polyradiculopathy
2. Acute sensory ataxia with sphincter involvement (rare)
3. Multiple mononeuropathies
4. Slowly progressive sensory > motor polyneuropathy
5. Pure small sensory neuropathy

Neuropathology

1. Nerve biopsy:

- a. Necrotizing granulomas that infiltrate the endoneurium, perineurium, and epineurium
2. Lymphocytic necrotizing angitis
 3. A combination of demyelination and axonal degeneration are seen in the nerve
 4. Muscle biopsy:
 - a. Noncaseating granulomas in the endomysium
 5. Skin biopsy:
 - a. Loss of intraepidermal nerve fibers in patients with the phenotype of small fiber neuropathy
 6. Recent studies support the contribution of heat shock proteins that act as DAMPs (tissue damage associated molecular patterns) or other microbial heat shock proteins that are recognized by pattern recognition receptors; these proteins may induce sarcoid inflammation

Laboratory Evaluation

1. Elevation of angiotensin converting enzyme in the serum (particularly in patients with lung disease) and in the CSF in those with CNS involvement
2. EMG:
 - a. Reduced or absent SNAPs are seen in the phenotype with sensorimotor neuropathy
 - b. In the lower extremities, there may be reduced or absent CMAPs, with borderline CMAPs in the upper extremities
 - c. Radiculopathy or polyradicular EMG pattern
 - d. QST:
 - i. Altered thermal thresholds

Celiac Disease (CD)

General Characteristics

1. A chronic small intestinal immune-mediated enteropathy precipitated by exposure to dietary gluten in genetically predisposed individuals
2. Gluten is a protein in wheat and its products
 - a. The classic disorder is defined with signs and symptoms of malabsorption, diarrhea, weight loss or growth failure
3. Clinical and laboratory diagnosis requires:
 - a. Malabsorption
 - b. Alterations of jejunal villi
 - c. Clinical and histologic improvement seen with a gluten free diet
 - d. Approximately 10% of patients have neurologic complications

Clinical Manifestations

1. The neuropathies include:
 - a. Generalized sensorimotor polyneuropathy
 - b. Autonomic neuropathy
 - c. Motor neuropathy
 - d. Multiple mononeuropathies
 - e. Neuromyotonia

2. Neurological examination reveals:
 - a. Loss of large fiber sensory modalities (often leading to ataxia in association with the neuropathy)
 - b. Mild distal extremity muscle weakness
 - c. Diminished or absent muscle stretch reflexes
 - d. Ataxic gait
 - e. Less frequent signs of a small fiber neuropathy

Neuropathology

1. Inflammation in celiac disease:
 - a. Increased intraepithelial lymphocyte count (>25/100 cells)
 - b. An adaptive T-cell mediated response to gluten (the protein component of wheat, rye, and barley, but not oats) that occurs in HLA-DQ2/DQ8-positive patients
2. Nerve biopsy:
 - a. Loss of myelinated fibers
3. Autopsy material:
 - a. Loss of Purkinje cells in the cerebellum
 - b. Degeneration of the spinal cord posterior columns and corticospinal tracts
 - c. Loss of neurons throughout the neuraxis in conjunction with cortical atrophy
 - d. Some features suggest malabsorption of B12 and vitamin E

Laboratory Evaluation

1. Presence of specific endomysial antibodies (EMA); anti-tissue transglutaminase antibodies (TTG a-tTG, TTA) and/or disassociated antigliadin antibody
2. Requires biopsy of the duodenum when patients are on a gluten free diet
3. EMG:
 - a. NCS reveal reduced SNAP amplitudes with minimally reduced NCVs or mildly prolonged distal latencies
 - b. Motor CVs are mildly reduced with normal distal motor latencies and CMAP amplitudes
 - c. Rare neuromyotonic discharges have been reported
 - d. Alterations in autonomic parameters may be detected in patients with autonomic features

Inflammatory Bowel Disease (IBD)

General Characteristics

1. Extraintestinal manifestations occur in approximately 1/3 of patients with ulcerative colitis and Crohn's disease (the major inflammatory bowel diseases)
2. These extraintestinal manifestations may occur several years prior to the onset of gastrointestinal symptoms
3. Immunosuppressant and biological therapies for IBD may be a component mechanism of the pathology of neurological complications
4. Neurological complications occur in approximately 3% of patients with IBD

Clinical Manifestations

1. Patterns of peripheral neuropathy:
 - a. Acute and chronic demyelinating neuropathies
 - b. Multifocal motor neuropathy
 - c. Axonal sensory or sensorimotor polyneuropathy
 - d. Multiple mononeuropathies

Neuropathology

1. Patients treated with biologics for a prolonged period:
 - a. PML a. Only reported in IBD patients treated with natalizumab as well as a few patients treated with anti-TNF therapy
 - b. CNS vasculitis
 - c. Posterior reversible encephalopathy syndrome (PRES)
 - d. Exacerbations of MS on TNF-alpha blocker therapy
 - e. Anti-TNF associated neuropathy:
 - i. Encompasses both a T and humoral attack directed against peripheral nerve myelin epitopes as well as disruption of trophic support for axons
 - f. Both Miller-Fisher variant and GBS have been described in patients undergoing treatment with TNF-alpha antagonists
 - g. Other neuropathology in patients with IBD include:
 - i. Toxicity of treatment with metronidazole
 - ii. B12 deficiency
 - h. Associated neurologic diseases:
 - i. Myasthenia gravis
 - ii. Inflammatory muscle disease

Laboratory Evaluation

1. Anti-GM1 antibodies in 50% of patients with multifocal motor neuropathy with conduction block
2. Evidence of anti-nuclear antibodies and anti-ds-DNA autoantibodies in patients with CNS vasculitis that are under anti-TNF-alpha therapy
3. EMG:
 - a. Multiple conduction blocks noted in some patients undergoing anti-TNF therapy
 - b. Demyelinating and axonal features in those with the appropriate phenotype

Primary Biliary Cirrhosis (PBC)

General Characteristics

1. Primary biliary cirrhosis is a chronic immune-mediated liver disease with progressive cholestasis, biliary fibrosis that may lead to cirrhosis
2. The primary autoimmune attack is against the biliary ducts in the liver
3. PBC may be associated with Sjögren's syndrome, myasthenia gravis, Lambert-Eaton syndrome, and myositis

Clinical Manifestations

1. A predominantly large fiber peripheral neuropathy
2. A CIDP clinical syndrome has been described

Neuropathology

1. Loss of large myelinated nerves without segmental demyelination
2. Autoimmune attack against biliary epithelia:
 - a. B-cells, cytotoxic and helper T-cells are involved in the chronic inflammation mediated by altered expression of proinflammatory cytokines

Laboratory Evaluation

1. Elevated liver function tests
2. Antimitochondrial antibodies are detected in a subgroup of patients
3. EMG:
 - a. Reduced or absent SNAPs; needle EMG and motor conduction velocities are usually normal
 - b. One patient has been reported with slow conduction velocities and conduction blocks

Henoch-Schönlein Syndrome*General Characteristics*

1. A systemic small vessel vasculitis that most often presents in childhood
2. Often self-limiting, although approximately 20% of patients suffer permanent sequelae

Clinical Manifestations

1. Erythematous macules that become papules; urticarial purpuric and necrotic lesions occur on the external portions of limbs and buttocks
2. Abdominal pain, joint and renal involvement
3. Severe hypertension may supervene
4. CNS manifestations:
 - a. Focal neurologic deficits
 - b. Altered level of consciousness
5. Peripheral neuropathies:
 - a. Mononeuropathy multiplex
 - b. Peripheral VIIth nerve palsy
 - c. Brachial plexopathy
 - d. Guillain-Barré syndrome

Neuropathology

1. Leukocytoclastic reaction in the skin
2. IgA vascular deposits
3. Arterioles, capillaries, and venules are primarily affected

Laboratory Evaluation

1. Occasional eosinophilia
2. Elevated IgA is detected in 50% of patients
3. EMG:
 - a. Mononeuropathy multiplex
 - b. Demyelinating feature in a subgroup of patients
4. Factor XIII deficiency (rare)
5. Decreased complement (rare)
6. Increased ESR in approximately 20% of patients

Hypereosinophilic Syndrome (HES)*General Characteristics*

1. Eosinophilic disorders that are characterized by chronic blood eosinophilia for more than six months, characterized by eosinophilic mediated damage to organs
2. Myeloproliferative HES has interstitial deletions on chromosome 4q12
3. Lymphocytic HES:
 - a. A primary lymphoid disorder characterized by a non-malignant expansion of a T-cell population that produces eosinophilopoietic cytokines
 - b. Other variants have not been molecularly identified

Clinical Manifestations

1. Associated skin, cardiac, hematologic or gastrointestinal manifestations are defined
2. Patterns of peripheral neuropathy:
 - a. Generalized peripheral sensorimotor neuropathy; radiculopathy
 - b. Mononeuropathy multiplex
 - c. Neuropathies occur in approximately 6 to 14% of patients
3. Associated neurologic involvement:
 - a. Inflammatory myopathy
 - b. Ataxia
 - c. Cerebral infarction
 - d. Leptomeningeal dissemination
 - e. Cognitive dysfunction
 - f. Ophthalmologic involvement

Neuropathology

1. Myeloproliferative variant that includes chronic eosinophilic leukemia
2. Deficits are secondary to toxic components of eosinophils

Laboratory Evaluation

1. Elevated levels of eosinophilia for more than six months (often as high as 20,000 cells/mm³)
2. EMG:
 - a. Features of axonal sensorimotor neuropathy

Uremic Neuropathy*General Characteristics*

1. Approximately 60% of patients with renal failure develop neuropathy
2. Glomerular filtration rates <12 ml/minute
3. In adults, peripheral neuropathy occurs in 50 to 60% of patients on dialysis
4. Evidence supports the contribution of diabetes, advanced age, low creatinine and urea to the neuropathy
5. Nerve damage may occur from toxins associated with uremia

Clinical Manifestations

1. Most commonly there is a length dependent numbness, tingling, and mechano-allodynia

2. Cramping of the calves may be prominent at the initiation of the neuropathy
3. Restless legs are common
4. Large fiber sensory modalities are most frequently involved
5. There is mild distal > proximally weakness and loss of muscle stretch reflexes
6. An AIDP phenotype occurs with rapidly progressive weakness and sensory loss
7. Mononeuropathies are documented:
 - a. May be related to hemodialysis equipment with a cuprophane membrane which incompletely removes beta-2 microglobulin that is catabolized by the kidney; this protein may be deposited in the transverse ligament of the carpal tunnel as well as the cubital tunnel and at the fibular level. An ischemic median neuropathy may occur from the shunt; the radial and ulnar nerves may rarely be similarly affected as well

Neuropathology

1. Sural nerve biopsy:
 - a. Loss of large myelinated nerve fibers
 - b. Axonal degeneration
 - c. Segmental and paranodal demyelination
2. Autopsy material:
 - a. Chromatolysis of anterior horn cells
 - b. Degeneration of the fasciculus gracilis
3. Two phases of recovery after transplantation
 - a. Dramatic early improvement with protracted recovery over time
4. Excitability studies have demonstrated a correlation between hyperkalemia and nerve dysfunction
5. Nerve damage may occur from guanidine compounds, parathyroid hormone and myoinositol molecules in the range of 300–2000 daltons

Laboratory Evaluation

1. Sensory studies demonstrate reduced or unobtainable SNAP amplitudes; slow conduction velocities and prolonged distal latencies are usual
2. Prolonged or absent H-reflexes
3. Somatosensory evoked potentials reveal slow peripheral and central conduction

Liver Disease

General Characteristics

1. Peripheral neuropathy occurs in between 20 to 80% of patients with chronic liver failure by EMG evaluation
2. Major confounders in association with liver disease that may be etiologic in the neuropathy are alcoholism and viral etiologies of the cirrhosis

Clinical Manifestations

1. Numbness and paresthesias of the distal, lower extremities with minimal weakness is the most common presentation
2. Autonomic alterations occur in approximately 50% of patients

Neuropathology

1. Sural nerve biopsy:
 - a. Segmental demyelination and axonal degeneration

Laboratory Evaluation

1. NCS reveal decreased SNAP amplitudes with usually normal motor studies
2. QST:
 - a. Abnormal mechanical and thermal thresholds

Whipple's Disease

General Characteristics

1. Tropheryma whipplei is the causative agent of Whipple's disease
2. The bacterium is transmitted among humans via oro-oral or feco-oral routes
3. The classic features of large joint arthropathy, diarrhea, and weight loss are rare
4. Asymptomatic carriage of T. whipplei is common but overt disease is rare

Clinical Manifestations

1. The clinical spectrum of disease includes:
 - a. An acute self-limiting disease in children
 - b. Localized forms that affect cardiac valves
 - c. Involvement of the CNS and PNS
2. A complicated Whipple's disease causes a T. whipplei endocarditis and may accompany immunosuppression, particularly with TNF-alpha blockade
3. CNS manifestations:
 - a. Dementia
 - b. Supranuclear ophthalmoparesis
 - c. Myorhythmia:
 - i. Rhythmic repetitive slow (1–4 Hz) movements that affect cranial and limb muscles; may be oscillatory or jerky
 - ii. Oculomasticatory myorhythmia is more typically associated with Whipple's disease:
 1. Slow, repetitive, and asymmetrical
 2. Facial and ocular movements are prominent
 - d. Convergence nystagmus
 - e. Myoclonus
 - f. Hyperphagia, insomnia, and polydipsia may occur in the disorder
4. Peripheral manifestations:
 - a. Sensorimotor polyneuropathy

Neuropathology

1. Peripheral lymphadenopathy accompanied by enlargement of the celiac, mesenteric and periaortic lymph nodes
2. May present as an acute infection that includes gastroenteritis, pneumonia and/or bacteremia
3. Jejunal biopsy:
 - a. Macrophages filled with periodic acid-Schiff positive organisms

4. PAS-positive histiocytes may be seen in the CSF; periventricular areas, hypothalamus and scattered diffusely through the brain
5. There are no reports of nerve histology

Laboratory Evaluation

1. CSF:
 - a. Pleocytosis of polymorphonuclear cells and macrophages; rarely PAS-positive histiocytes
2. Specific quantitative PCR of saliva and stool specimens may be diagnostic
3. MRI:
 - a. Gadolinium enhancement of the ependyma
4. EMG:
 - a. NCS of sensory and motor nerves reveal reduced amplitudes and mildly slow conduction velocities

Critical Illness Polyneuropathy

General Characteristics

1. Increased survival of critically ill patients has revealed the syndrome of ICU-acquired weakness
2. The most common neuromuscular cause is polyneuropathy, although many authorities suggest that critical illness myopathy may be equally frequent; prolonged neuromuscular blockade also may cause severe weakness
3. The illness of critical care polyneuropathy and myopathy most often occurs in a setting of multi-organ failure and sepsis. It prolongs mechanical ventilation and hospitalization time and increases mortality and disability

Clinical Manifestations

1. The neuropathy usually develops after 2–3 weeks, but the often altered sensorium precludes accurate assessment of sensory loss. Sepsis, multi-organ failure, and severe burns are significant confounds to pathogenesis. A systemic inflammatory response syndrome has been implicated
2. Presentation is often difficulty in weaning the patient from mechanical ventilation
3. The neuropathy is primarily motor that varies from just an electrodiagnosis without clinical deficits to quadriplegia with respiratory insufficiency
4. Sensory symptoms and signs are variable, but often mild and hard to document due to confounding mental status alterations
5. Cranial nerves are most often not affected
6. Little or no autonomic dysfunction

Neuropathology

1. Nerve biopsy:
 - a. Axonal degeneration
2. Autopsy material demonstrates:
 - a. Chromatolysis of anterior horn cells, loss of dorsal root ganglion cells, as well as degeneration of motor and sensory nerve axons

3. Muscle biopsy:
 - a. Features of neurogenic atrophy that include target or core-like lesions
 - b. Loss of myosin thick filaments

Laboratory Evaluation

1. Serum creatine kinase is usually normal (high values would indicate critical illness myopathy)
2. EMG:
 - a. Reduced amplitudes or absent CMAPs with normal motor conduction velocities and distal latencies
 - b. SNAPs are reduced in amplitude or absent (may be due to age, diabetes, uremia, or other underlying illness)
 - c. Needle EMG:
 - i. Positive sharp waves and fibrillation potentials
 - ii. Decreased MUAPs; if recruited they may be small and polyphasic; early recruitment small duration polyphasic MUAPs suggest myopathy
3. Screening for neuropathy with single nerve conduction studies reveals decreased amplitudes
4. Another method to distinguish critical neuropathy from myopathy is the ratio of nerve stimulation evoked CMAP to direct muscle stimulation CMAPs
 - a. Expected is 1:1 (>.9) in myopathy and zero (.1 μ V) with neuropathy or neuromuscular junction disorder

Amyloid Polyneuropathy

Overview

Amyloid is a 10 to 20 nm non-branching protein fibril which when aggregated forms β -pleated sheets that are resistant to proteolytic degradation. It causes proteinaceous deposition in the kidney, heart, liver, and GI tract, as well as in muscle and peripheral nerves. It has genetic forms and can be acquired. Genetic forms are autosomal dominant and are caused by mutations in the transthyretin (TTR), apolipoprotein A-I (APOA1) or gelsolin genes. Primary AL amyloidosis causes deposition of immune globulin light chains and occurs with multiple myeloma, Waldenström's macroglobulinemia, lymphoma, plasmacytomas, and lymphoproliferative disease. It may be idiopathic. Approximately 10% of patients that have amyloid light-chain (AL) amyloidosis are thought to have a genetic form.

AA amyloidosis, also known as "secondary amyloidosis," may be associated with rheumatoid arthritis and other chronic inflammatory conditions, deposits in visceral organs, but is not associated with a polyneuropathy.

In peripheral nerves, amyloid deposition occurs in the endoneurium, perineurium, epineurium, and around blood vessels. There may be a concomitant inflammatory cell infiltrate. Muscle biopsy demonstrates amyloid deposition that encases muscle fibers.

The variety of amyloid is determined by immunohistochemistry in which antibodies distinguish light chains, apolipoprotein A, gelsolin, and TTR. Genetic testing is optimal for distinguishing the various forms of familial amyloidosis.

Primary or AL Amyloidosis*General Characteristics*

1. Primarily associated with multiple myeloma and other myeloproliferative disease
2. Formerly known as “primary amyloidosis”
3. The amyloid is most often derived from a circulating para-protein which is cleared by macrophage enzymes
4. The cleared light chains aggregate and deposit in visceral organs, peripheral nerves, and muscle
5. In light chain disease, plasma cells produce light chains directly
6. Lambda light chains are more often seen in idiopathic disease, while kappa light chains are predominant in multiple myeloma

Clinical Manifestations

1. AL (light chain) amyloidosis is primarily a disease of older men (55–65 years of age)
2. Has a more rapid course than occurs in hereditary forms
3. Presenting signs and symptoms may be due to visceral involvement which includes:
 - a. Nephrotic syndrome
 - b. Congestive heart failure and cardiac arrhythmia
 - c. Gastrointestinal dysmotility
 - d. Bleeding into the skin
 - e. Constitutional symptoms of fatigue and weight loss

Neuropathology

1. Approximately one-third of patients develop a peripheral neuropathy
2. Initially, it presents as numbness or paresthesias, but a significant proportion of patients develop neuropathic pain and thermal sensitivity changes (small fiber modalities). The pain and autonomic involvement are helpful in differential diagnosis from paraprotein neuropathies
3. Weakness occurs initially in distal leg muscles but evolves to affect the hands and arms
4. Later in the course, large sensory fiber modalities are affected
5. The trunk may be involved
6. In approximately 20% of patients, it presents as mononeuropathy multiplex
7. Carpal tunnel syndrome is present in 25% of patients, from amyloid infiltration of the flexor retinaculum
8. There may be preferential involvement of:
 - a. Lumbar roots
 - b. Plexus
 - c. Motor nerves
 - d. Amyloidomas may involve single nerves (such as the sciatic or trigeminal)
9. Autonomic involvement may be severe and may present early in the illness; signs and symptoms include:
 - a. Alterations of gastrointestinal motility
 - b. Bowel and bladder dysfunction

- c. Impotence
 - d. Decreased sweating
 - e. Pupillary light-near dissociation
10. Rarely, enlarged peripheral nerves can be palpated
 11. Associated features of the general exam include:
 - a. Macroglossia
 - b. Hoarse voice (vocal cord infiltration)
 - c. Peripheral lower extremity edema
 - d. Hepatomegaly
 12. Infiltrative amyloid myopathy is rare
 - a. Enlargement and indurations of muscles (including the tongue)
 13. Nerve biopsy:
 - a. Axonal degeneration
 - b. Loss of small myelinated and unmyelinated fibers; less density of large myelinated fibers
 14. Congo red stains reveal:
 - a. Amyloid deposition of either globular or diffuse pattern in the endoneurium, epineurium, and perineum
 - b. Blood vessel walls
 - c. Other sites that may be biopsied to demonstrate amyloid deposition are:
 - i. Rectum
 - ii. Salivary glands
 - iii. Abdominal fat pad
 - iv. Kidney
 - v. Stomach
 - vi. Liver

Laboratory Evaluation

1. Serum monoclonal proteins are composed of IgG, IgM, or IgA; only free Lambda or K-light chain (more common in multiple myeloma) can be seen
2. Initial screen of the urine and serum for an abnormal paraprotein
3. Only a small subgroup of genetic amyloid patients have a monoclonal gammopathy
4. Immunoelectrophoresis or immunofixation of the serum and urine are sensitive for detecting light chains (more sensitive than serum or urine electrophoresis)
5. Hypogammaglobulinemia, renal failure, increased liver enzymes are frequently associated
6. Elevated CK occurs if there is concomitant myopathy
7. CSF has slightly elevated protein without pleocytosis
8. EMG:
 - a. Sensory nerve amplitudes are reduced or absent; distal latencies and conduction velocities are only minimally affected
 - b. Motor conduction velocities are less affected than sensory; distal motor latencies are more prolonged in the lower than upper extremities
 - c. CMAP amplitudes are slightly reduced in the early course of the disease and are not as severely involved as SNAPs
 - d. Carpal tunnel is common

- e. Needle EMG:
 - i. Signs of denervation in affected muscles
 - ii. Patients with myopathy may demonstrate:
 - 1. Myotonic discharges
 - 2. Myopathic MUAPs

Differential Diagnosis of Acquired Amyloid Neuropathy

1. Familial forms of amyloid
2. Small fiber neuropathies
3. Myeloproliferative neuropathies
4. Paraneoplastic disease
5. Diabetic neuropathy
6. Sjögren's disease
7. Idiopathic small fiber neuropathy

Secondary Amyloidosis or AA Amyloidosis

General Characteristics

1. Is caused by chronic infection or chronic inflammatory disease
2. Formerly known as "secondary amyloidosis"
3. Generally, is not associated with neuropathy

TTR-Related Amyloidosis (FAP Type I and II)

General Characteristics

1. Transthyretin (TTR) amyloidosis is characterized by extracellular deposition of amyloid fibrils composed of TTR (transthyretin)
2. TTR is a plasma transport protein for thyroxine and vitamin A
3. It is produced in the liver, dissociates from its usual tetramer, is misfolded, and aggregates into amyloid fibrils
4. TTR amyloidosis is the most common form of familial amyloidosis; the mutations destabilize the TTR protein
5. TTR amyloid also causes senile systemic amyloid, which is acquired and primarily affects men over 60 years of age, and results from deposition of wild-type TTR amyloid

Genetics

1. There are more than 80 mutations that have been identified in the TTR gene which maps to chromosome 18q 11.2-12.1
 - a. Mutation at position 30 (Val 30 Met) is the most common mutation associated with FAP I
 - b. The most common mutations for FAP II involve serine at position 84 and histidine at position 58
 - c. There is variability within families regarding age of onset and severity in those with the Val 30 Met mutations
 - d. Endemic areas for TTR-FAP mutations are Portugal, Sweden, Japan, Brazil, and Majorca
 - e. Incidence in the USA is 1/100,000 individuals

Clinical Manifestations

1. There are two major clinical forms of TTR mutations:
 - a. FAP I (severe)

- b. FAP II (milder phenotype)
2. Onset is usually between the second and fourth decades
 - a. Associated with variations across different populations
 - b. Portuguese and Japanese patients have an early onset mean age of 33 years, whereas Swedish patients have a near age of onset at 56 years
 3. Pattern of neuropathies:
 - a. Typical insidious onset of numbness and painful paresthesias in the distal lower extremities; small fiber sensory modality loss predominates
 - b. Carpal tunnel syndrome is not common, as opposed to AL primary amyloidosis
 - c. Autonomic involvement is often severe:
 - i. Postural hypotension
 - ii. Constipation or continual diarrhea
 - iii. Erectile dysfunction
 - iv. Dyshidrosis
 - d. Distal extremity weakness and atrophy evolve
 - e. Cranial nerve involvement occurs
 - f. Visceral involvement from amyloid deposition occurs in the heart, liver, kidneys and cornea
 - g. Symptoms may be similar in patients with different genotypes; phenotypes may not be uniform, and the same point mutation may produce different phenotypes
 - h. Clinical manifestations of Val 30 Met TTR-FAP differ according to specific endemic foci
 - i. Patients usually succumb to the illness 10 to 15 years after onset, from cardiac and renal involvement

Clinical Manifestations of Type II FAP

1. Originally described in families from Indiana and Switzerland
2. Early carpal tunnel syndrome
3. Later stages of the disease patients develop a mild generalized sensorimotor polyneuropathy
4. Accompanied by vitreous opacities that also occur with TTR-FAP Type I
5. Severe autonomic dysfunction is unusual
6. Rare development of cardiac or renal complications
7. Patients with Val 30 Met TTR-FAP from non-endemic foci usually have onset of disease after the age of 60 years, are predominantly male and have a sporadic presentation
8. FAP II usually has a long survival

Neuropathology

1. Multifocal (or diffuse) deposition of amyloid within the endoneurium, epineurium, or perineurium
2. Amyloid deposition within and around blood vessels
3. Amyloid deposits around blood vessels in the autonomic ganglia and peripheral nerves
4. Predominant loss of thinly myelinated and unmyelinated nerve fibers
5. Axonal degeneration and segmental demyelination occur
6. Other organ involvement:

- a. Cardiac disease occurs in approximately 50% of patients
- b. Ocular involvement causes:
 - i. Vitreous opacity
 - ii. Dry eyes
 - iii. Glaucoma
 - iv. Light-near pupillary dissociation

Laboratory Evaluation

1. Biopsy of the abdominal fat pad; rectal mucosa
2. Deposits of amyloid in nerve biopsies
3. Genetic testing:
 - a. In contrast to acquired forms, there are no monoclonal gammopathies and there is no immunostaining for light chains
4. EKG:
 - a. Bundle branch block, AV and sinoatrial block
 - b. Abnormalities in the long-axis function of both ventricles on tissue Doppler imaging

Leptomeningeal TTR Amyloidosis

General Characteristics

1. Induced by point mutations in the TTR gene and is also seen in advanced Val 30 Met TTR-FAD
2. The source of the TTR in leptomeningeal amyloidosis is thought to be the choroid plexus

Clinical Manifestations

- a. Cerebral amyloid angiopathy
- b. Ocular amyloidosis
- c. CNS manifestations include:
 - i. Infarction of:
 1. Medium-sized and small arteries
 2. Cerebral hemorrhage
 3. Hydrocephalus
 4. Focal neurologic deficits
 5. Dementia
 6. Amyloid deposition in the vitreous bodies and other tissues of the eye

Neuropathology

1. Amyloid deposition in the media and adventitia of medium-sized and small arteries, arterioles, and veins of the cortex and leptomeninges
2. TTR Val 30 Gly mutation was associated with refractory bilateral intermediate uveitis and elevated intraocular pressure with meningeal amyloid

Laboratory Evaluation

1. Ocular findings of uveitis
2. Meningeal biopsy that demonstrates amyloid
3. MRI:
 - a. Familial amyloid patients with the ATTRY114C mutations revealed gadolinium enhancement from the brainstem to the spinal cord

Apolipoprotein A1 Related Amyloidosis (Type III FAP or the Van Allen Type)

General Characteristics

1. FAP type III is caused by mutations in the apolipoprotein A1 gene on chromosome 11q23-qter that cause an arginine substitution for glycine at position 26
2. High-density lipoproteins and their major protein apolipoprotein A-1 (apo A-1) promote vascular health by removing excess cellular cholesterol. In FAP III amyloidosis non-variant full-length apo A-1 deposits as fibrils

Clinical Manifestations

1. Onset of neuropathy is in the fourth decade
2. Neuropathy usually starts in the distal lower extremities with paresthesias and painful dysesthesia. It evolves over time to affect the upper extremities that may involve proximal muscles
3. Autonomic neuropathy is usually not severe
4. Patients usually succumb 12–15 years after onset of the illness from renal failure

Neuropathology

1. N-terminal fragments of variant apo A-1 deposit in vital organs as well as the peripheral nerve

Laboratory Evaluation

1. Biopsy of the abdominal fat pad or peripheral nerve
2. Genetic testing

Gelsolin-Related Amyloidosis (FAP Type IV, Finnish)

General Characteristics

1. Type IV amyloidosis results from mutations in the gelsolin gene that maps to chromosome 9q32-q34
2. Gelsolin is a widespread binding protein that can be recovered from plasma and leukocytes

Clinical Manifestations

1. Onset of the disease is usually in the third decade
2. Primary clinical manifestations are:
 - a. Lattice corneal dystrophy
 - b. Severe facial and bulbar weakness
 - c. A mild generalized sensorimotor polyneuropathy without autonomic dysfunction

Neuropathology

1. Deposition of gelsolin amyloid in vascular walls and perineural sheaths
2. Nerve roots are more severely affected than distal nerves
3. Large myelinated fibers are preferentially involved

Laboratory Evaluation

1. Ophthalmologic evaluation of the distinctive corneal lattice degeneration
2. Genetic testing

Neuropathies Associated with Infections

Leprosy (Hansen's Disease)

Overview

The disease is caused by the acid-fast bacteria *Mycobacterium leprae* and *Mycobacterium lepromatosis*. It is a common cause of infectious peripheral neuropathy in Southeast Asia, Africa, and South America. The spectrum of disease ranges from tuberculoid leprosy, an intermediate form, to lepromatous leprosy. The clinical manifestations are dependent on the host's immunological response to the infection.

Tuberculoid Leprosy

General Characteristics

1. The cell-mediated immune response is intact

Clinical Manifestations

1. The skin lesions are well circumscribed, scattered hypopigmented patches with raised erythematous borders. They may have a plaque-like morphology
2. The cutaneous nerves are affected, which causes loss of sensation in the center of the skin lesions
3. Cooler regions of the body (face, ears, nose, and limbs) are most often affected
4. Other sites of nerve involvement include:
 - a. The ulnar nerve at the elbow (medial epicondyle)
 - b. The median nerve near in the distal forearm
 - c. The superficial radial nerve at the wrist
 - d. The peroneal nerve at the fibular head
 - e. The greater auricular nerve
 - f. The nerve involvement causes mononeuropathy or mononeuropathy multiplex; pure neuritic leprosy occurs; the nerves are often palpable

Neuropathology

1. There is granuloma formation by macrophages and Th1 cells that are surrounded by Th2 cells
2. Caseation may occur; the lesions extend throughout the dermis
3. The Fite stain is negative for bacteria
4. Cell-mediated immunity is intact:
 - a. Th1 > Th2 lymphocytes
 - b. Increased cytokine expression
 - c. IL-2

Laboratory Evaluation

1. Lepromin test is positive (>5 mm of induration)
2. Bacterial index 0
3. Morphological index is low

Lepromatous Leprosy

General Characteristics

1. Cell-mediated immunity is decreased, which causes extensive bacterial infiltration and hematogenous spread

Clinical Manifestations

1. Confluent and symmetrical rash that is anesthetic and anhidrotic
2. Predilection for cooler areas of the body; older lesions form plaques and nodules
3. Loss of eyebrows and eyelashes
4. Skin infiltration exaggerates natural skin folds causing "leonine facies"
5. The superficial cutaneous nerves of the skin and distal extremities are often involved
6. A slowly progressive symmetric sensorimotor polyneuropathy evolves:
 - a. Distal extremity weakness occurs
 - b. Relative sparing of large myelinated sensory afferents
 - c. Muscle stretch reflexes are relatively spared
 - d. Facial neuropathy
 - e. Mononeuropathies may be superimposed on the generalized neuropathy
 - f. No pure neuritic phenotype

Neuropathology

1. Infiltrating bacilli, Th2 lymphocytes, and macrophages with bacilli are noted
2. Electron microscopy of bacilli reveals the bacillus to be a dense osmophilic rod surrounded by a clear halo
3. Fite stain is positive
4. Cell-mediated immunity is markedly depressed or absent
 - a. Th2 > Th1 lymphocytes
 - b. IL4, IL5 and IL10 are the expressed cytokines

Laboratory Evaluation

1. Lepromin test is negative (0–2 mm of indurations)
2. Bacterial index is high (5–6)
3. Morphological index is high (0–10)

Borderline Leprosy

General Characteristics

1. The most common form with neuropathy
2. Associated with both the clinical and histological features of both the tuberculoid and lepromatous forms of the disease
3. There is partial spread of disease that provokes an inflammatory response
4. The clinical picture may shift toward the tuberculoid or lepromatous form of the disease depending on the immunological status of the patient

Clinical Manifestations

1. Skin lesions are intermediate between those seen in the tuberculoid or lepromatous form of the disease
2. Generalized symmetric sensorimotor polyneuropathy
3. Mononeuropathy
4. Mononeuropathy multiplex
5. Brachial plexopathy

Effects of Treatment

1. Immunologic interactions during the course of treatment may affect the course of the disease and the patient's subsequent disability
2. The three types of immunologic reactions with leprosy are:
 - a. Reversal reaction (type 1):
 - i. Most commonly seen in borderline leprosy
 - ii. Occurs at any time during treatment and is due to an increase in cellular immunity
 - iii. Associated with increased levels of tumor necrosis factor alpha (TNF- α), gamma interferon 2 and interleukin 2:
 1. New granulomas may form
 2. Exacerbation of the rash and worsening of the neuropathy
 - b. Nodosum leprosum (type 2):
 - i. Most commonly occurs during treatment
 - ii. Erythematous, painful nodules (subcutaneous) are seen that may be associated with worsening of the neuropathy
 - iii. Most likely the result of new antigen exposure from degenerating bacilli (Toll-like receptor response from the newly released antigens)
 - c. Lucio phenomenon:
 - i. A rare form of lepra reaction
 - ii. Tender nodules with ulceration and necrotic areas
 - iii. A cutaneous vasculitis involving medium- and small-sized vessels

Neuropathology

1. Granulomas contain epithelioid cells but no giant cells
2. Lymphocytes are scant, but if seen are diffusely infiltrating
3. Usually, there is evidence of cell-mediated immunity

Laboratory Evaluation

1. Lepromin reaction (2–5 mm of induration)
2. Bacterial index (2–4)
3. Morphologic index is moderate

Pure Neuritic Leprosy**General Characteristics**

1. Most patients have the tuberculoid or borderline phenotype

Clinical Manifestations

1. Patients have isolated peripheral neuropathy without skin lesions

Laboratory Evaluation for All Forms of Leprosy

1. EMG:
 - a. The pattern of involvement on both needle EMG and NCS is that of mild to moderate active denervation
 - b. Sensory nerve conduction velocities are usually de-

creased in the lower extremities and are reduced in amplitude in the arms

- c. Motor NCS are usually normal, but a subgroup of patients may have reduced NCVs
- d. The pattern of involvement is generally a symmetrical polyneuropathy, mononeuropathy or multiple mononeuropathies
- e. Evaluation of leprosy by NCS may be independent of the patient's degree of infection

Lyme's Disease**General Characteristics**

1. Lyme neuroborreliosis is the designation of the neurologic syndromes caused by the spirochete *Borrelia burgdorferi* (Bb)
2. The deer tick (*Ixodes* genus) is the responsible vector
3. The three stages of Lyme's disease are:
 - a. Early infection characterized by localized erythema migrans
 - b. Disseminated infection
 - c. Late stage infection

Clinical Manifestations

1. Stage I:
 - a. In general, approximately one month after the tick bite, an circular erythematous lesion appears which expands. The center clears giving it a bull's-eye appearance. The rash clears within a month. Some patients with Lyme's disease do not develop erythema migrans
2. Stage II:
 - a. Dissemination of the spirochete occurs throughout the body
 - b. Systemic symptoms of fever, chills, localized adenopathy, fatigue, and myalgia are common, and may be associated with additional skin lesions
 - c. Associated cardiac involvement (conduction blocks and pericarditis), as well as small and large joint infection, may occur
3. Neurologic manifestations start in the second and third stages and include:
 - a. Unilateral and bilateral VIIth nerve palsies; occurs in approximately 50% of patients
 - b. Painful sensory radiculitis
 - c. Multifocal motor radiculopathy
 - d. May present with GBS phenotype
 - e. Meningitis signs and symptoms are more frequent in children than adults
 - f. Approximately 4–8% of patients develop cardiac complications, 11% develop neurologic manifestations, and 45–60% have an inflammatory arthritis
4. In late stage disease:
 - a. Destructive joint inflammation
 - b. Distal extremities may become cyanotic, associated with paresthesia and weakness with large fiber sensory loss and decreased muscle stretch reflexes

- c. Cognitive decline is controversial
- d. Rare inflammatory myopathy

Neuropathology

1. Nerve biopsy:
 - a. Perivascular infiltration of plasma cells and lymphocytes around the blood vessels that supply the endoneurium, perineurium, and epineurium
 - b. Axonal degeneration with secondary demyelination
 - c. Root inflammation and dorsal root ganglia pathology are seen

Laboratory Evaluation

1. Immunofluorescence enzyme-linked immune absorbent assay
2. Western blot analysis confirms a positive enzyme-linked immune absorbent assay
3. Patients with CNS involvement, polyradiculitis, and facial nerve involvement demonstrate CSF lymphocytic pleocytosis with moderately increased protein elevation
4. EMG:
 - a. Electrodiagnostic studies are most consistent with a primary axonopathy
 - b. Patients with mononeuropathy demonstrate:
 - i. Reduced compound muscle action potentials (CMAP) and SNAP amplitudes
 - ii. Demonstrated abnormalities are most often asymmetric
 - iii. Fibrillation, positive sharp waves, and decreased recruitment of neurogenic MUAPs are seen in affected muscles
 - iv. In late stage disease, a subgroup of patients may develop an inflammatory myopathy

Diphtheria

General Characteristics

1. Diphtheritic polyneuropathy is caused by an exotoxin-producing strain of *Corynebacterium diphtheriae*
2. Spread by respiratory secretions and cutaneous lesions (human-to-human contact)
3. The disease is vaccination preventable; the last reported patient in the USA was in 2003

Clinical Manifestations

1. Diphtheria is a biphasic illness:
 - a. Patients may initially present with a low-grade fever, sore throat, neck swelling and some degree of palatal paralysis within 7 to 10 days of exposure
 - b. A whitish membranous exudate in the pharynx may occur with or without lymph node involvement
 - c. Cardiac involvement causes arrhythmias and hypotension
 - d. Approximately 3 to 4 weeks after the initial infection, patients develop:
 - i. Decreased pharyngeal sensation
 - ii. Dysphagia, dysarthria, and hoarseness
 - iii. Diplopia (adductor function of the IIIrd nerve) initially
 - iv. Pupil responds to light but fails accommodation
 - v. Respiratory weakness

- e. Diphtheritic polyneuropathy:
 - i. Is caused by hematogenous dissemination of intracellular toxin A
 - ii. Occurs 2–4 months following the initial infection
 - iii. Characteristic polyneuropathy with numbness, paresthesias, and extremity weakness; all sensory modalities are affected with distal > proximal weakness
 - iv. Muscle stretch reflexes are reduced or absent
 - v. Autonomic dysfunction of bowel and bladder is rare

Neuropathology

1. Nerve biopsy:
 - a. Segmental demyelination and axonal degeneration are evident
 - b. There is involvement of nerve roots and the dorsal root ganglia
 - c. The diphtheria toxin binds to Schwann cells and inhibits myelin protein synthesis

Laboratory Evaluation

1. CSF protein is often elevated, with or without a lymphocytic pleocytosis
2. EMG:
 - a. Sensory NCS demonstrates absent SNAPs
 - b. Motor NCS reveal moderately prolonged distal latencies with decreased nerve conduction velocities
 - c. NCS abnormalities are generally noted by two weeks following the onset of symptoms and reach maximum intensity between 5–8 weeks
 - d. NCS improvement frequently lags behind clinical recovery, which usually occurs after several months

Human Immunodeficiency Virus (HIV)

General Characteristics

1. The global prevalence of HIV infection is approximately 37 million people (as of the end of 2014)
2. Combination antiretroviral therapy (cART) has greatly expanded life expectancy to almost normal ranges
3. HIV sensory neuropathy affects between 27% to 57% of ambulatory patients; approximately 38% to 90% of patients with sensory neuropathy have neuropathic pain
 - a. The prevalence of HIV-sensory neuropathy is approximately 40% even in patients with no exposure to dNRTI (nucleoside reverse transcriptase inhibitors)
 - b. Recent cART-era populations and gene association studies have identified additional patient-related risk factors which include:

- i. Ethnicity
- ii. Elevated plasma triglycerides
- iii. Association with genes involved in inflammation and mitochondrial function

Clinical Manifestations

1. Patterns of neuropathy:
 - a. Distal symmetric polyneuropathy
 - b. Inflammatory demyelinating polyneuropathy (phenotype similar to AIDP and CIDP)
 - c. Multiple mononeuropathies (Vasculitis and CMV-related)
2. Polyradiculopathy (usually lumbar and sacral) that is CMV-related
3. Autonomic neuropathy
4. Sensory ganglionitis
5. Associated with retroviral treatment

HIV-Related Distal Symmetric Polyneuropathy (DSP)

General Characteristics

1. The most common form of peripheral neuropathy associated with HIV infection, most often seen in patients with AIDS

Clinical Manifestations

1. Numbness and paresthesias of the distal extremities
2. There is usually slight distal muscle weakness, which may evolve to proximal leg weakness and moderate distal arm weakness
3. Asymptomatic patients may have sensory loss in the extremities to all modalities on examination
4. Reduced muscle stretch reflexes in the ankles, but usually spared at the knee and in the upper extremities
5. Many patients have moderate to severe burning pain in a stocking and glove distribution, most often in patients being treated with dideoxynucleoside reverse transcription inhibitors (d-drugs)
6. May affect 50% of all HIV-infected patients

Neuropathology

1. Two major mechanisms have been proposed for the neuropathy:
 - a. Neurotoxicity from the virus and its products
 - b. Neurotoxic effects of medications used in its treatment
2. Nerve biopsy:
 - a. Axonal degeneration, with loss of both myelinated and demyelinated axons
 - b. Loss of neurons in the dorsal root ganglion, with secondary degeneration in the posterior columns
 - c. Minimal perivascular inflammation, with macrophages and T-lymphocytes
3. Increased levels of proinflammatory cytokines
4. A subset of patients has vitamin B12 deficiency
5. Skin biopsy:
 - a. Reduced density of small myelinated epidermal nerve fibers

Laboratory Evaluation

1. CSF:
 - a. Mild lymphocytic pleocytosis with moderate protein elevation
2. EMG:
 - a. Nerve conduction studies are consistent with a symmetric axonal sensory greater than motor polyneuropathy

HIV-Related Inflammatory Demyelinating Polyradiculopathy

General Characteristics

1. AIDP most often develops at the time of seroconversion, while CIDP occurs at any point during the infection

Clinical Manifestations

1. Similar to idiopathic AIDP and CIDP

Neuropathology

1. Nerve biopsy: similar to AIDP and CIDP

Laboratory Evaluation

1. CSF:
 - a. Lymphocytic pleocytosis
 - b. Elevated protein
2. EMG:
 - a. Similar to idiopathic AIDP and CIDP

CMV-Related Progressive Polyradiculopathy

General Characteristics

1. Most often seen in severely affected AIDS patients (CD4⁺ counts of less than 200 cells/mm³)

Clinical Manifestations

1. Severe leg radicular pain and numbness that is usually asymmetric
2. Loss of perineal sensation
3. Bowel and bladder incontinence
4. Moderate to severe weakness of the legs; weakness of the arms may evolve during the course of the illness
5. Cranial nerves may be involved
6. Decreased or absent muscle stretch reflexes in the legs; reduced reflexes in the arms
7. CMV retinitis is frequently a concomitant infection
8. Plantar responses are flexor if the infection is relegated to the lumbosacral roots; Babinski sign occurs with CMF myelitis

Laboratory Evaluation

1. CSF:
 - a. Decreased glucose concentration
 - b. Neutrophilic pleocytosis
 - c. Increased protein
2. CMV can be cultured from the CSF, urine, and blood
3. EMG:
 - a. Decreased amplitudes of SNAPs and CMAPs
 - b. Denervation with fibrillation potentials and positive sharp waves in the affected muscles

Neuropathology

1. Lumbosacral axonal loss in both dorsal and ventral roots
2. Inflammatory infiltrates
3. Rare cranial nerve inflammation, often associated with myelitis
4. CMV may be demonstrated in endothelial cells and macrophages (with the nerve biopsy)
5. Ischemic vasculitis and direct CMV infection are putatively causative

HIV-Related Multiple Mononeuropathies*General Characteristics*

1. Mononeuropathies may develop in AIDS patients

Clinical Manifestations

1. Weakness, sensory loss and pain occur in the distribution of affected nerves

Neuropathology

1. Axonal degeneration
2. Necrotizing vasculitis
3. Perivascular inflammation
4. Vasculitis may occur from the deposition of HIV antigen-antibody complexes on vascular walls, or from concomitant CMV or hepatitis B or C infection

Laboratory Evaluation

1. CSF:
 - a. Mononuclear cell pleocytosis
 - b. Elevated protein
2. EMG:
 - a. Reduced amplitudes of motor and sensory potentials
 - b. Symmetry of amplitudes
 - c. Distal latencies are normal or slightly prolonged
 - d. Conduction velocities are normal or only slightly reduced
 - e. Denervation changes in affected muscle

HIV-Related Autonomic Neuropathy*General Characteristics*

1. Distal symmetric polyneuropathy (DSP) is often associated with autonomic impairment
2. The composite autonomic severity score (CASS) in patients with autonomic impairment with HIV correlated with:
 - a. Increased total neuropathy score (TNS)
 - b. Age
 - c. Viral load
 - d. Hypertension
 - e. Use of medications, primarily anticholinergic
3. There was no correlation with:
 - a. Antiretroviral treatment
 - b. CD4⁺ count
 - c. HIV duration
 - d. Metabolic factors
 - e. CNS diseases

Clinical Manifestations

1. Orthostatic hypotension
2. Impaired sweating
3. Bladder dysfunction
4. Impotence
5. Diarrhea
6. Autonomic dysfunction may develop insidiously

Neuropathology

1. Distal axonal degeneration
2. Neuronal loss in DRG and autonomic ganglia
3. Inflammatory cell infiltration
4. Reduced epidermal nerve fiber density (ENFD)
5. Pathogenesis:
 - a. Glycoprotein (Gp) 120 expressed on the surface of the HIV envelope
 - b. Gp 120 may activate macrophages to release TNF-alpha and IL-1; induces Schwann cells to release RANTES that induces DRG cells (possibly autonomic ganglia cells) to release TNF-alpha, which induces cell death through TNF receptor 1-mediated neurotoxicity
6. Mitochondrial damage appears most severe in patients with NRT1 exposure. A proposed mechanism is inhibition of mitochondrial DNA polymerase

Laboratory Evaluation

1. Cerebrospinal fluid:
 - a. Lymphocytic pleocytosis is present in greater than 50% of asymptomatic HIV patients, usually up to 50 cells/mm³ in seropositive patients
 - b. CSF protein is elevated in both seronegative and seropositive patients (50–80 mg%)
 - c. DSP and mononeuropathy multiplex patients may demonstrate a mild mononuclear pleocytosis
 - d. CSF glucose is normal in HIV patients
 - e. A low glucose (30–40 mg%), high PMN pleocytosis (as high as 2000 cells/mm³); high protein up to 1 gram/dl has been reported in CMV lumbosacral plexitis
 - f. CMV detection of DNA by PCR is important as culture is only positive in 50% of patients
2. EMG:
 - a. Similar to that seen with DSP
 - b. Abnormal autonomic testing

HIV-Related Sensory Neuropathy/Ganglionopathy*General Characteristics*

1. Dorsal root ganglionitis during HIV infection is rare
2. Occasionally it is the presenting peripheral nerve presentation

Clinical Manifestations

1. Sensory ataxia
2. Large myelinated fiber deficits cause proprioception and vibration loss
3. Decreased or absent motor stretch reflexes
4. Preserved strength

Neuropathology

1. Inflammatory cell infiltrates of the dorsal root ganglia
2. Loss of large dorsal root ganglia neurons
3. Degeneration of myelinated nerve fibers in peripheral nerves

Laboratory Evaluation

1. Decreased-amplitude or unobtainable SNAPs

Differential Diagnosis of HIV Distal and Sensory Polyneuropathy

1. Concomitant diseases that cause neuropathy in AIDS patients:
 - a. Diabetes mellitus
 - b. Uremia
 - c. Drug abuse (ethanol)
 - d. Standard HAART therapy
 - e. B12 deficiency
 - f. Diffuse infiltrative lymphocytosis syndrome that consists of:
 - i. Painful distal neuropathy
 - ii. Acute onset
 - iii. Primarily motor involvement
 - iv. May be asymmetric and restricted to the arms

Differential Diagnosis of HIV Polyradiculopathy

1. CMV
2. Mechanical bone and disc compression of the cauda equina
3. Lymphomatosis of the meninges
4. Syphilis

Differential Diagnosis of Neuropathy in Late HIV Infection

1. Superimposed CMV infection
 - a. Patient is not responding to therapy as expected
 - b. A rapidly progressive course
 - c. Associated myelitis and retinitis
 - d. CD4⁺ count of fewer than 200 lymphocytes/mm³
2. Diffuse infiltrative lymphocytosis syndrome

HTLV-1*General Characteristics*

1. Human T-lymphotropic virus type 1 (HTLV-1)-associated myelopathy/tropical spastic paraparesis is a chronically progressive myelitis that dominates symptomatology
2. There is an associated axonal sensorimotor polyneuropathy
3. Approximately 20 million people are affected worldwide with approximately 0.3–0.4% destined to get TSP/HAM
4. Endemic areas are Southern Japan, the Caribbean, Africa and some areas of South and Central America
5. The incidence is 2 patients/100,000 people in endemic areas

Clinical Manifestations

1. Slowly progressive severe spastic paraparesis with sphincter involvement
2. The neuropathy can occur in the absence of the myelopathy
3. A myositis may occur
4. A sensory greater than motor axonal length-dependent polyneuropathy is characteristic

Neuropathology

1. Sural nerve biopsy:
 - a. Axonal degeneration with secondary demyelination associated with inflammatory infiltrates
 - b. The HTLV-1 proviral DNA and mRNA activated T-cells CD8⁺ specific for Tax protein that up-regulates proinflammatory cytokines

Laboratory Evaluation

1. HTLV-1 proviral DNA and mRNA are increased in the CSF
2. EMG:
 - a. Characteristics of an axonal sensory greater than motor neuropathy

Cytomegalovirus Virus*General Characteristics*

1. One of the most important opportunistic infections in AIDS patients (usually with CD4⁺ counts <200/mm³)

Clinical Manifestations

1. Retinitis
2. Encephalitis
3. Polyradiculopathy (particularly of lumbosacral roots) often associated with myelitis
4. Multifocal neuropathy (radial, ulnar, and peroneal nerves)
5. Cranial nerves may be involved

Neuropathology

1. Patients with AIDP after CMV infection demonstrate serum autoantibodies against moesin (membrane-organizing extension spike protein)
2. Moesin:
 - a. Expressed in Schwann cell process at the nodes of Ranvier
 - b. Pivotal for myelination
 - c. Possible antigen in CMV AIDP

Laboratory Evaluation

1. EMG:
 - a. Characteristic of polyradiculopathy
2. Mononeuropathy of ulnar, radial, and peroneal nerves
3. PCR positive for CMV in the CSF
4. MRI:
 - a. May demonstrate gadolinium enhancement of the cauda equina

Herpes Varicella-Zoster*General Characteristics*

1. Ubiquitous neurotropic herpes virus
2. The primary infection causes varicella (chicken pox), after which the virus becomes latent in dorsal root ganglia along the entire neuraxis
3. A decline in cell-mediated immunity with age or immunosuppression causes virus reactivation
4. Approximately 95% of the USA population is infected
5. Reactivation is common in HIV patients and those undergoing chemotherapy
6. Transmission is respiratory or by direct contact

Clinical Manifestations

1. Radicular distribution of severe lancinating pain:
 - a. 50% of patients have a thoracic dermatome distribution
 - b. 20% lumbosacral distribution
 - c. 30% cervical distribution
 - d. The diaphragmatic innervations can be affected
2. Decreased threshold to primary modalities of cold and pin-prick in affected dermatomes
3. Mechanical dynamic and static allodynia in the affected dermatomes
4. There may be secondary mechano-hyperalgesia in the dermatomes above and below the affected dermatome with analgesia in the zone of the affected root
5. Sensory symptoms (usually bring pain) may occur prior to the skin eruption; at times greater than 2–3 months; herpes sine herpette
6. Weakness of muscles in the affected dermatome occurs in 5 to 30% of patients, usually within the first 14 days after the skin eruption, but can be delayed up to a month
7. Cranial nerve involvement is infrequent:
 - a. Ophthalmoplegia is rare
 - b. IIIrd cranial nerve is most frequently involved if cranial nerve involvement occurs
 - c. VI cranial nerve involvement is often associated with meningoencephalitis
8. Rarely optic neuritis occurs
9. VII–VIII involvement with vesicles in the external auditory canal constitutes the Ramsay Hunt syndrome
10. Other HZV neurologic complications include:
 - a. Post-herpetic neuralgia
 - b. Meningoencephalitis (particularly with VI involvement)
 - c. VZV temporal arteritis
 - d. VZV vasculopathy may occur in large or small cerebral arteries; cerebral aneurysms and hemorrhage may develop from viral invasion of vessels
 - e. Myelopathy
 - f. Retinal necrosis
 - g. Delayed MCA stroke is associated with VI infection

Neuropathology

1. The virus, when reactivated, migrates down sensory fibers that originate in the dorsal root ganglia to invade the skin and subcutaneous tissue in a dermatomal distribution
2. Axonal degeneration with secondary segmental demyelination
3. Necrosis of dorsal root ganglion cells
4. Loss of dorsal column spinal cord fibers

Laboratory Evaluation

1. Cerebral spinal fluids:
 - a. RBC may be seen (40–50 RBC/mm³)
 - b. Increased protein occurs in 50% of patients
 - c. Normal glucose; rarely glucose is less than 40 mg%
2. Rarely, detection of the virus by PCR is more successful in the serum than the CSF
3. EMG:
 - a. Sensory NCS demonstrate reduced or absent SNAPs
 - b. Motor NCS are normal or have reduced CMAP amplitudes
 - c. Needle EMG of affected muscles reveal positive sharp waves, fibrillation potentials, decreased recruitment and neurogenic MUAPs
4. MRI:
 - a. Meningoencephalitis if VIth nerve is involved with dural enhancement
 - b. Delayed carotid or MCA stroke if VIth nerve is involved

Differential Diagnosis of Radicular Pain on the Thorax Without Rash

1. Cancer of the lung
2. Diabetic neuropathy
3. Disc disease
4. Lymphoma
5. Vascular malformation of a nerve root
6. Sjögren's syndrome

Hepatitis B*General Characteristics*

1. Hepatitis B has extrahepatic complications that include the skin, renal, hematological, and nervous system

Clinical Manifestations

1. Hepatitis B-related vasculitic mononeuritis multiplex
 - a. The course is subacute to chronic
 - b. Rarely, the course may be acute and present as a distal symmetric sensorimotor polyneuropathy
 - c. Associated with mixed cryoglobulinemia
 - d. Acute AIDP and CIDP occur

Neuropathology

1. Immune complexes on nerves
2. Vasculitis
3. Demyelinating features and axonal degeneration on nerve biopsy

4. Exacerbation of neuropathy during alpha-interferon therapy

Hepatitis C

General Characteristics

1. Chronic hepatitis C virus infection is associated with a wide spectrum of extrahepatic manifestations, primarily immunologic and rheumatologic
2. Hepatitis C virus-associated neuropathy is most often associated with mixed cryoglobulinemia and vasculitis

Clinical Manifestations

1. Primary axonal neuropathies include:
 - a. Sensorimotor polyneuropathy
 - b. Large or small fiber sensory neuropathy
 - c. Mononeuritis multiplex
 - d. Rare AIDP and CIDP
2. Peripheral demyelinating disorders include:
 - a. CIDP
 - b. Lewis-Sumner syndrome
 - c. Cryoglobulin-associated polyneuropathy
 - d. Pegylated interferon treatment associated central and peripheral demyelination
 - e. Approximately 20% have components of autonomic neuropathy

Neuropathology

1. Nerve biopsy
 - a. Inflammatory vascular lesions that include:
 - i. Necrotizing arteritis
 - ii. Small-vessel vasculitis of either lymphocytic or leukocytoclastic type
 - b. Perivascular inflammatory infiltrates
 - c. Tissues demonstrating vasculitis may contain intracellular HCV
 - d. Cryoglobulin deposition in the vasa vasorum

Laboratory Evaluation

1. Detection of cryoglobulins and mixed cryoglobulins in the serum
2. Evidence of cirrhosis in a subset of patients
3. Positive PCR identification

Epstein-Barr Virus

General Characteristics

1. Acute Epstein-Barr virus (EBV) may be associated with both central and peripheral neurologic complications

Clinical Manifestations

1. Mononeuropathy
2. Mononeuropathy multiplex
3. Autonomic neuropathy
4. Polyradiculopathy
5. Brachial plexopathy
6. Lumbosacral radiculoplexopathy
7. Cranial neuropathy
8. Sensory neuropathy

Neuropathology

1. Nerve biopsy:
 - a. Axonal degeneration from leukocytoclastic vasculitis
2. Immune-mediated
 - a. Successful immunosuppressant treatment of a patient with EBV-positive T/natural killer cell lymphoproliferative disease

Laboratory Evaluation

1. Positive serological tests for EBV virus antibodies
2. EMG:
 - a. Consistent with mononeuropathy multiplex
 - b. Brachial plexopathy characteristics in both adult and pediatric patients

Toxic Neuropathies

Misonidazole

General Characteristics

1. Used as an adjuvant in the treatment of malignancies

Clinical Manifestations

1. After 3 to 5 weeks of treatment subgroups of patients develop:
 - a. Painful paresthesias
 - b. Distal length-dependent weakness
 - c. Usually, the total dose prior to symptoms is 18 grams
 - d. Loss of vibratory and temperature sensibilities
 - e. Improvement occurs after discontinuation of the drug

Neuropathology

1. Sural nerve biopsy:
 - a. Axonal degeneration and segmental demyelination primarily of large myelinated fibers
 - b. Remyelination
2. Electron microscopy:
 - a. Neurofilament accumulation with axonal swelling

Laboratory Evaluation

1. EMG:
 - a. Sensory nerve conduction studies demonstrate reduced or unobtainable amplitudes in the legs, with less involvement in the arms
 - b. Motor conduction velocities are normal; slightly reduced amplitudes of CMAPs

Metronidazole

General Characteristics

1. Nitroimidazole antibiotic with activity against protozoa and most gram-negative and gram-positive anaerobic bacteria
2. Used for prophylaxis and treatment of Crohn's disease

Clinical Manifestations

1. Length-dependent sensorimotor neuropathy

2. Painful paresthesias
3. Both large and small fiber sensory modulated neurons are affected
4. Slight distal weakness

Neuropathology

1. Nerve biopsy:
 - a. Axonal degeneration
 - b. Loss of myelinated fibers

Laboratory Evaluation

1. EMG:
 - a. Decreased-amplitude or absent SNAPs
 - b. Normal CMAPs

Chloroquine and Hydroxychloroquine

General Characteristics

1. Chloroquine and hydroxychloroquine are 4-aminoquinoline compounds used as antimalarial and immune suppressants, and as disease-modifying antirheumatic drugs
2. Newer uses are for treatment of SLE, rheumatoid arthritis, primary Sjögren's disease, sarcoidosis, and antiphospholipid syndrome
3. Chloroquine analogs are being evaluated for their effects on metabolic, cardiovascular, antithrombotic and neoplastic diseases

Clinical Manifestations

1. Length-dependent loss of small and large fiber sensory modalities
2. Distal extremity weakness from the neuropathy; proximal weakness may be concomitant from a superimposed myopathy
3. Decreased muscle stretch reflexes
4. The usual dose required for muscle and nerve toxicity is 500 mg/day for greater than one year

Neuropathology

1. Nerve biopsy:
 - a. Autophagic vacuoles and Schwann cell inclusions
 - b. Vacuolar myopathy occurs in muscle cells
2. The hydrophilic and hydrophobic amphiphilic properties of the drug allow interaction with ionic phospholipids of cell membranes and organelles; the drug-lipid complex, resistant to lysosomal enzymes, form autophagic vacuoles whose myeloid debris may be neurotoxic
3. The drugs reduce T-cell and B-cell hyperactivity and proinflammatory cytokine gene expression
4. Axonal degeneration associated with autophagic vacuoles
5. Hydroxychloroquine:
 - a. Absent vacuoles on nerve and muscle biopsy
 - b. Electron microscopy
 - i. Abnormal accumulation of myeloid and curvilinear bodies in Schwann cells and muscle

Laboratory Evaluation

1. Sensory NCS reveal decreased or absent SNAPs

2. Normal or reduced CMAP amplitudes
3. Needle EMG:
 - a. Distal denervation
 - b. Myopathic MUAPs in proximal muscles in patients with concomitant myopathy

Amiodarone

General Characteristics

1. Amiodarone toxicity affects:
 - a. Lungs
 - b. Thyroid gland
 - c. Skin
 - d. Liver
 - e. Nervous system
 - f. Optic nerves
 - g. Parotid gland hypertrophy occurs

Clinical Manifestations

1. Greater than 90% of patients develop corneal micro deposits; less than 5% report halo vision; 2% develop visual loss from optic neuropathy; usually, ocular symptoms occur after one year of use
2. Weakness is both proximal and distal, worse in the legs than arms
3. Distal paresthesias and burning pain
4. Sensory loss is to all modalities
5. Associated depression of muscle stretch reflexes

Neuropathology

1. Nerve biopsy:
 - a. Axonal degeneration and segmental demyelination
 - b. Electron microscopy:
 - i. Lamellar or dense inclusions in Schwann cells, pericytes, and endothelial cells
 - c. Muscle biopsy:
 - i. Autophagic vacuoles
 - ii. Neurogenic atrophy

Laboratory Evaluation

1. Sensory NCS:
 - a. Reduced amplitudes and mild to moderately slow conduction velocities
 - i. Prolonged distal latencies
 - b. Motor NCS are affected similarly but not to the same degree
 - c. Needle EMG:
 - i. Positive sharp waves and fibrillation potentials
 - ii. Mixture of myopathic and neuropathic MUAPs; rare myotonic discharges

Colchicine

General Characteristics

1. Primarily disrupts inflammation activation; modulates multiple pro- and anti-inflammatory pathways

Clinical Manifestations

1. Presentation is usually a proximal myopathy with concomitant distal numbness and paresthesias of the extremities; distal weakness
2. Length-dependent loss of vibration and proprioception sensory modalities
3. Decreased to absent muscle stretch reflexes

Neuropathology

1. Colchicine effects:
 - a. Prevents microtubule assembly
 - b. Disrupts inflammation activation
 - c. Disrupts microtubule-based inflammatory cell chemotaxis
 - d. Decreases generation of leukotrienes and cytokines
 - e. Decreases phagocytosis
 - f. Inhibits polymerization of tubulin in microtubules; decreased axoplasmic flow
2. Nicotine protects against colchicine-induced apoptosis through the P13-kinase-AKT pathways
3. Nerve biopsy:
 - a. Axonal degeneration
4. Muscle biopsy:
 - a. Focal myofibrillar disorganization with accumulation of autophagic vacuoles in muscle fibers

Laboratory Evaluation

1. Serum CK levels may be increased if there is concomitant myopathy
2. EMG:
 - a. Low amplitude SNAPs
 - b. Normal or reduced CMAPs
 - c. Myopathic MUAPs (in patients with concomitant myopathy)
 - d. Neurogenic MUAPs in distally affected muscles
 - e. Positive sharp waves and fibrillation potentials

Podophyllin*General Characteristics*

1. The primary condition treated with podophyllin was anogenital warts (condylomata acuminata)
2. Systemic side effects of podophyllin include:
 - a. Gastrointestinal paresis
 - b. Urinary retention
 - c. Pancytopenia
 - d. Liver and renal dysfunction
3. Due to severe toxicity, podophyllin has been removed from treatment options in favor of podophyllotoxin-derived products

Clinical Manifestations

1. Both CNS and PNS toxicity:
 - a. Psychosis
 - b. Altered mental status

2. Length-dependent peripheral neuropathy characterized by:
 - a. Slowly progressive distal weakness
 - b. Paresthesias
 - c. Reduced muscle stretch reflexes
 - d. Autonomic dysregulation:
 - i. Nausea and vomiting
 - ii. Constipation
 - iii. Orthostatic hypotension
 - iv. Urinary retention
 - v. Tachycardia
 - vi. "Slide" is common; the neuropathic side effects may continue after the medication has been discontinued
 - vii. Improvement occurs over months; urinary deficits are common

Neuropathology

1. Nerve biopsy: axonal degeneration
2. Podophyllin disrupts microtubular function and possibly axoplasmic flow

Laboratory Evaluation

1. CSF: elevated protein
2. Pancytopenia
3. Evidence of liver and renal involvement
4. EMG:
 - a. Sensory NCS:
 - i. Reduced-amplitude or unobtainable SNAPs
 - ii. Reduced amplitudes of CMAPs

Thalidomide*General Characteristics*

1. Thalidomide is primarily used in the USA to treat multiple myeloma (often with bortezomib, which also causes neuropathy), graft-versus-host, and other autoimmune disorders. It is used extensively in leprosy treatment protocols

Clinical Manifestations

1. Approximately 20 grams of thalidomide are required for neurotoxicity, which is dose related
2. Primarily a length-dependent sensory neuropathy with paresthesias, numbness, and burning pain
3. Distal muscle weakness with minimal neurogenic atrophy
4. Loss of large fiber sensory modalities greater than small fibers (occasionally can be seen with an accumulative dose of 12 grams)
5. Hypo or absent muscle stretch reflexes

Neuropathology

1. Nerve biopsy:
 - a. A greater loss of large fiber myelinated fibers than small
 - b. Axonal degeneration

2. Loss of large diameter DRG neurons
3. The incidence of neuropathy with thalidomide treatment varies from 25% to 75% and is dose-dependent
4. Reduces levels of proinflammatory cytokines (TNF-alpha; interleukin-1B (IL-1B), IL-6); malondialdehyde and myeloperoxidase (MPO) activity

Laboratory Evaluation

1. EMG:
 - a. Reduced amplitudes of SNAPs; normal sensory conduction velocities
 - b. Motor NCS are usually normal

Adjunctive Therapy with Bortezomib

1. Used in conjunction with thalidomide in multiple myeloma treatment:
 - a. Incidence of sensory neuropathy is 40%
 - b. Reversible in greater than 60% of patients with discontinuance of the medication
2. Mechanism of toxicity is putatively disruption of calcium homeostasis, or proteasome inhibition by bortezomib increasing IL-8 expression, which is proinflammatory as a neutrophilic chemoattractant and inducer of leukocyte-mediated inflammation

Disulfiram

General Characteristics

1. Primarily used for the treatment of alcohol abuse and dependence
2. Some studies suggest its benefit for cocaine dependence
3. Mechanism of action for its use in alcohol abuse:
 - a. Inhibits liver aldehyde dehydrogenase, preventing the breakdown of acetaldehyde, a product of ethanol metabolism, causing a severe "instant hangover" on drinking alcohol
4. Disulfiram is metabolized to carbon disulfide, which is toxic to both the central and peripheral nervous system

Clinical Manifestations

1. Induced Parkinsonism
2. Frontal lobe syndrome
3. May cause adverse events at less than the daily dose of 500 mg
4. Disulfiram neuropathy usually occurs after 5 to 6 months of use; progression of deficits is steady
5. Peripheral neuropathy is consistent with a length-dependent axonal neuropathy:
 - a. Distal weakness
 - b. Sensory loss, large fiber greater than small myelinated fibers; sensory deficits may appear as early as 10 days after initiation of therapy

Neuropathology

1. The CNS and PNS toxicities are correlated with the production of carbon disulfide, a metabolite of disulfiram

2. Sural nerve biopsy:
 - a. Loss of predominately large diameter myelinated fibers to a greater degree than of thinly myelinated fibers
 - b. Axonal degeneration and segmental demyelination
 - c. Electron microscopy:
 - i. Axonal swellings from the accumulation of neurofilament debris within both myelinated and unmyelinated axons
3. Bilateral lentiform lesions

Laboratory Evaluation

1. EMG:
 - a. Unobtainable SNAPs generally; in those that can be studied low amplitude is noted
 - b. CMAP amplitudes are normal or may be slightly reduced

Dapsone

General Characteristics

1. Dapsone is primarily used for:
 - a. Treatment of leprosy
 - b. Dermatologic conditions that include:
 - i. Acne conglobate
 - ii. Dermatitis herpetiformis
 - iii. Pemphigoid
 - iv. Pemphigus
 - v. Behçet's disease
 - vi. Polychondritis
 - vii. Leukocytoclastic vasculitis

Clinical Manifestations

1. The onset of peripheral neuropathy is variable, and may be seen as early as 5 days to as long as several years
2. Distal weakness of arms and legs is initially seen, and may progress to proximal muscles
3. Rarely there are paresthesias and sensory symptoms without weakness
4. The neuropathy usually occurs after prolonged therapy; cumulative doses that have been reported with neuropathy are from 25–600 mg
5. Signs and symptoms usually resolve after 12 months from cessation of the drug

Neuropathology

1. Axonal atrophy and Wallerian degeneration of distal motor nerve terminals
2. Sural nerve biopsy:
 - a. Loss of myelinated fibers (segmental demyelination and axonal degeneration)

Laboratory Evaluation

1. EMG:
 - a. CMAPs are unobtainable or demonstrate low amplitude
 - b. Normal or minimally reduced SNAP amplitudes

Leflunomide*General Characteristics*

1. Leflunomide is converted into A771726 in the liver which inhibits dihydroorotate dehydrogenase
2. The enzyme is required for biosynthesis of pyrimidine nucleotides by T-lymphocytes
3. The drug is used primarily for the treatment of rheumatoid arthritis
4. Other adverse effects of the drug are:
 - a. Diarrhea
 - b. Liver toxicity
 - c. Alopecia
 - d. Rash
 - e. Hypertension
 - f. Drug-induced pneumonia

Clinical Manifestations

1. Length-dependent peripheral neuropathy
2. Distal numbness and paresthesias
3. The median duration of treatment prior to the onset of neuropathy is 7.5 months; rarely, it may start within three weeks

Neuropathology

1. Not known

Laboratory Evaluation

1. EMG:
 - a. Low amplitude SNAPs with normal or slightly reduced CMAPs
2. Quantitative sensory testing
 - a. Higher cold detection threshold

Nitrofurantoin*General Characteristics*

1. Primary use is the treatment of urinary tract infection
2. Elderly patients and those with renal compromise have the highest risk

Clinical Manifestations

1. Acute GBS presentation has been described
2. Distal extremity numbness and paresthesias that may be painful
3. Absent or reduced muscle stretch reflexes

Neuropathology

1. Sural nerve biopsy:
 - a. Loss of large myelinated fibers
 - b. Autopsy material:
 - i. Degeneration of spinal roots, dorsal greater than ventral
 - ii. Chromatolysis of anterior horn cells
 - c. Skin biopsy: (2 patients)
 - i. Clustered terminal nerve swellings without nerve fiber degeneration; nerve conduction studies were normal

Laboratory Evaluation

1. EMG:
 - a. Reduced-amplitude or absent SNAPs and CMAPs
 - b. Axonopathy pattern

Pyridoxine (Vitamin B6 Toxicity)*General Characteristics*

1. A coenzyme for transformation and decarboxylation reactions
2. Doses of greater than 100 mg/day may cause neurotoxicity

Clinical Manifestations

1. Loss of large diameter myelinated fiber modalities of proprioception and vibration
2. The neuropathy may begin in the arms
3. Sensory ataxia with an associated wide-based unsteady gait
4. Muscle stretch reflexes are reduced or absent

Neuropathology

1. Nerve biopsy:
 - a. Axonal loss in all fiber diameters
 - b. Loss of DRG cells (experimental studies)
 - c. Glutamate carboxypeptidase inhibition has been protective (experimental evidence in rats)

Laboratory Evaluation

1. Toxic levels in the serum (usually by excessive vitamin supplementation)
2. EMG:
 - a. NCS reveal absent or reduced SNAPs with normal or slightly reduced CMAPs

Isoniazid*General Characteristics*

1. Primarily used for the treatment of tuberculosis
2. Neuropathy develops in approximately 17% of patients taking high doses (6 mg/kg/d) and in 2% of patients taking the standard 3–5 mg/kg/d
3. Increased risk of neuropathy occurs in elderly, malnourished, and slow drug acetylators
4. Usually, the neuropathy begins after six months on the usual doses

Clinical Manifestations

1. Usual presentation is paresthesias and numbness in the distal extremities
2. With continued use, proximal weakness may occur
3. There is sensory loss to all modalities, and sensory ataxia may develop in severely affected patients
4. Distal muscle atrophy
5. Reduced or absent muscle stretch reflexes
6. An isolated motor neuropathy has been described
7. Isoniazid-induced myopathy may occur concomitantly with the neuropathy; rarely there may be an isolated myopathy

Neuropathology

1. Inhibition of pyridoxal phosphokinase, causing pyridoxine deficiency, is the major mechanism of toxicity
2. Patients who are “slow acetylators” have higher serum concentrations of the medication
3. Sural nerve biopsy:
 - a. Axonal degeneration
 - b. Loss of myelinated and unmyelinated fibers
 - c. Loss of neurons in the DRG with secondary dorsal column degeneration

Laboratory Evaluation

1. EMG: Reduced SNAPs and CMAPs amplitude

Ethambutol*General Characteristics*

1. Ethambutol is primarily used in the treatment of tuberculosis; it is frequently combined with isoniazid for treatment of multi-drug-resistant disease
2. Its most common complication is toxic optic neuropathy characterized by a decrease in visual acuity, deficits in color vision and centrocecal scotoma

Clinical Manifestations

1. Neurotoxicity is seen with prolonged therapy with doses of 20 mg/kg/day or greater
2. Patients develop severe optic neuropathy
3. A sensory neuropathy develops in the extremities with numbness and minimal weakness
4. Loss of large fiber modalities of proprioception and vibration
5. Reduction or loss of distal muscle stretch reflexes
6. May exacerbate the neuropathy of CMT2A2 and possibly other neuropathies with mitochondrial fusion defects

Neuropathology

1. Nerve biopsy:
 - a. Axonal degeneration with secondary loss of myelinated fibers

Laboratory Evaluation

1. Decreased amplitude of SNAPs with normal distal latencies and conduction velocities
2. Normal motor conduction velocities

Chloramphenicol*General Characteristics*

1. Chloramphenicol is a broad-spectrum antibiotic rarely used in the USA, but still utilized in developing countries
2. Severe bone marrow toxicities:
 - a. Dose-dependent toxicity that causes anemia and is reversible
 - b. Idiosyncratic reaction causing irreversible aplastic anemia

Clinical Manifestations

1. Severe optic neuropathy
2. A sensory neuropathy affecting all modalities
3. Absent or reduced deep tendon reflexes, primarily in the legs

Neuropathology

1. Nerve biopsy: Not reported

Laboratory Evaluation

1. EMG: Not reported

Nucleoside Analogues (Dideoxycytidine, Dideoxyinosine, Stavudine, Lamivudine)*General Characteristics*

1. Nucleoside analogs and antiretroviral nucleoside reverse transcriptase inhibitors are used to treat HIV
2. Most often there is subacute onset of neuropathy (mean of 16 weeks with dideoxycytidine)

Clinical Manifestations

1. Sensory length-dependent peripheral neuropathy
2. Hyperpathia of the extremities that is usually symmetrical
3. Loss of pin-prick and temperature modalities greater than large myelinated fiber modalities
4. Decreased muscle stretch reflexes in the legs greater than in the arms
5. Mild distal muscle weakness and slight atrophy in the intrinsic foot muscles
6. “Coasting effect” for approximately one month after the drug (ddc) is discontinued; improvement occurs after several months

Neuropathology

1. Nucleoside analogs inhibit mitochondrial DNA
2. Possible deficit of acetylcarnitine may contribute to the neuropathy
3. Axonal neuropathy

Laboratory Evaluation

1. EMG:
 - a. Decreased SNAPs with normal sensory conduction velocities and distal sensory latencies
 - b. Motor NCS are usually normal
2. QST:
 - a. Impaired temperature and vibratory thresholds

Phenytoin*General Characteristics*

1. Genetic polymorphisms of CYP2C9 may lead to interindividual variations of drug level, adverse drug reactions, and toxicity

Clinical Manifestations

1. Generally a sensory neuropathy

2. Decreased light touch, vibration and proprioception primarily in the distal leg
3. Minimal weakness
4. Decreased ankle muscle stretch reflexes

Neuropathology

1. Sural nerve biopsy:
 - a. Loss of large myelinated axons
 - b. Segmental demyelination

Laboratory Evaluation

1. Rare megaloblastic anemia
2. EMG:
 - a. Decreased amplitude of SNAPs with normal sensory conduction velocities and distal latencies
 - b. Approximately 20% of patients may have slightly reduced conduction velocities and amplitude of SNAPs

Lithium

General Characteristics

1. CNS side effects are much more common than peripheral neuropathy and include:
 - a. Myoclonus
 - b. Tremor
 - c. Dysarthria
 - d. Altered mental status
 - e. Seizures
 - f. Hyperhidrosis
2. Renal and thyroid toxicity

Clinical Manifestations

1. Peripheral neuropathy is characterized by slight weakness and primarily large fiber modality sensory loss
2. Reduced muscle stretch reflexes

Neuropathology

1. Sural nerve biopsy:
 - a. Loss of large myelinated fibers
 - b. Axonal degeneration

Laboratory Evaluation

1. EMG:
 - a. Low amplitude SNAPs
 - b. Normal or reduced CMAPs

Acrylamide

General Characteristics

1. Acrylamide is a "type-2-alkene", which is a vinyl monomer
2. Absorption occurs through the skin, gastrointestinal tract (contaminated with water) or lungs
3. It is used industrially as a flocculating and grouting agent

Clinical Manifestations

1. Contact dermatitis

2. CNS manifestations include:
 - a. Confusion and irritability
 - b. Ataxia and dysarthria
 - c. Hallucinations
3. A distal symmetrical polyneuropathy
 - a. Loss of large fiber modalities of touch, vibration, and proprioception
 - b. Minimal loss of temperature and pain
 - c. Positive Romberg sign
 - d. Mild distal muscle atrophy and weakness
 - e. Decreased muscle stretch reflexes

Neuropathology

1. Putative mechanisms of toxicity:
 - a. Inhibition of kinesin-based fast axonal transport
 - b. Alteration of neurotransmitter levels
 - c. Direct inhibition of neurotransmission
2. Sural nerve biopsy:
 - a. Axonal degeneration with loss of large myelinated fibers
 - b. Experimental studies reveal:
 - i. Early paranodal accumulation of 10 nm neurofilaments at the distal terminal arbors of peripheral nerves
 - ii. Distal axons enlarge and degenerate
3. Autopsy material demonstrates
 - a. Demyelination of the dorsal columns, spinocerebellar tracts, optic tracts, corticospinal tracts and the mammillary bodies

Laboratory Evaluation

1. EMG:
 - a. Decreased SNAP amplitude with normal sensory distal latencies and conduction velocities
 - b. Slightly reduced CMAPs; high levels of exposure may be associated with temporal dispersion of CMAPs

Carbon Disulfide

General Characteristics

1. Carbon disulfide is a widely used industrial solvent in the vulcanization of rubber, rayon, cellophane, and adhesives
2. It can be absorbed through the skin and lungs
3. CNS alterations from higher levels of exposure cause psychosis and Parkinsonism

Clinical Manifestations

1. Reflexes
2. Presentation is usually numbness and tingling distally in the extremities
3. Loss of all sensory modalities
4. Minimal distal muscle weakness and atrophy
5. Decreased muscle stretch reflexes

Neuropathology

1. Experimental studies reveal:

- a. Accumulation of 10 nm neurofilaments and axonal swelling
- 2. Low levels of chronic exposure cause a length-dependent sensorimotor symmetrical polyneuropathy

Laboratory Evaluation

- 1. Reduced amplitude of SNAPs and CMAPs
- 2. Slowing of sensory greater than motor conduction velocities

Ethylene Oxide

General Characteristics

- 1. Primarily used to sterilize heat sensitive materials (surgical packs)
- 2. Associated with:
 - a. Dermatological lesions
 - b. Inflammation of mucosal membranes
 - c. Altered sensorium
 - d. Nausea and vomiting

Clinical Manifestations

- 1. Peripheral neuropathy characterized by:
 - a. Distal numbness and paresthesias
 - b. Mild distal weakness
 - c. Sensory ataxia
 - d. Decreased muscle stretch reflexes

Neuropathology

- 1. Sural nerve biopsy:
 - a. Loss of large diameter greater than small diameter myelinated fibers

Laboratory Evaluation

- 1. EMG:
 - a. Low amplitude SNAPs
 - b. Normal or reduced CMAP amplitudes

Organophosphates

General Characteristics

- 1. Used for insecticides, in the plastics industry and petroleum products
- 2. Affects both the central and peripheral nervous systems
- 3. Basic mechanism of toxicity is cholinergic neuronal excitotoxicity induced by irreversible ACHE (acetylcholinesterase) inhibition

Clinical Manifestations

- 1. CNS effects include:
 - a. Emotional lability and anxiety
 - b. Altered mental status
 - c. Seizures
 - d. Ataxia
- 2. Muscarinic effects include:
 - a. Nausea, vomiting, abdominal cramping and pain

- b. Diarrhea
- c. Pulmonary edema
- d. Bradycardia
- 3. Nicotinic side effects include:
 - a. Generalized weakness
 - b. Fasciculations
- 4. Peripheral neuropathy:
 - a. A distal sensory motor delayed polyneuropathy (OPIDP)
 - b. Evolves after several weeks from the initial exposure
 - c. Early symptoms include:
 - i. Cramping in calf muscles
 - ii. Paresthesias and burning of the feet
 - iii. Distal extremity weakness of the feet which over time evolves to affect the hands
 - iv. Hyperreflexia and increased tone develop from concomitant CNS involvement

Neuropathology

- 1. Nerve biopsy:
 - a. A distal axonopathy
 - b. Autopsied patient who died from Sarin poisoning:
 - i. Loss of myelinated and unmyelinated fibers in the sural and sciatic nerves
 - ii. Degeneration of fasciculus gracilis and the corticospinal tracts
- 2. Organophosphates inhibit neuropathy target esterase (NTE)
 - a. The cleavage of a side chain of NTE, which leads to neurotoxicity (requires time from the initial exposure)

Laboratory Evaluation

- 1. In the acute phase:
 - a. Repetitive firing of CMAPs from a single stimulus
 - b. Decrementing response to low rates of stimulation that may persist for 4 to 11 days
- 2. During OPIDPI
 - a. Decreased amplitudes of SNAPs and CMAPs most consistent with an axonal sensorimotor neuropathy

Hexacarbons (N-Hexane, Methyl-N-Butyl Ketone/Glue Sniffer's Neuropathy)

General Characteristics

- 1. N-Hexane and methyl-n-butyl ketones are industrial organic solvents
- 2. Inhalation is the usual route of exposure although they can be absorbed through the skin
- 3. Many patients have been exposed by glue sniffing

Clinical Manifestations

- 1. A subacute onset over 4 to 6 weeks of a severe sensorimotor neuropathy
- 2. The presentation is with numbness and tingling of the feet that evolves proximally to affect the upper and lower extremities

3. Progressive weakness of the extremities occurs; respiratory muscles are not affected
4. Loss of muscle stretch reflexes
5. High dose exposure has been associated with muscle wasting, weakness, foot drop, and spasticity

Neuropathology

1. Sural nerve biopsy:
 - a. Severe loss of myelinated fibers
 - b. Giant axonal swelling with secondary demyelination; giant axons demonstrate an accumulation of 10 nm neurofilaments
 - c. Hexacarbons putatively lead to cross-linking between axonal neurofilaments, aggregation and disrupted axonal transport

Laboratory Evaluation

1. EMG:
 - a. Prolongation of distal latencies, slowing of nerve conduction velocities and conduction block with temporal dispersion in some severely affected patients
2. "Coasting" occurs over 2 to 3 months followed by a slow recovery over 1 to 2 years

Styrene (Vinyl Benzene)

General Characteristics

1. Vinyl benzene is a colorless, oily liquid that is a component of paints, plastics, and resins

Clinical Manifestations

1. Altered mental status occurs with inhaled exposure over extended periods
2. Along with other organic solvents causes:
 - a. Corneal ulcers
 - b. Ventricular enlargement
 - c. Visual field deficits
 - d. Retinal lesions
 - e. Decreased visual acuity
 - f. Acquired dyschromatopsia
3. A primarily sensory neuropathy characterized by:
 - a. Burning pain and paresthesias in the legs
 - b. Loss of pain and temperature modalities, with only slight involvement of large fiber modalities
 - c. Strength is preserved
 - d. Muscle stretch reflexes are slightly depressed

Neuropathology

1. Nerve biopsy:
 - a. Axonal degeneration

Laboratory Evaluation

1. Slight reduction of motor nerve conduction velocities in the lower extremities
2. Features of a mixed axonal and/or demyelinating sensorimotor neuropathy

Lead

General Characteristics

1. Industrial lead exposure (burning batteries) and exposure to lead-containing products occur in adults
2. Children may be exposed by ingestion of lead-based paints in old buildings

Clinical Manifestations

1. In children who have been exposed, encephalopathy with increased intracranial pressure and seizures may be the presentation
2. Lead is associated with a primarily motor neuropathy:
 - a. Insidious onset of weakness
 - b. Early predilection for the wrist-finger extensors and wrist extensors that give the appearance of a radial palsy. It most often occurs in the dominant arm (acute intermittent porphyria also may appear first in the dominant arm)
 - c. May also cause foot drop
 - d. Weakness is frequently asymmetric
 - e. Sensation is most often preserved
 - f. Autonomic involvement is common with constipation and rarely severe hypertension
 - g. Decreased muscle stretch reflexes occurs
 - h. A lead line (bluish discoloration of the gums) is now rarely seen

Neuropathology

1. Sural nerve biopsy:
 - a. Loss of large myelinated axons
2. A possible toxic mechanism is its ability to substitute for other polyvalent cations, particularly divalent cations, such as calcium or zinc
3. Membrane ion channels and their signaling systems may be disrupted

Laboratory Evaluation

1. High serum lead levels
2. Microcytic hypochromic anemia with basophilic stippling of erythrocytes
3. Elevated serum coproporphyrin level
4. Urinary levels are elevated
5. EMG:
 - a. Denervation
 - b. Reduced CMAP amplitudes with normal SNAPs

Mercury

General Characteristics

1. Mercury neurotoxicity occurs from exposure both to organic or inorganic mercurials
2. Organic mercurials are methyl- or ethylmercury
3. Inorganic mercury is used primarily in industry and is composed of mercury salts that are ingested or inhaled
4. Methylmercury poisoning occurs from high consumption of seafood or primarily consumption of marine mammals from Arctic regions

Clinical Manifestations

1. Organic mercury intoxications causes:
 - a. Dysarthria
 - b. Ataxia
 - c. Decreased cognition
 - d. Visual and hearing loss
2. Peripheral neuropathy is characterized by:
 - a. Paresthesias of the distal extremities that evolves proximally and may involve the face and tongue
3. Inorganic mercury poisoning:
 - a. Entry may be inhalation or ingestion
 - b. Gastrointestinal symptoms and the nephritic syndrome predominate
 - c. Encephalopathy
 - d. Sensorimotor polyneuropathy

Neuropathology

1. Nerve studies:
 - a. Axonal degeneration
2. Autopsy studies (Minamata Bay series):
 - a. Cortical and cerebellar cortex degeneration
 - b. Loss of cells in the dorsal root ganglia
3. Amyloid protein aggregation in the cell nucleus may be a pathway for Hg-bio-interactions
 - a. Purified protein aggregates, spliceosomal components, and the nucleoskeletal protein lamin B1 constitutes components of an Hg-induced nuclear aggregate network; Hg enhances proteasomal activity in the nucleus; experimental evidence suggests that these interactions may be a component of Hg toxicity

Laboratory Evaluation

1. EMG:
 - a. Sensory NCS demonstrate slow low amplitude SNAPs and minimally slow conduction velocities
 - b. Motor conduction is normal or demonstrates borderline velocities
 - c. Needle EMG:
 - i. May demonstrate positive sharp waves or fibrillation potentials

Thallium*General Characteristics*

1. May be monovalent or trivalent
2. Primarily a rodenticide; food poisoning has been reported

Clinical Manifestations

1. First week of exposure:
 - a. Pigmentation of the hair
 - b. Arciform malar rash
 - c. Hyperreflexia
2. Second and third weeks following exposure:
 - a. Autonomic instability with varying heart rate and blood pressure

- b. Alopecia may only occur after the fourth week in a subset of patients
3. CNS manifestations include:
 - a. Increased thirst
 - b. Sleep alterations
 - c. Psychotic behavior
4. Burning paresthesias of the feet associated with abdominal pain and vomiting may be acute or appear after a few days
5. The peripheral neuropathy is characterized by:
 - a. Loss of pain and temperature

Laboratory Evaluation

1. EMG:
 - a. Early after exposure NCS may be normal
 - b. After 1 to 2 weeks there are low amplitude SNAPs and normal or decreased CMAP amplitudes

Arsenic*General Characteristics*

1. Industrial and agricultural exposure; chronic exposure a common problem in parts of South East Asia

Clinical Manifestations

1. System signs and symptoms:
 - a. Dermatologic involvement (exfoliative changes in palms and soles)
 - b. Mees lines in the nails (after 1–2 months of exposure)
 - c. Hepatomegaly occurs in approximately 1/3 of patients with chronic exposure
 - d. Alopecia in approximately 10% of patients with chronic exposure
 - e. Lung involvement in approximately 20% of patients with chronic exposure
2. Acute exposure:
 - a. Abdominal pain with nausea and vomiting, diarrhea
3. Peripheral neuropathy:
 - a. Starts 5 to 10 days after exposure
 - b. Burning pain in the distal extremities
 - c. Distal weakness evolves; after severe intoxication proximal muscles and cranial nerves are involved which can simulate Guillain-Barré syndrome
 - d. There may be respiratory compromise requiring ventilation
 - e. Muscle stretch reflexes are decreased or absent
 - f. Autonomic involvement occurs

Neuropathology

1. Sural nerve biopsy:
 - a. Axonal degeneration
 - b. Loss of large and small diameter myelinated fibers
 - c. Rare “onion bulb” formation
 - d. Loss of anterior horn cells

Laboratory Evaluation

1. Arsenic levels are increased in the urine, hair, and nails

2. Bone marrow depression with anemia and pancytopenia
3. Stippled erythrocytes
4. Increased CSF protein without pleocytosis
5. EMG:
 - a. Characteristics of an axonal neuropathy; some features of demyelination have been reported
 - b. Sensory NCS demonstrate low amplitude SNAPs with relative preserved distal latencies and conduction velocities
 - c. Conduction block and prolongation of F-wave latencies
 - d. Progressive deterioration of CMAPs with slowing of conduction velocities
6. Needle EMG:
 - a. Positive sharp waves and fibrillation potentials in distal muscles
 - b. Decreased number of motor units

Gold

General Characteristics

1. Gold salts have been primarily used for treatment of rheumatoid arthritis
2. Neuropathy usually occurs following several months of therapy

Clinical Manifestations

1. Rash and pruritus often are associated with the neuropathy
2. Presentation is usually with distal extremity paresthesias
3. Loss of all sensory modalities
4. Loss of muscle stretch reflexes
5. Myokymia and fasciculations may be prominent

Neuropathology

1. Sural nerve biopsy:
 - a. Axonal degeneration with segmental demyelination

Laboratory Evaluation

1. EMG:
 - a. Low amplitude or absent SNAPs
 - b. Myokymia and fasciculations may be demonstrated

Neuropathies Associated with Cancer

Overview

Peripheral neuropathies that occur in a setting of cancer may be caused by:

1. Metastasis
2. Primary tumors of the nerve or its sheaths
3. X-RT associated
4. Effects of chemotherapy
5. Dysproteinemic states
6. Paraneoplastic effects
7. Immune-mediated:
 - a. Immunosuppressive drugs

- b. Associated bone marrow transplantation
- c. Graft-versus-host disease

The incidence of peripheral neuropathy in patients suffering from cancer is estimated at between 15 to 30%. However, it is dramatically increased with electrophysiological testing and effects may be seen in between 30 to 40% of patients.

Paraneoplastic neuropathy is a possibility in all patients with malignancy and can occur at any stage of the illness, including after chemotherapy, radiation or stem cell transplantation. They are rare. The neuropathy may occur as an isolated finding or in combination with involvement in other areas of the peripheral or central nervous system. Loss of dorsal root ganglion cells due to CD8-positive cytotoxic T-cells that mediate the classic subacute sensory neuropathy. Patients may present with Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy as well as brachial and lumbosacral plexopathy, vasculitic neuropathy, autoimmune autonomic ganglionopathy and chronic intestinal pseudo-obstruction. Multiple onconeural antibodies that include anti-Hu, CV2/CRMP-5 and anti-ganglionic acetylcholine receptor are associated with these neuropathies. Neurologic signs and symptoms may precede the effects of the primary tumor. A paraneoplastic sensorimotor neuropathy may be similar to other forms of an axonal polyneuropathy.

Paraneoplastic Sensory Neuronopathy/Ganglionopathy

General Characteristics

1. Small cell cancer of the lung is most often the cause of paraneoplastic encephalomyelitis (PEM)/sensory neuronopathy (SN)
2. Other tumors associated with the syndrome include:
 - a. Esophageal
 - b. Breast
 - c. Ovarian
 - d. Kidney
 - e. Lymphoma

Clinical Manifestations

1. PEM/SN is most often seen in the sixth or seventh decade
2. There is a 2:1 ratio of women to men
3. The syndrome may precede the diagnosis of the underlying cancer; in general, the underlying cancer is diagnosed within 4–12 months after the onset of the neurological symptoms but, rarely, it may be several years before diagnosis
4. Presentation is most often with numbness and paresthesias of the distal extremities
5. In more than 50% of patients, symptoms may begin in the hands
 - a. Maybe asymmetric in 30–40%
6. The onset may be acute, but is most often insidiously progressive
7. All fiber modalities of sensation are affected and when severe proprioceptive loss causes sensory ataxia with

- pseudoathetosis to a greater degree than proprioception and vibration sensibility
8. Distal muscle atrophy and weakness evolve
 9. Loss of distal muscle stretch reflexes
 10. Other concomitant paraneoplastic syndromes may cause weakness and include:
 - a. Myelitis
 - b. Lambert-Eaton syndrome
 - c. Motor neuronopathy
 11. May be associated with components of autonomic neuropathy
 12. CNS signs and symptoms occur concomitantly in 20% of patients and include:
 - a. Memory loss, altered mental status, seizures
 - b. Brainstem dysfunction
 - c. Cerebellar signs occur in approximately 30% of patients
 - d. Cranial nerve involvement occurs in 15%; VIIIth nerve is often involved
 - e. Oculomotor abnormalities are seen in approximately 30% of patients
 - f. Myelitis occurs in approximately 15%

Neuropathology

1. Sural nerve biopsy:
 - a. Perivascular infiltration of T- and B-cells, macrophages and plasma cells
 - b. Degeneration of DRG sensory neurons and secondary degeneration of the posterior columns of the spinal cord
 - c. Inflammation of autonomic ganglia and the myenteric plexus
 - d. Deposition of anti-Hu antibodies
2. Putative mechanism is antigenic mimicry between proteins expressed on the surface of tumor cells and sensory neurons of the DRG and central neurons
3. There is correlation of high titer of anti-Hu antibodies in the CSF and serum titer correlates with the sensory neuropathy
 - a. Human studies suggest that the pathology is an antigen-driven cytotoxic T-cell response

Laboratory Evaluation

1. IgG polyclonal antineuronal antibodies are directed against a protein or a complex of proteins and are detected in the serum and CSF
2. Serum antibodies correlate with the sensory neuropathy; CSF antibodies correlate with paraneoplastic sensory neuropathy
3. CSF may demonstrate lymphocytic pleocytosis and elevated protein
 - a. Oligoclonal bands and IgG may be demonstrated in most patients

Neuroimaging

1. MRI:

- a. A subset of patients with concomitant paraneoplastic neuropathies have increased T2-weighted signal in the temporal and frontal lobes as well as periventricularly. There is frontal, temporal and cerebellar atrophy
2. EMG:
 - a. Low amplitude SNAPs
 - b. In the absence of motor neuronopathy or Lambert-Eaton syndrome, the CMAPs are normal

Differential Diagnosis of Sensory Neuropathy/Ganglionopathy

1. Anti-Hu paraneoplastic syndrome
2. Sjögren's syndrome
3. HIV
4. Chemotherapy (particularly cisplatinum)
5. Pyridoxine deficiency or excess
6. Anti-nucleoside toxicity
7. Guillain-Barré syndrome (Richter's variant)
8. Idiopathic sensory neuronopathy (possibly autoimmune)

Differential Diagnosis of Antibodies Associated with Sensory Neuronopathy

1. Anti-Hu
2. Anti-CV2
3. ANNA-3
4. Anti-Ma
5. Amphiphysin

Paraneoplastic Sensorimotor Polyneuropathy

General Characteristics

1. Associated with anti-CV2/CRMP antibodies (collapsing/response-mediating protein, CRMP-5)
2. CV2 antigen is found in the cytoplasm of oligodendrocytes
3. Most often seen with small cell cancer of the lung and thymoma

Clinical Manifestations

1. CNS involvement causes:
 - a. Limbic encephalitis
 - b. Cerebellar ataxia
 - c. Chorea
 - d. Uveo/retinal involvement
2. Peripheral neuropathy:
 - a. Primarily sensorimotor with moderate distal weakness
 - b. Motor involvement is greater in the lower than upper extremities
 - c. The peripheral neuropathy may be isolated in 30% of patients
 - d. Mononeuropathies occur (probably associated with vasculitis)

Neuropathology

1. Sural nerve biopsy:
 - a. Perivascular inflammation

- b. Loss of all sizes of myelinated fibers
- c. An axonal polyneuropathy has been described with CV2/CRMP-Ab
- d. Rare necrotizing vasculitis

Laboratory Evaluation

1. EMG
 - a. Low amplitude SNAPs with borderline slowing of conduction velocities; prolonged distal latencies
2. Motor NCS may be normal or only slightly involved
3. A demyelinating neuropathy has been described with melanoma

Differential Diagnosis Between Anti-Hu and Anti-CV2/CRMP Antibody Syndromes

1. CV2/CRMP
 - a. More frequent chorea, ataxia, uveo/retinal involvement and myasthenic symptoms
2. Anti-Hu antibody syndrome
 - a. More frequent brainstem encephalitis and peripheral neuropathy
3. Limbic encephalitis was similar

Paraneoplastic Autonomic Neuropathy

General Characteristics

1. Pandysautonomia may occur:
 - a. As an isolated phenomenon or associated with peripheral and CNS signs, due to the spectrum of anti-Hu immunity
2. Pandysautonomia is often severe, rare, and may present as an acute, subacute or chronic syndrome
3. Most commonly associated with small cell lung cancer, but has also been described with breast, ovarian, testicular, pancreatic and lymphoma malignancies

Clinical Manifestations

1. Orthostatic hypotension
2. Gastroparesis (when severe may cause pseudo-obstruction)
3. Urinary retention
4. Dry eyes and dry mucosal surfaces
5. Pupillary dysfunction
6. Hypohidrosis

Neuropathology

1. Inflammatory T-cell infiltrate in the DRG and autonomic ganglia (myenteric plexus)
2. Neuronal loss in autonomic ganglia
3. Antiganglionic acetylcholine receptor antibodies
4. CRMP-5 may be associated with an isolated neuropathy
5. Autoantibodies have been detected against a nuclear antigen of the myenteric neurons

Laboratory Evaluation

1. Detected autoantibodies including anti-Hu, anti-CRMP, anti-acetylcholine receptor, anti-neuronal (neurons of the myenteric plexus) and anti-VGKC
2. Abnormal autonomic testing

Idiopathic Sensory or Sensorimotor Polyneuropathy Associated with Cancer

General Characteristics

1. More common than paraneoplastic neuropathies
2. Most often associated with small cell cancer of the lung, but can be seen in a wide range of malignancies

Clinical Manifestations

1. Slowly progressive distal numbness in the lower extremities that evolves to affect the hands
2. All sensory modalities are affected
3. Minimal distal extremity weakness
4. Distal loss of muscle stretch reflexes

Neuropathology

1. Sural nerve biopsy:
 - a. Axonal degeneration with secondary segmental demyelination

Laboratory Evaluation

1. Anti-Hu, anti-CV2 and ANNA-3 antibodies have been detected
2. EMG:
 - a. Characteristics of a length dependent axonal, sensory or polyneuropathy
 - b. Decreased SNAP and CMAP amplitudes
 - c. Minimally prolonged distal latencies and reduced conduction velocities
 - d. Needle EMG:
 - i. Minimal distal muscle denervation

Tumor Infiltration of Peripheral Nerve

Leukemia

General Characteristics

1. Leukemic infiltration of peripheral nerve is rare and is designated as neuroleukemiosis
2. Peripheral neuropathy occurs in 5% of patients with leukemia

Clinical Manifestations

1. Symmetric sensorimotor polyneuropathy is rare
2. Mononeuropathy may present acutely, and mononeuropathy multiplex has been described
3. Brachial and lumbar plexopathy

Neuropathology

1. Axonal degeneration and segmental demyelination is the usual nerve pathology
2. Vasculitic neuropathy may occur with hairy cell leukemia
3. Root infiltration by leukemic cells
4. Acute hemorrhage occurs into nerves

Laboratory Evaluation

1. EMG:
 - a. Characteristics of a multifocal axonal sensorimotor neuropathy
 - b. Setting of chronic lymphocytic leukemia is most common; cases with myeloid and hairy cell leukemia have been described
- c. CSF:
 - i. Leukemic cell pleocytosis is seen with a moderate increase in protein
- d. Neuroimaging
 - i. Fluorodeoxyglucose (FDG) uptake that is useful for diagnosis and monitoring treatment

Large Cell Lymphoma*General Characteristics*

1. Intravascular large B-cell lymphoma is a rare extranodal lymphoma with exclusive intravascular tumor growth
2. In a third of patients, the disease starts with involvement of the nervous system; during the course of the illness, 2/3 of patients develop neurological signs

Clinical Manifestations

1. Peripheral nervous system involvement includes:
 - a. Progressive sensorimotor neuropathy
 - b. Guillain-Barré presentation
 - c. Focal peroneal or sciatic neuropathy
 - d. Relapsing neuropathy
 - e. Cauda equina syndrome
 - f. Multiple cranial neuropathies
 - g. 25% of patients develop a radiculopathy or polyradiculopathy
2. Approximately 50% of patients will demonstrate widespread systemic lymphoma

Neuropathology

1. Sural nerve biopsy:
 - a. Greater than 80% of patients demonstrate lymphomatous infiltrations, endoneurial involvement is greater than that in the perineum

Laboratory Evaluation

1. Absence of malignant cells in the peripheral blood or lymph nodes
2. Diagnosis is secured by demonstration of endoneurial lymphocytic B-cell infiltration

Differential Diagnosis of Lymphoma Related to Non-Tumor Associations

1. Irradiation
2. Chemotherapy
3. Paraneoplastic syndrome
4. Vasculitis
5. Immune antibody mechanisms

Lymphomatoid Granulomatosis (LYG)*General Characteristics*

1. Lymphomatoid granulomatosis is a rare angiocentric Epstein-Barr virus-associated B-cell lymphoproliferative disorder due to dysregulated immune surveillance of EBV

Clinical Manifestations

1. LYG may present with bilateral pulmonary nodules (same series 100% of patients)
2. Subcutaneous skin nodules
3. Renal nodules
4. Peripheral and cranial neuropathies
5. Peripheral nerve involvement:
 - a. Occurs in 10–15% of patients and is characterized by:
 - i. Distal symmetric polyneuropathy
 - ii. Mononeuropathy multiplex
 - iii. Polyradiculoneuropathies
 - iv. Cranial neuropathies (including optic neuropathy)

Neuropathology

1. Epstein-Barr virus (EBV), a member of the γ -herpes virus family, is pivotal in the pathology of some lymphomas and lymphoproliferative diseases. These include B-cell, T-cell, and NK cell processes
2. LYG is an angiocentric and angi destructive EBV-associated B-cell lymphoproliferative disorder. Its putative mechanism is dysregulated immune surveillance of the EBV
3. Almost all patients have had post EBV exposure, demonstrated by serologic testing, and carry a low median viral load
4. The angiocentric lesions demonstrate T-cells, large atypical B-cells and are positive for EBV
5. Sural nerve biopsy:
 - a. Perivascular infiltrates of the above cells in the epineurium
 - b. Necrosis and thrombosis of the vasa vasorum
 - c. Loss of axons between and within nerve fascicles due to ischemia

Laboratory Evaluation

1. Chest x-ray; almost 100% of patients have pulmonary nodules
2. Lesions biopsied demonstrate EBV and large atypical B-cells
3. EMG:
 - a. Demonstrate a multifocal axonal sensorimotor neuropathy

Infiltrating Tumors**Carcinomatosis of the Meninges***General Characteristics*

1. Results from diffuse or focal infiltration of the leptomeninges by malignant cells that originate from an extrameningeal primary tumor

2. Carcinomatosis of the meninges occurs in 5–10% of patients with solid tumors
3. The most common types of tumors seen with this form of metastasis are lung, breast, and melanoma. It has been seen in almost all type of tumors

Clinical Manifestations

1. Approximately 10 to 25% of patients with lung cancer may have leptomeningeal metastasis
2. The median survival is 4 to 6 weeks after diagnosis
3. Polyradiculopathy:
 - a. Radicular pain and sensory loss (may involve the trunk)
 - b. Weakness of specific roots
 - c. Most often there are decreased muscle stretch reflexes
4. Generalized spread can simulate a sensorimotor neuropathy
5. Concomitant spinal cord compression can lead to hyperreflexia and upper motor neuron signs
6. Cranial nerve involvement:
 - a. Metastasis most often involves the VIth, IIIrd, Vth, and VIIth cranial nerves
 - b. Nasopharyngiomas most commonly involve the Vth and VIth cranial nerves
 - c. “Numb chin” syndrome may occur with breast metastasis, from invasion of the mental or inferior alveolar nerves that derive from the mandibular branch of V
 - d. Most patients are lethargic; a subgroup that maintains consciousness have clear leptomeningeal involvement by neuroimaging
 - e. Central signs:
 - i. Headache (85%)
 - ii. Nausea and vomiting (58%)

Laboratory Evaluation

1. Classic CSF pattern is:
 - a. Pleocytosis of cancer cells
 - b. Elevated protein (80–150 mg/dl)
 - c. Sugar depressed, usually to 30–40 mg/dl
 - d. Neuroimaging:
 - i. MRI with gadolinium enhancement may have a sensitivity of greater than 90%
 - e. NMR metabolomics:
 - i. Myoinositol, creatine, lactate, alanine, and citrate are elevated in the nuclear magnetic spectra
 - f. The concentrations of CYFRA 21-1, NSE, and CEA in the CSF are indicators of meningeal carcinomatosis from lung cancer

Brachial Plexus Involvement by Cancer

General Characteristics

1. The brachial plexus is commonly involved in cancer due to the spread of local tumors, primarily lung, and breast
2. Delayed plexopathy occurs from radiation treatment
3. Sarcoma involving the brachial plexus may occur secondarily from regional breast irradiation

4. Anatomical spread of tumors is most often from the lymphatics to the lateral group of axillary lymph nodes to involve the divisions that form the lower trunk

Clinical Manifestations of Pancoast Tumors

1. Pancoast tumors (superior sulcus or apical lung tumors) involve the C8–T1 nerve roots, lower trunk of the plexus, the sympathetic chain, and often the stellate ganglion
2. The initial complaint is paresthesia or burning pain in the shoulder, and from the medial forearm to the fourth and fifth fingers
3. Weakness and atrophy of the hand evolves
4. A Horner’s syndrome (miosis, partial ptosis, anhidrosis of the face, and apparent enophthalmos) is common
5. The arm may be swollen from a combination of lymphedema and neurogenic edema (release of vasoactive neuropeptides and sympathetic nerve involvement)
6. Upper and middle trunk brachial plexus involvement is rare and is most often from the epidural extension of the tumor
7. The most common cause of Pancoast tumor is bronchogenic carcinoma of the lung

Radiation Plexitis

General Characteristics

1. XRT doses often exceed 6000 rads

Clinical Manifestations

1. The C5–C6 roots are most commonly involved
2. Paresthesias are the rule rather than pain; occurs in approximately 15% of patients
3. There is no Horner’s syndrome
4. Approximately 70% of patients have upper plexus involvement, and in 20%, diffuse involvement occurs
5. Symptoms are delayed from three months to years (mean of six years)

Neuropathology

1. Direct extension of cancer cells that encase the nerve roots, trunks, and cords of the plexus
2. Perineural spread of tumor cells
3. In patients treated with XRT, components of the plexus demonstrate demyelination and there is a proliferative endarteritis of the vasa vasorum

Laboratory Evaluation

1. MRI and CT:
 - a. Demonstrate anatomical abnormalities of the plexus and enhancement with gadolinium
 - b. Magnetic resonance neurography is able to differentiate neurogenic and non-neurogenic neoplasms
2. EMG:
 - a. Motor and sensory NCS demonstrate decreased amplitudes of SNAPs and CMAPs

- b. Myokymic discharges are noted in patients who have been irradiated

Lumbosacral Plexopathy from Cancer

General Characteristics

1. Perineural spread has been demonstrated from the prostate bed to the lumbosacral plexus; distal spread to the sciatic nerve and lumbosacral roots as well as intradural spread occurs
2. Bilateral neoplastic lumbosacral plexopathy may occur, utilizing the dural sac as a bridge to connect opposite sacral roots
3. There are multiple reports of carcinomatous involvement of the lumbosacral plexus, sciatic, obturator, pudendal, and spinal nerves. Recently reported patients with rectal cancer and perineural spread of cancer to the inferior hypogastric plexus by the conduits of the pelvic and sacral splanchnic nerves have been described
4. The most common tumors that affect the lumbosacral plexus are:
 - a. Colorectal
 - b. Cervical
 - c. Prostate
 - d. Breast
 - e. Lymphoma
 - f. Sarcoma
5. Distribution of lumbosacral involvements:
 - a. Lumbar plexus in 31%
 - b. Lumbosacral trunk in 5%
 - c. The entire lumbosacral plexus in 18%

Clinical Manifestations

1. Initiated by an insidious onset of pain, numbness, and paresthesias in root and nerve distributions of a lower extremity
2. Weakness and edema of the extremity evolve
3. 25% of patients have bilateral involvement
4. Bowel, bladder, or sexual dysfunction occurs in approximately 10% of patients

Radiation-Induced Plexopathy of the Lumbosacral Plexus

Clinical Manifestations

1. Delayed onset of between 1–3 years (mean is 5 years)
2. Insidious onset of a slowly progressive weakness of the affected muscle distribution, with appropriate loss of muscle stretch reflexes
3. Pain occurs in less than 50% of patients
4. Symmetric involvement of the lower extremities with distal > proximal muscle weakness
5. Bowel and bladder involvement occurs from both root and nerve injury, as well as radiation-induced proctitis or cystitis

Neuropathology

1. Radiation-induced demyelination and proliferative endarteritis of the vasa vasorum

Laboratory Evaluation

1. MRI or CT:
 - a. Enlargement of nerve roots and nerves from the infiltrating tumor
 - b. Gadolinium enhancement
 - c. Extension of tumor into the epidural space
2. EMG:
 - a. Paraspinal muscles demonstrate fibrillation potentials and positive sharp waves
 - b. Myokymic discharges are demonstrated in approximately 50% of patients

Secondary Non-Infiltrative Peripheral Neuropathies Associated with Lymphoproliferative Disorders and Plasmacytomas

Overview

1. Monoclonal gammopathies are detected in patients with peripheral neuropathy
2. Approximately 10% of patients with idiopathic peripheral neuropathies have monoclonal proteins, while only 2.5% of identified neuropathies (cause known) have these antibodies
3. The association of IgA and IgG antibodies to peripheral neuropathy is not clear
 - a. These antibodies are not deposited on nerve sheaths in patients with neuropathy, although they may be detected in the serum
4. IgM gammopathy is associated with a demyelinating sensorimotor polyneuropathy
5. Myeloproliferative disorders that may demonstrate a monoclonal gammopathy are:
 - a. Waldenström's macroglobulinemia
 - b. Osteosclerotic myeloma
 - c. Plasmacytoma
 - d. Multiple myeloma
 - e. Lymphoma
 - f. Leukemia
 - g. Cryoglobulinemia
6. Most patients with monoclonal gammopathies have no underlying myeloproliferative disorder and are designated monoclonal gammopathy of undetermined significance (MGUS)
7. Approximately 20% of patients with a monoclonal gammopathy may develop leukemia, lymphoma, myeloma, or plasmacytoma
8. Serum and urine protein electrophoresis are the screening tests for monoclonal gammopathies. In those patients in whom a myeloproliferative disorder is suggested, the more

sensitive immunoelectrophoresis or immune fixation studies are employed in the laboratory evaluation

Lymphoma

General Characteristics

1. Approximately 8% of lymphoma patients have clinical signs of neuropathy or radiculopathy, which is increased to 35% with electrophysiological testing
2. Neurolymphomatosis (NL) is the direct invasion of cranial or peripheral nerves or plexi by subtypes of non-Hodgkin's lymphoma
3. Hodgkin's and non-Hodgkin's lymphoma cause sensorimotor polyneuropathies
4. Lymphomas may affect any part of the nervous system, and can occur at any stage of the disease

Clinical Manifestations

1. The course may be acute, subacute, chronic progressive, or relapsing and remitting
2. Neuropathy patterns:
 - a. Sensorimotor (most common)
 - b. Pure sensory or motor
 - c. Rarely, severe autonomic features occur
 - d. CIDP pattern
 - e. Sensory ganglionopathy
 - f. Vasculitic neuropathy
 - g. Paraneoplastic neuropathy
 - h. Multiple mononeuropathies
 - i. Pain suggests neurolymphomatosis

Neuropathology

1. Sural nerve biopsy:
 - a. Neurolymphomatosis with direct invasion of lymphoma cells into the nerve is more prominent in the proximal portions of the nerve trunk
 - i. Demyelination without macrophage invasion, and associated axonal degeneration distal to the site of demyelination
 - b. Endoneurial inflammation
 - c. Features of chronic inflammatory demyelinating polyneuropathy

Laboratory Evaluation

1. CSF:
 - a. Lymphocytic pleocytosis (frequently 50–100 cells/mm³)
 - b. Increased protein
2. EMG:
 - a. Reduced amplitudes of SNAPs and CMAPs with normal conduction velocities
 - b. CIDP pattern:
 - i. Prolonged distal and F-wave latencies
 - ii. Slow conduction velocities
 - iii. Temporal dispersion
 - iv. Conduction block

Multiple Myeloma

General Characteristics

1. Multiple myeloma-related peripheral neuropathy may occur in up to 54% of patients, due to the disease or as a complication of treatment
2. New antimyeloma medications can trigger or exacerbate a pre-existing neuropathy (occurs in 3–13% of untreated patients, although up to 40% may show a subacute neuropathy by electrodiagnostic testing)

Clinical Manifestations

1. Multiple myeloma occurs primarily in the fifth through seventh decade
2. Systemic signs and symptoms include:
 - a. Bone pain
 - b. Fatigue
 - c. Anemia
 - d. Hypercalcemia
3. Peripheral neuropathy patterns:
 - a. Distal axonal sensory or sensorimotor polyneuropathy
 - b. Chronic demyelinating polyneuropathy
 - c. May be associated with amyloid polyneuropathy that is suggested by:
 - i. Loss of small fiber modalities of pain and temperature
 - ii. Painful paresthesias of the distal extremities
 - iii. Autonomic dysfunction
 - iv. Carpal tunnel syndrome
 - v. Enlarged plasmacytoma that can involve cranial nerves, spinal roots and occasionally intracranial structures

Neuropathology

1. Sural nerve biopsy:
 - a. Amyloid deposition occurs in 2/3 of patients
 - b. Axonal degeneration and segmental demyelination

Laboratory Evaluation

1. Monoclonal protein abnormalities detected in the serum or urine
2. Mild to moderate anemia and hypercalcemia
3. Osteolytic lesions of the spine and long bones; may have collapsed vertebrae with spinal cord compression (three or more contiguous vertebral body involvement suggests multiple myeloma rather than metastasis)
4. Bone marrow biopsy demonstrates at least 10% plasma cells
5. EMG:
 - a. Sensory and motor NCS reveal decreased amplitudes with normal or minimally prolonged distal latencies and conduction velocities
 - b. Common carpal tunnel median nerve compression
6. 18F-FDG PET is excellent for diagnosis and monitoring treatment

POEMS Syndrome (Osteosclerotic Myeloma)*General Characteristics*

1. POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) is a multisystemic disorder associated with osteosclerotic myeloma (a variant of plasma cell dyscrasia)
2. POEMS is seen in approximately 3% of myelomas
3. Approximately 50% of patients develop a peripheral neuropathy, which may be the presenting symptom
4. Most patients do not have all the features of the disease
5. The syndrome can occur with Castleman's disease, although the great majority of patients have osteosclerotic myeloma. It has been described with Waldenström's macroglobulinemia, extramedullary plasmacytoma, and rarely with no discovered malignancy
6. The major criteria include:
 - a. Polyradiculoneuropathy
 - b. Clinical plasma cell disorder (PCD)
 - c. Sclerotic bone lesions
 - d. Elevated vascular endothelial growth factor (VEGF)
 - e. Presence of Castleman's disease
7. Minor criteria:
 - a. Organomegaly
 - b. Endocrinopathy
 - c. Skin changes
 - d. Papilledema
 - e. Extravascular overload
 - f. Thrombocytosis

Clinical Manifestations

1. Systemic signs:
 - a. Hepatosplenomegaly
 - b. Cutaneous pigmentation
 - c. Hypertrichosis
 - d. Severe edema
 - e. Pericardial and pleural effusions
 - f. Clubbing
 - g. Gynecomastia
 - h. Testicular atrophy
 - i. Amenorrhea
 - j. Diabetes mellitus
 - k. Hypothyroidism
 - l. Endocrinopathy (hyperprolactinemia)
2. Pattern of peripheral neuropathy:
 - a. Symmetric distal lower extremity paresthesias, numbness, and weakness
 - b. Gradual spread to proximal-distal upper extremity muscles
 - c. Primarily affects large fiber sensory modalities
 - d. Loss of muscle stretch reflexes
 - e. Cranial nerves and muscles of respiration may be affected
 - f. Papilledema occurs in 30–55% of patients
 - g. Patients may develop an inflammatory myopathy or a proximal myopathy from hypothyroidism

Neuropathology

1. Sural nerve biopsy:
 - a. Combination of segmental demyelination and axonal degeneration
 - b. Endomysial perivascular cell infiltration
 - c. High expression of VEGF in blood vessels and non-myelin-forming Schwann cells
 - d. Increased thickness of the basal lamina of the vasa vasorum
 - e. Electron microscopy:
 - i. Proliferation of endothelial cells
 - ii. Separation of tight junctions
 - iii. Demonstration of uncompacted myelin

Laboratory Evaluation

1. The monoclonal gammopathies are usually of immunoglobulin (Ig) type A with lambda light chain restriction (in multiple myeloma (MM) the light chains are of the kappa type)
2. Rare Bence-Jones protein in the urine (common with MM)
3. Bone marrow biopsy reveals less than 5% plasma cells
4. The monoclonal protein is low and is best demonstrated with immunofixation; in 15% of patients, it is not detected, although biopsy of a sclerotic lesion may be positive
5. Increased levels of VEGF and IL1B, TNF-alpha and IL-6
6. In 20% of patients, erythropoietin clonal protein is detected in the urine but not in the serum
7. CSF:
 - a. Greatly elevated protein (greater than in CIDP)
8. Skeletal X-ray survey:
 - a. Lesions are usually found in the vertebral bodies and ribs; occasionally in the pelvis
 - b. In 50% of patients, there are multiple lesions (focal plasmacytomas)
 - c. X-ray evaluation of bone lesions:
 - i. A radiolucent central component ringed by a sclerotic margin (pure osteolytic lesion in MM)
 - ii. Lesions may precede clinical symptoms; rare cranial lesions
9. EMG:
 - a. NCS are similar to CIDP but with less conduction block
 - b. Characteristics of a demyelinating neuropathy or a mixed axonal and demyelination neuropathy

Castleman's Disease (Angiofollicular Lymph Node Hyperplasia)*General Characteristics*

1. Castleman's disease is a rare lymphoproliferative disorder characterized by enlarged hyperplastic lymph nodes that mimic lymphoma
2. It has several histologic variants that include:
 - a. Hyaline vascular plasma cell

- b. Plasma cell
- c. Mixed types

Clinical Manifestations

1. Localized or unicentric form: indolent
2. Multicentric systemic form: usually involves the plasma cell variant
3. Systemic manifestations include:
 - a. Diffuse lymphadenopathy
 - b. Hepatosplenomegaly
 - c. Fever
 - d. Night sweats
 - e. Fatigue
4. CNS complications:
 - a. Intracranial extra-axial lesions that simulate meningiomas and may cause seizures; one report of limbic encephalitis; rare optic neuropathy
 - b. Associated with POEMS syndrome:
 - i. Similar but less severe peripheral neuropathy; usually a mild sensory predominant neuropathy
 - c. Associated with:
 - i. Paraneoplastic pemphigus
 - ii. Systemic lupus erythematosus
 - iii. Rheumatoid arthritis
 - iv. Myasthenia gravis

Neuropathology

1. Herpes virus 8 has been associated with the plasmablastic variant
2. These patients are at risk for Kaposi sarcoma, lymphoma, and follicular dendritic cell tumors
3. Polyclonal lymphocyte and plasma cell proliferation induced primarily by IL-6
4. Human herpes virus 8 (HHV-8) drives the hypercytokinemia in most HIV-positive patients and a subgroup of HIV-negative patients
5. Reactivated HHV-8, in immunosuppressed patients, induces IL-6 that stimulates B-cell proliferation and lymphoid hyperplasia

Laboratory Evaluation

1. Increased VEGF and IL-6 in the serum
2. No osteosclerotic lesions on skeletal survey
3. EMG:
 - a. Similar to POEMS (but less severe)
4. Differences from lymphoma by CT:
 - a. Calcification (with Castleman's disease) in 30%
 - b. Heterogeneous enhancement in 20%
5. MRI:
 - a. Nodes are hypointense to isointense on T1-weighted sequences; isointense to hyperintense on T2-weighted images. All patients demonstrate homogeneous enhancement with gadolinium F¹⁸-2DG
 - i. Nodes were avid

Waldenström's Macroglobulinemia and IgM-MGUS

General Characteristics

1. Defined by WHO and the revised European-American Lymphoma Association as a bone marrow infiltrated lymphoplasmacytic lymphoma and IgM paraproteinemia
2. Occurs in approximately 2% of patients with monoclonal gammopathies
3. Approximately 80% are associated with a K light chain
4. Waldenström's macroglobulinemia is differentiated from IgM myeloma by:
 - a. Absence of lytic lesions in bones
 - b. No hypercalcemia
 - c. Evidence of hepatosplenomegaly and lymphadenopathy
 - d. There are similarities to IgM-MGUS

Clinical Manifestations

1. Age of onset is between 50 to 70 years in men > women
2. Systemic symptoms include:
 - a. Progressive fatigue
 - b. Weight loss
 - c. Lymphadenopathy
 - d. Hemorrhages (nose bleeds; petechial hemorrhages below the knees; platelet dysfunction due to coating by IgM protein)
 - e. Hepatomegaly and splenomegaly
3. Peripheral neuropathy:
 - a. Insidious onset of paresthesias in the distal lower extremities which evolves proximally, and goes on to involve the distal upper extremities
 - b. Sensory ataxia
 - c. Minimal distal extremity weakness
 - d. Loss of muscle stretch reflexes
 - e. Gait instability and loss of fine movements in the fingers due to sensory loss

Neuropathology

1. Sural nerve biopsy:
 - a. IgM deposition on the outer myelin membranes
 - b. Rare deposition in the periaxonal space; no deposition on compact myelin
2. Neuropathy may be associated with concurrent:
 - a. POEMS
 - b. Secondary amyloidosis
 - c. Vasa vasorum ischemia due to serum hyperviscosity
 - d. Neurolymphomatosis

Laboratory Evaluation

1. Serum IgM monoclonal protein in a concentration greater than 3 g/L
2. Antibodies against myelin-associated glycoprotein (MAG) or sulfatide occur in some patients
3. Bone marrow biopsy:
 - a. Infiltrated by lymphoplasmacytic lymphoma

4. EMG:
 - a. Usually, features of a demyelinating sensorimotor neuropathy are demonstrated
 - b. An axonal sensorimotor neuropathy is sometimes seen

Monoclonal Gammopathy of Undetermined Significance (MGUS)

General Characteristics

1. Monoclonal gammopathy of undetermined significance (MGUS) is a common premalignant condition
2. It affects approximately 3.5% of the population older than 50 years of age
3. IgG and IgA MGUS are defined:
 - a. An M protein less than 30 g/L
 - b. Bone marrow plasma cell percentage of less than 10%
 - c. Absence of signs and symptoms of other lymphoproliferative malignancies that include:
 - i. Multiple myeloma
 - ii. Waldenström's macroglobulinemia
 - iii. Immunoglobulin light-chain (AL) amyloidosis
 - iv. Chronic lymphocytic leukemia
 - v. B-cell lymphoma
4. IgA or IgG MGUS have an increased risk of progression to multiple myeloma
5. IgM-MGUS may progress to Waldenström's or other lymphoproliferative disorders
6. Light-chain MGUS may progress to light-chain multiple myeloma; it has a prevalence of 0.7–0.8% in persons over 50 years of age
7. Progression of MGUS to MM is approximately 1% per year
8. The disappearance of the M-protein occurs in approximately 2–5% of patients with MGUS
9. Secondary MGUS:
 - a. Refers to the emergence of a new monoclonal gammopathy of an isotype distinct from the original multiple myeloma (MM) during its course; it occurs in 10–73% of MM patients after autologous stem cell transplantation and 1.6–33% of non-transplant patients

Clinical Manifestations

1. Neuropathies associated with an IgM monoclonal protein are primarily demyelinating
2. IgA or IgG monoclonal gammopathies can be either axonal or demyelinating
3. Demyelinating neuropathies:
 - a. May present with proximal and distal weakness
 - b. Primarily large fiber sensory modality loss
 - c. Similar to CIDP
 - d. Distal symptoms similar to DADS (distal acquired demyelinating sensory neuropathy)
4. Numbness, paresthesias and tingling distally, in both upper and lower extremities that evolve proximally
5. IgM-MGUS has weakness of primarily the distal extremities

6. IgG and IgA have more symmetrical proximal and distal weakness
7. Muscle stretch reflexes are depressed or absent throughout
8. Axonal neuropathy patients are indistinguishable from idiopathic sensorimotor polyneuropathies
9. Length-dependent sensory neuropathy

Neuropathology

1. Nerve biopsy:
 - a. Primarily loss of large diameter myelinated fibers, with minimal involvement of thinly myelinated and unmyelinated fibers
 - b. A subgroup of patients demonstrates demyelination and remyelination
 - c. IgM-MGUS:
 - i. Immunoglobulin deposition on the outer myelin membranes, minimal involvement of the periaxonal spaces, and no deposition on compact myelin
 - ii. Electron microscopy:
 1. Separation of myelin sheaths with IgM deposits in areas of myelin splitting

Associated MGUS Medical Conditions

1. Possibly related to MGUS by clone-related alterations in the bone marrow microenvironment:
 - a. Suppression of normal plasma cells
 - b. Depressed osteoblast activation
2. Infection:
 - a. Increased risk of bacterial and viral infection
 - i. Relative immune deficiency due to low levels of normal immunoglobulins
 - ii. Lower absolute number of CD4⁺ and CD8⁺ T-cells
3. Osteoporosis:
 - a. MGUS patients have an increased risk of fractures
 - b. The prevalence of MGUS is higher in patients that present with acute vertebral fractures from osteoporosis
 - c. Altered bone microstructure:
 - i. Biochemical markers of bone formation are reduced, and markers of resorption are increased
 - ii. Possibly related to elevated levels of DKK1 (a Wnt pathway inhibitor) that decrease bone formation
4. Progression to malignancy:
 - a. There is a 2 to 8 fold risk of progression to myeloid malignancies that include:
 - i. Myelodysplastic syndrome
 - ii. Acute myeloid leukemia
 - iii. Polycythemia vera
 - b. Risk factors:
 - i. M-protein > 15 mg/L
 - c. MGUS patients have a slightly higher risk of developing non-hematologic malignancies
5. Thrombosis:
 - a. MGUS patients have a 2 to 3 times higher risk of developing deep vein thrombosis and pulmonary emboli

- b. Possible increased risk of arterial thrombosis:
 - i. Increased factor VIII and von Willebrand factor levels are similar to those of MM
- c. The increased prothrombotic risk is only seen in IgG and IgA isotypes

M-Protein Related Medical Complications

1. Clonal MGUS may cause organ damage by:
 - a. Production of an M-protein with autoantibody characteristics
 - b. Deposits of the protein in tissues that occur with:
 - i. AL amyloidosis
 - ii. Monoclonal immunoglobulin deposition disease
 - iii. Type I cryoglobulinemia

Laboratory Evaluation

1. Approximately 50% of patients with IgM-MGUS neuropathy have antibody titers against myelin-associated glycoprotein (MAG)
2. M-protein concentration of 15 g/L helps to discriminate between MM and non-myeloma patients
3. Bone lesions are rare with IgG or IgA isotypes on skeletal survey
4. Bone marrow examination is suggested for patients with IgA and IgM M-proteins
5. CT of the chest, abdomen, and pelvis for IgM-MGUS
6. Elevated CSF protein may be seen with IgM-MGUS
7. EMG:
 - a. IgM neuropathies demonstrate demyelinating features:
 - i. Prolonged distal latencies
 - ii. Moderately slow conduction velocities
 - b. NCS in patients with IgG or IgA MGUS may be axonal or demyelinating

Differential Diagnosis of Peripheral Neuropathies with Monoclonal Protein

1. Cryoglobulinemia (mixed):
 - a. Raynaud's phenomena
 - b. Acrocyanosis
 - c. Subacute painful multiple mononeuropathies
 - d. Positive for hepatitis C-virus
2. AL amyloidosis:
 - a. Insidious onset of a symmetric painful autonomic and sensorimotor neuropathy
3. POEMS:
 - a. Insidious demyelinating polyradiculopathy
 - b. Diabetes, hypothyroidism, testicular atrophy, amenorrhea
 - c. Skin and nail changes
 - d. Severe peripheral extremity edema
4. IgM-MGUS:
 - a. Insidious painless distal sensory ataxic neuropathy
 - b. Demyelinating
5. Waldenström's macroglobulinemia:

- a. Numbness of the distal lower extremities
- b. Tumor (sensory loss)
- c. Positive Romberg sign
- d. Bleeding disorder; nosebleeds and petechiae in the distal lower extremities
- e. More axonal than demyelinating features on EMG; IgM-MGUS demonstrates greater demyelinating features

Graft-Versus-Host Disease

General Characteristics

1. Graft-versus-host disease (GVHD) is a systemic immune-mediated disease
2. The leading morbidity after allogeneic hematopoietic stem cell transplantation
3. Neurological complications may occur in as many as 64% of long-term survivors of allo-HSCT, and are associated with:
 - a. Long-term immunosuppression
 - b. GVHD
 - c. Chemotherapy
 - d. Infection
 - e. Radiation
 - f. Autoimmunity

Clinical Manifestations of GVHD

1. Cranial neuropathies (often loss of taste and smell)
2. Sensorimotor polyneuropathy
3. Multiple mononeuropathies
4. Guillain-Barré syndrome
5. CIDP and brachial plexopathy
6. Peripheral neurologic involvement usually has a delayed onset
 - a. Occurs most commonly in setting of chronic GVHD
7. May be associated with muscle cramps

Neuropathology

1. Sural nerve biopsy:
 - a. Vasculitis
 - b. Infiltration of T-cells and immunoglobulin deposits
 - c. Perineural fibrosis
 - d. Loss of myelinated fibers

Laboratory Evaluation

1. EMG:
 - a. NCS may demonstrate demyelinating, axonal, or mixed characteristics

Chemotherapy-Induced Peripheral Neuropathy (CIPN)

Overview

The primary chemotherapeutic agents used in practice cause toxic peripheral neuropathy and include taxanes, platinum

compounds, vinca alkaloids and proteasome inhibitors, and anti-angiogenic immunomodulatory agents. Only a proportion of chemotherapy-treated patients develops persistent CIPN, which is greater in patients with pre-existing neuropathic, diabetes and Charcot-Marie-Tooth disease. CIPN is often dose limiting and can persist and worsen long after cessation of chemotherapy. CIPN often affects the DRG (a less stringent blood-nerve barrier) but also affects nerve terminals as well as the axon. Clinical features depend on the chemotherapeutic agent and its site of action.

Taxanes (Paclitaxel)

General Characteristics

1. Paclitaxel (Taxol®) is more neurotoxic than docetaxel
2. It has an incidence of up to 85% of a subclinical or mild neuropathy often to 3 to 7 cycles of Taxol at doses of 135–200 mg/m²; doses between 250 and 350 mg/m² patient may be symptomatic after the first or second cycle
3. Approximately 70% of patients have a severe neuropathy; only 2% develop severe neuropathy with ten doses
4. Risk factor for developing a severe neuropathy are:
 - a. A cumulative dose of 1500 mg/m²
 - b. A pre-existing neuropathy
 - c. Concurrent exposure to neurotoxic agents
5. The neurotoxic threshold for paclitaxel is 1000 mg/m²
6. Duration of infusion (1 to 3 hours per 24 hours)

Clinical Manifestations

1. Paresthesias, numbness, and at times, neuropathic pain, develop in a length-dependent manner
2. Loss of large myelinated fiber modalities of sensation
3. Minimal distal extremity weakness
4. Loss of muscle stretch reflexes
5. Signs and symptoms usually improve with cessation of chemotherapy

Neuropathology

1. Final nerve biopsy:
 - a. Primary loss of large diameter myelinated nerve fibers
 - b. Axonal degeneration with secondary demyelination and remyelination
 - c. Disruption of microtubule-based axonal transport by:
 - i. Increasing microtubule assembly by inducing polymerization
 - ii. Aggregation and accumulation of bundles of microtubules in DRG sensory neurons, axons, and Schwann cells
 - d. Nociceptor Beta 11, delta and epsilon isoforms of PKC differentially mediate paclitaxel in clinical spontaneous evoked pain
 - e. Paclitaxel is also associated with the induction of chemokine monocytes chemoattractant protein-1 (MCP-1) and its receptor CCR2 in primary sensory nerves of the DRG

Laboratory Evaluation

1. Electron microscopy:
 - a. Accumulation of tubercular and membranous structure within axons

Docetaxel (Taxotere®)

General Characteristics

1. Docetaxel is a semisynthetic analog of Taxol
2. Utilized for a wide range of malignancies
3. Cumulative dose of 400 mg/m² is the neurotoxic threshold

Clinical Manifestations

1. Primarily a sensory neuropathy that is less severe than that seen with Taxol
2. Pain in the extremities
3. Lhermitte's sign
4. Large fiber sensory modalities are primarily affected
5. Decreased or absent ankle reflexes
6. Between 5 to 19% of patients have mild distal extremity weakness
7. Many patients improve after 1 to 2 months following treatment, but "slide" (continuing worsening) can occur

Neuropathology

1. Serial nerve biopsy
 - a. Loss of large diameter myelinated fibers
 - i. Axonal degeneration

Laboratory Evaluation

1. NCS studies reveal decreased SNAPs and CMAPs with minimal slowing of conduction velocities

Platinum Compounds

General Characteristics

1. Cisplatin has evidence of peripheral neuropathy in approximately 60% of patients that receive a cumulative dose of 225–500 mg/m²
2. The combination of cisplatin/paclitaxel is additive in causing neuropathy

Clinical Manifestations

1. Predominant sensory neuropathy involving large myelinated fibers and primarily affecting proprioception and vibration in sensibilities
2. Distal extremity paresthesia and hypoaesthesia
3. Gait ataxia and pseudoathetosis
4. Approximately 2% of patients develop weakness
5. Approximately 40% of patients demonstrate Lhermitte's sign
6. Onset of symptoms may be delayed as long as 8 weeks after cessation of therapy and "coasting" can occur for up to six months
7. Generalized loss of muscle stretch reflexes

Neuropathology

1. Sural nerve biopsy:

- a. Predominant loss of large diameter myelinated fibers
- b. Axonal degeneration with sign of sprouting
- c. Segmented demyelination
- d. Ganglionopathy with loss of large sensory neurons
- e. Autopsy studies:
 - i. The DRG is primarily affected by deposition of platinum compounds
 - ii. Suggested mechanism of toxicity:
 1. Alteration of the tertiary structure of DNA:
 - a. Formation of intrastrand adducts
 - b. Interstrand crosslinks
 2. Neuronal apoptosis of sensory neurons in the DRG induced by oxidative stress, mitochondrial dysfunction or by increased activation of p53, p38 and ERK 1/2

Laboratory Evaluation

1. EMA:
 - a. Low amplitude or unobtainable SNAPs
 - b. Normal or slightly prolonged distal latencies
 - c. Normal CMAPs
 - d. Minimal prolonged sensory latencies and slowed conduction velocities
2. QST
 - a. Abnormal vibrating thresholds

Oxaliplatin

General Characteristics

1. There are two distinct forms of toxicity:
 - a. Acute or chronic
 - b. Due to specific aspects of neurotoxicity
2. The vast majority of patients treated with oxaliplatin-based regimens that have between 85–130 mg/m² exposure develop some form of neurotoxicity
3. Severe acute OXLIPN (oxaliplatin-induced peripheral neuropathy) occurs in approximately 22% of patients
 - a. Major risk factors are:
 - i. Cold temperature
 - ii. Time of the infusion
4. Chronic oxaliplatin-induced neurotoxicity is found in 60 to 70% of patients that are treated with oxaliplatin-based regimens that include:
 - a. FOLFOX4
 - b. FOLFOX6
 - c. XELOX
5. Risk factors for chronic oxaliplatin neuropathy are:
 - a. Cumulative dose
 - b. Time of infusion
 - c. Prior peripheral neuropathy
 - d. Chemotherapy regimen

Clinical Manifestations

1. Signs and symptoms of acute OXLIPN may start during or within 1 to 2 days of the infusion

2. Primarily, there are distal and perioral cold-induced paresthesias and dysesthesias
3. Clinical symptoms include:
 - a. Shortness of breath
 - b. Jaw spasm
 - c. Fasciculations
 - d. Cramps
 - e. Difficulty swallowing
 - f. Voice and visual changes
 - g. Ptosis and pseudolaryngospasm

Neuropathology

1. Chronic sensory form:
 - a. Due to degeneration of sensory neurons in the DRG from local deposition and accumulation of oxaliplatin
2. Acute form:
 - a. Dysfunction of nodal axonal voltage-gated sodium channels due to oxalate chelating effects on Ca²⁺ and Mg²⁺

Laboratory Evaluation

1. EMG:
 - a. Repetitive CMAPs
 - b. High-frequency discharge of motor unit
 - c. Neuromyotonia

Suramin

General Characteristics

1. Suramin is a hexasulfonated naphthyl urea
2. The most common dose-limiting side effects are fatigue, anorexia, and peripheral neuropathy
3. 1440 mg/m² appears to be the maximal tolerated dose
4. Peripheral neuropathy occurs in 25 to 90% of patients

Clinical Manifestations

1. Distal axonopathy form of toxicity:
 - a. Distal numbness and paresthesias
 - b. Mild weakness of the distal extremities
 - c. Reduced light touch pain, vibration, and proprioceptive sensibility
 - d. Diminished or absent ankle reflexes
 - e. This form of the neuropathy is reversible
2. A subacute sensorimotor demyelinating neuropathy:
 - a. More severe than axonal neuropathy
 - b. Develops in 10 to 20% of patients
3. Different protocols for administration are used; neuropathy occurs with:
 - a. Usually 1 to 5 months of treatment
 - b. Peak plasma concentrations of >300 mg/m² or exposure to 200 mg/m² for more than 25 days a month
 - c. Cumulative dose of 40,000 mg-h/L
 - d. Presentation is numbness and paresthesias of the distal extremities and face
 - e. Proximal > distal extremity weakness

- f. Absent muscle or stretch reflexes throughout
- g. Weakness progresses and a significant number of patients require mechanical ventilation
- h. The neuropathy can “coast” for approximately one month following cessation therapy
- i. Recovery occurs to some degree over months often with residual deficits

Neuropathology

1. Sural nerve biopsy:
 - a. Patients with demyelination neuropathy:
 - i. Loss of both large and small myelinated fibers
 - ii. Demyelination and remyelination with secondary axonal degeneration
 - iii. Mononuclear inflammatory infiltrates of the epi and endoneurium
 - iv. Glycolipid lysosomal inclusions in axons (produced in experimentally exposed animals)
 - v. Competition between the agent and nerve growth factor at the high-affinity NGF receptor

Laboratory Evaluation

1. CSF:
 - a. Elevated protein access with the subacute demyelinating polyradiculoneuropathy
 - b. Minimal reduction of distal latencies and conduction velocities
2. EMG:
 - a. In patients with axonal form:
 - i. Decrease SNAPs and CMAPs amplitudes
 - ii. Minimal reduction of distal latencies and conduction velocities
3. QST of axonal pathology
 - a. Abnormal vibration and cooling thresholds
4. Needle EMG:
 - a. Positive sharp waves, fibrillation potentials and neurogenic MUAPs are demonstrated in affected distal musculature
5. Subacute demyelinating polyradiculoneuropathy:
 - a. Slow conduction velocities
 - b. Prolonged distal latencies including F waves
 - c. Temporal dispersion
 - d. Conduction block
6. QST
 - a. Increased vibratory and cold thresholds

Etoposide (VP-16®)

General Characteristics

1. VP-16 is a semisynthetic derivative of podophyllotoxin whose effect may be due to nucleolar disruption and apoptosis due to individual DNA damage
2. Approximately 4 to 10% of patients suffer a neuropathy

Clinical Manifestations

1. Length-dependent primarily sensory axonal neuropathy

2. Severe autonomic neuropathy associated with orthostatic hypotension and gastrointestinal symptomatology

Neuropathology

1. Experimental models demonstrate loss of neurons in the DRG
2. Blockage of RNA polymerase-1-driven transcription
3. Acts as a topoisomerase inhibitor
4. The DNA damage induced by the drug has been suggested to cause reduced ribosomal biogenesis

Laboratory Evaluation

1. EMG:
 - a. JNCs demonstrate low amplitude SNAPs and CMAPs

Vinca Alkaloids

General Characteristics

1. Toxic effects of vincristine are usually evident after a cumulative dose of 12 mg; however, the neuropathy has been reported as early as two weeks after a single 2 mg/m² dose
2. “Coasting” often occurs in 24 to 30% of patients for several weeks following cessation of therapy
3. Symptoms remain for approximately three months following therapy

Clinical Manifestations

1. Initially, patients suffer numbness and paresthesias in the distal extremities. The upper extremity may be affected first
2. In 25 to 35% of patients, there is distal extremity weakness with accumulating dosage
3. Autonomic neuropathy is common and causes:
 - a. Orthostatic hypotension
 - b. Gastrointestinal symptomatology
 - c. Urinary retention
 - d. Impotence
4. Cranial neuropathies are uncommon but include:
 - a. Optic neuropathy
 - b. Oculomotor dysfunction
 - c. VIIth cranial nerve paralysis
 - d. Laryngeal weakness
5. A subset of patients has painful paresthesias and hyperesthesia
6. There is generalized diminution or loss of muscle stretch reflexes

Neuropathology

1. Serial nerve biopsy:
 - a. Loss of myelinated and unmyelinated nerve fibers
 - b. Axonal degeneration with clusters of regenerating axonal sprouts
2. Interferes with both fast and slow axonal transport at the level of the cell body and alters cellular microtubular structure; binds to tubulin

Laboratory Evaluation

1. NCS demonstrate:

- a. Axonal sensorimotor peripheral neuropathy
- b. Decreased amplitude of SNAPs and CMAPs
- c. Normal or minimally prolonged latencies and mildly slow nerve conduction velocities
2. Needle EMG:
 - a. Positive sharp waves and fibrillation potentials in affected muscles
3. QST:
 - a. High vibration threshold
4. Inherited polymorphism of the promoter of CEP72 may cause increased risk of neuropathy

Vinorelbine

General Characteristics

1. Vinorelbine is a semisynthetic vinca alkaloid that is used most often in combination for a variety of cancers
2. Causes a dose-related peripheral neuropathy in 20 to 50% of patients
3. Less neurotoxic than vincristine
 - a. A severe neuropathy has been described in 1% of patients

Clinical Manifestations

1. Usual presentation is a distal sensory loss with paresthesias
2. Distal muscle weakness may occur after 3 to 6 months of treatment
3. Autonomic neuropathy may occur but is less severe than that which occurs with vincristine
4. Usually, there is diminution of muscle stretch reflexes with their loss at the ankles

Neuropathology

1. Nerve biopsy results are not available

Laboratory Evaluation

1. Decreased SNAP and CMAP amplitudes
2. Normal distal latencies and conduct in velocities

Cytosine Arabinoside

General Characteristics

1. Cytarabine (ara-C) is an antimetabolite used in the treatment of leukemia and lymphoma and is often combined with other chemotherapeutic agents
2. Its intrathecal use has been associated with myelopathy and cauda equine syndrome
3. Cumulative doses of 60 mg/m² to 36 g/m² have caused peripheral neuropathy

Clinical Manifestations

1. Rarely patients may have an RBS presentation or bronchial plexopathy
2. Primarily a sensory neuropathy

3. The neuropathy may begin within hours or be delayed for several weeks
4. Central effects following intrathecal administration often with methotrexate include:
 - a. Cauda equina syndrome
 - b. Myelopathy
 - c. Diffuse cerebral vasospasm rarely occurs in children

Neuropathology

1. Small nerve biopsy:
 - a. Loss of myelinated nerve fibers
 - b. Axonal degeneration with segmented demyelination
 - c. No inflammation

Laboratory Evaluation

1. CSF:
 - a. In patients with a GBS phenotype, the protein is elevated
2. EMG:
 - a. NCS may be compatible with a demyelinating or primary axonal sensorimotor polyneuropathy

Ifosfamide

General Characteristics

1. Ifosfamide is a cyclophosphamide analog metabolized by the cytochrome P450 system to its active form ifosfamide mustard
2. Ifosfamide is used in the treatment of several solid tumors and hematologic malignancies
3. It is associated with a polyneuropathy after a total dose of 14 g/m²

Clinical Manifestations

1. Approximately 10 to 14 days after treatment, patients experience numbness and painful paresthesias in the hands and feet
2. The onset is rarely in the hands rather than the feet, which occurs with a ganglionopathy
3. Systemic manifestations:
 - a. Bone marrow suppression
 - b. Alopecia
 - c. Nausea and vomiting
4. If combined with aprepitant for nausea and vomiting (a neurokinin-1 inhibitor), there may be a higher incidence of neurotoxicity
5. Ifosfamide may be associated with neuropsychiatric toxicity

Neuropathology

1. A well-known systemic complication is renal dysfunction that may be progressive and permanent
2. In a patient with encephalopathy:
 - a. Increased excretion of glutaric acid and sarcosine suggestive of a defect in the mitochondrial fatty acid oxidation that results from defective electron transfer to flavoproteins

Laboratory Evaluation

1. There are no available electrodiagnostic studies

Bortezomib (Velcade®)*General Characteristics*

1. Bortezomib is a proteasome inhibitor primarily utilized in the treatment of multiple myelomas that has been relapsed or with refracting or primary therapies
2. The risk of neuropathy is associated with increasing dosage and in patients with pre-existing neuropathy or comorbidities for peripheral nerve damage
3. The estimates of peripheral neuropathy in patients treated vary widely 37 to 75%. The accumulated neurotoxic dose may be 80 mg/m²

Clinical Manifestations

1. Length-dependent paresthesias, burning dysesthesias and numbness
2. Burning dysesthesias suggest a small fiber component clinically
3. Distal sensory loss to all modalities including proprioception
4. Muscle stretch reflexes are reduced or absent
5. Predominant motor polyradiculoneuropathy (one patient)

Neuropathology

1. Nerve biopsy (one reported patient)
 - a. Microvasculitis
2. Experimental studies suggest:
 - a. Metabolic dysfunction from bortezomib accumulation in dorsal root ganglia cells
 - b. Mitochondrial-mediated dysregulation of Ca²⁺ homeostasis
 - c. Proteasome inhibitor
 - d. Increased alpha-tubulin polymerization
 - e. Endoplasmic reticulum damage
 - f. Dysregulation of neurotrophins through inhibition of NFκB activation
 - g. Specific functional alterations in A-delta and C fibers
 - h. Increase density of TRPV1 and CGRP labeled neurons after treatment that suggest bortezomib treatment selectively affects pain processing cells in the DRG

Laboratory Evaluation

1. EMG:
 - a. Characteristic of an axonal sensory neuropathy with primarily small fiber involvement
2. QST:
 - a. Increased temperature thresholds
 - b. Abnormal autonomic function

Thalidomide*General Characteristics*

1. Thalidomide is most often used in cancer therapy for relapsed multiple myelomas; it has often been combined with proteasome inhibitors

2. Thalidomide monotherapy may lead to a peripheral neuropathy in 44% of patients with relapsed multiple myelomas; severe neuropathy occurs in approximately 6% of patients
3. There are no established risk factors for thalidomide neurotoxicity
4. Lenalidomide, an analog, is less toxic and causes peripheral neuropathy in approximately 3% of patients
5. Pomalidomide:
 - a. Used in multiple myeloma patients who have received and failed at least two prior treatments that have included lenalidomide and bortezomib
 - b. Neuropathy occurs in approximately 9% of patients

Clinical Manifestations

1. Neuropathic pain in and paresthesias in the distal extremities
2. The sensory loss to all modalities
3. Depressed motor stretch reflexes throughout
4. Orofacial neuropathy has been reported
5. CNS manifestations
 - a. Treatment with the immunomodulatory drugs utilized for multiple myelomas (thalidomide, lenalidomide, and pomalidomide) have caused:
 - i. Reversible coma
 - ii. Amnesia
 - iii. Expressive aphasia
 - iv. Dysarthria

Neuropathology

1. Lenalidomide and pomalidomide are more potent, anti-inflammatory, and immunomodulatory than thalidomide
2. Cereblon (cerebral protein with ion protease; CRBN) has recently been shown to be the primary target of thalidomide teratogenicity
3. These small molecule immunomodulators (thalidomide, lenalidomide, and pomalidomide) are involved in the degradation of transcription factors
4. A-delta, C-fibers, and proprioceptive fibers, as well as sensory DRG cells, are involved in thalidomide neurotoxicity

Laboratory Evaluation

1. EMG:
 - a. Similar findings as those seen with bortezomib
 - b. Characteristics of a sensory axonal neuropathy with primarily small fiber involvement

Endocrinopathies Associated with Neuropathy**Diabetes Mellitus (DM)***General Characteristics*

1. The estimated prevalence of DM in the USA in the population 40 to 70 years of age is 12%

2. If children are included, DM may occur in 1 to 4% of the population
3. Approximately 2/3 of both insulin dependent DM (IDDM) and non-IDDM have subclinical or clinical peripheral neuropathy
4. Approximately 50% of diabetic patients have a symmetrical polyneuropathy:
 - a. 25% carpal tunnel syndrome
 - b. 5% autonomic neuropathy
5. Risk factors for diabetic neuropathy:
 - a. Duration of disease
 - b. Poor glycemic control
 - c. Retinopathy and nephropathy
6. Diabetes mellitus diagnostic criteria:
 - a. AIC $> 6.5\%$
 - b. FPG ≥ 126 mg/dl (7.0 mm/l)
 - c. Two hour plasma glucose ≥ 200 mg/dl during an oral glucose tolerance test
 - d. Symptomatic hyperglycemia or hyperglycemic crisis
 - i. A random glucose of ≥ 200 mg/dl

Diabetic Distal Symmetric Sensory and Sensorimotor Polyneuropathy (DSPN)

General Characteristics

1. DSPN is the most common form of diabetic neuropathy (approximately 50% of diabetic neuropathies)

Clinical Manifestations

1. Primarily a length-dependent sensory neuropathy with minimal motor weakness
2. Sensory loss initially starts in the feet and toes; as it progresses above the knees patients complain of numbness and paresthesias in the upper extremities
3. Severely affected patients develop intercostal nerve neuropathy and complain of sensory loss or paresthesias in the chest and abdomen
4. Hypesthesia may be accompanied by tingling, paresthesias, lancinating pain (A-delta fibers), burning pain (C-fiber mediated) or a deep ache
5. Severe denervation and sensory loss lead to ulceration, secondary infection and Charcot joints (a destroyed, degenerative joint; most often the shoulder)
6. Patients may develop autonomic dysregulation from small fiber involvement (impotence, gastroparesis, orthostatic hypertension)
7. There may be loss of all modalities of sensation or primarily small fiber sensibility (pain and temperature)
8. Loss of muscle stretch reflexes is common with large myelinated fiber loss but may be retained if the process involves primarily small fibers
9. Foot intrinsic muscles may be weak and atrophy observable (particularly EDB)

Neuropathology

1. Sural nerve biopsy:
 - a. Axonal degeneration and segmental demyelination
 - b. Clusters of small regenerating axons
 - c. Asymmetric loss of axons between and within nerve fascicles
 - d. Endothelial hyperplasia of epi- and endoneurial arterioles (vasa vasorum)
 - e. Redundant basement membranes around arterioles
 - f. Thickness of the basement membranes or perineurial cells
 - g. Occasional perivascular infiltrate of CD8⁺ T-cells
 - h. Patients with the small fiber phenotype may have a normal nerve biopsy; however skin biopsy reveals a less dense intraepidermal innervation
 - i. Frank DM patients have more involvement of large diameter myelinated fibers; patients with impaired small fiber phenotype are more likely to demonstrate impaired glucose tolerance

Laboratory Evaluation

1. Impaired glucose tolerance test
2. AIC $\geq 6.5\%$
3. EMG:
 - a. Reduced SNAPs amplitudes and slow sensory conduction velocities (in 50% of DM patients)
 - b. 80% of patients with symptomatic neuropathy have abnormal NCS
 - c. Motor NCS are less severely involved than sensory studies but frequently demonstrate low amplitude CMAPs, slightly prolonged latencies and mildly decreased NCVs
4. Needle EMG:
 - a. Positive sharp waves, fibrillation potentials, and large motor unit action potentials (MUAP) may be seen in affected distal muscles
5. QST evaluation
 - a. Higher temperature thresholds

Diabetic Autonomic Neuropathy

General Characteristics

1. Autonomic diabetic neuropathy most frequently occurs concomitantly with DSPN
2. Autonomic neuropathy is an under-recognized complication of diabetes (may be severe in 5% of patients)
3. Aggressive glycemic control, particularly in the face of peripheral neuropathy, may increase the risk of sudden death
4. In adults, cardiovascular autonomic neuropathy is an independent predictor of mortality due to cardiovascular disease, neuropathy and hypoglycemia
5. Overt autonomic neuropathy is rare in childhood and adolescence, but subclinical autonomic dysfunction is common soon after diagnosis
6. Risk factors for autonomic neuropathy in young patients include:
 - a. Duration of diabetes

- b. Poor glycemic control
- c. Possibly polymorphism in the aldose reductase gene (AKR1B1); the Z-2/Z-2 genotype

Clinical Manifestations

1. Hypo- or hyperhidrosis
2. Alteration in thermoregulation
3. Dry eyes and mouth
4. Pupillary abnormalities
 - a. Light-near disassociation
5. Gastrointestinal dysfunction:
 - a. Chronic and nocturnal diarrhea
 - b. Gastroparesis
 - c. Postprandial bloating
6. Impotence
 - a. Retrograde ejaculation
7. Cardiac autonomic neuropathy:
 - a. Resting tachycardia
 - b. Postural hypotension
 - c. Orthostatic bradycardia and orthostatic tachycardia (POTS)
 - d. Exercise intolerance
 - e. Decreased hypoxia-induced respiratory drive
 - f. Loss of baroreceptor sensitivity
 - g. Enhanced intraoperative or perioperative cardiovascular lability
8. Increased incidence of asymptomatic ischemia, myocardial infarction and congestive heart failure

Neuropathology

1. Degeneration of sympathetic and parasympathetic neurons
2. Inflammatory infiltrates of the sympathetic and parasympathetic systems

Laboratory Evaluation

1. Sensory and motored NCS are similar to those seen with DSPN
2. Abnormal qualitative sudomotor axon reflexes
3. Decreased sympathetic skin response
4. Heart rate variability during:
 - a. Deep breathing
 - b. Standing
 - c. Valsalva maneuver
 - d. Allows a quantitative measure of cardiac sympathetic and parasympathetic parameters
5. Spectral analysis of heart rate variability (HRV); variability is measured as a function of frequency
 - a. Sympathetic system modulates to low frequency components while the parasympathetic system modulates the high frequency component

Diabetic Neuropathic Cachexia (DNC)

General Characteristics

1. Although DNC is rare it can be the presenting manifestation of diabetes

2. More common in men than women and is associated with poor glycemic control
3. The disorder can affect both type one and type two diabetes and occurs irrespective of the duration of the illness; it generally occurs in the sixth or seventh decade

Clinical Manifestations

1. An abrupt onset of severe generalized paresthesias that involves the extremities and trunk
2. Severe weight loss occurs concomitantly
3. The cause is usually monophasic but can be recurrent
4. Examination reveals profound emaciation of fat and lean mass
5. Mild sensory loss
6. A subset of patients develop distal weakness and muscle atrophy
7. Muscle stretch reflexes are decreased or lost
8. The neuropathy may spontaneously improve usually preceded by weight gain

Neuropathology

1. Sural nerve biopsy
 - a. Severe axonal degeneration with relative sparing of thinly myelinated fibers or unmyelinated C-fibers

Laboratory Evaluation

1. CSF:
 - a. Increased protein
2. EMG:
 - a. Absent or low amplitude SNAPs
 - b. Normal or slightly reduced CMAPs with slight slowing of motor NCVs

Differential Diagnosis of DNC

"Insulin Neuritis"

General Characteristics

1. Preceded by a period of rapid glycemic control
2. Occurs in both type one and type two diabetes that has been treated with insulin or oral hypoglycemic drugs

Clinical Manifestations

1. Acute severe distal limb pain that may concurrently be associated with trunk involvement
2. Autonomic deregulation

Neuropathology

1. Proposed mechanisms include:
 - a. Endoneurial ischemia
 - b. Microvascular neuronal damage
 - c. Spontaneous discharge of regenerating C-fibers
2. Carcinomatosis
3. Acute alcoholic neuropathy
4. Acute intermittent porphyria
5. CIDP

Diabetic Amyotrophy*General Characteristics*

1. The most common form of polyradiculopathy or radiculoplexus neuropathy
2. Affects type two older patients primarily but can affect type one patients
3. In approximately one third of patients, it can be the presenting feature of DM

Clinical Manifestations

1. Presents most often with severe pain in the low back, hip, and thigh in one leg (often confused with a herniated disk)
2. Most patients have DSPN
3. Rarely, it is initiated bilaterally simultaneously; usually asymmetrically
4. Atrophy of both proximal and distal leg muscles with appropriate weakness
5. Approximately 50% of patients complain of numbness and paresthesias (often in femoral nerve or L5–S1 distributions)
6. The contralateral leg is often affected six weeks to several months later
7. The polyradiculopathy can be preceded or accompanied by severe weight loss
8. The weakness may progress gradually or stepwise over weeks or several months
9. Some patients have thoracic intercostal nerve involvement with weakness and sensory loss in the appropriate distributions
10. Rarely associated cervical polyradiculoneuropathy and brachial plexopathy are concurrent

Neuropathology

1. Nerve biopsies including the sural, lateral femoral cutaneous and superficial peroneal nerve demonstrate:
 - a. Loss of myelinated nerve fibers asymmetrically between and within nerve fascicles
 - b. Axonal degeneration with clusters of small thinly myelinated regenerating fibers may be seen
 - c. Perivascular inflammation
 - d. Vasculitic changes of the epineurial and perineurial blood vessels
 - e. Possible mechanism:
 - i. Immune-mediated microangiopathy

Laboratory Evaluation

1. CSF:
 - a. Increased protein with no pleocytosis
 - b. Increased ESR (erythrocyte sediment rate)
2. EMG:
 - a. Low amplitude SNAPs and CMAPs of the affected roots and plexi
 - b. Characteristics of multifocal axonal damages

- c. Conduction velocities normal or only slightly reduced
3. Needle EMG:
 - a. Positive sharp waves, fibrillation potentials and decreased recruitment of affected muscles
 - b. After reinnervation occurs, there are large amplitude long duration polyphasic MUAPs

Radiculoplexus Neuropathy (LRPN)*General Characteristics*

1. Progressive, often painless, symmetrical weakness of the legs > arms
2. Affects both proximal and distal muscles in a pattern that resembles CIDP
3. Occurs in both type one and type two diabetes

Clinical Manifestations

1. Weakness is usually symmetrical and involves both proximal and distal muscles; the legs are more severely involved than the arms with distal > proximal weakness
2. The onset is not accompanied by back and leg pain
3. A subset of patients has weight loss
4. Distal dysesthesia and numbness occur, some patients have pain in affected root and/or plexus distributions
5. Reduced or absent muscle stretch reflexes in affected areas

Neuropathology

1. Sural nerve biopsy:
 - a. Loss of large and small myelinated fibers
 - b. Axonal degeneration with clusters of small regenerating fibers
 - c. Rarely demyelinated fibers demonstrate onion bulb formation associated with infiltration of perivascular mononuclear cells in the peri- and epineurium

Laboratory Evaluation

1. CSF:
 - a. Elevated protein without pleocytosis
2. EMG:
 - a. Reduced or absent SNAPs and CMAPs amplitudes
 - b. Slow NCVs with prolonged distal latencies
 - c. Absent or prolonged F-wave latencies
 - d. Rare conduction blocks and temporal dispersion
3. Needle EMG:
 - a. Fibrillation potentials and positive sharp waves in affected muscles and associated paraspinal musculature
4. Autonomic evaluation
 - a. Alterations in sudomotor, cardiovagal, and adrenergic physiology

Diabetic Cervical Radiculoplexus Neuropathy*General Characteristics*

1. Review of the Mayo Clinic series of 85 patients
 - a. Mean age of 62 years (range of 32 to 85 year of age)
 - b. Primarily in type two diabetes

Clinical Manifestations

1. Major presenting complaint was pain and numbness
2. Upper, middle and lower brachial plexus segments were equally involved; pain plexopathy occurred in approximately 20% of patients
3. Approximately 50% of patients had signs and symptoms in another body region including the thorax and lumbosacral plexus
4. Recurrent attacks occurred in approximately 10% of patients

Neuropathology

1. Nerve biopsy:
 - a. Ischemic injury with axonal degeneration and multifocal fiber loss
 - b. Focal perineurial thickening
 - c. Epineurial perivascular inflammation
 - d. Microvasculitis

Laboratory Evaluation

1. CSF:
 - a. Elevated protein (median 70 mg/dl)
2. EMG:
 - a. An axonal neuropathy
 - b. Paraspinal denervation
3. Alteration in autonomic function
4. MRI:
 - a. All patients demonstrate brachial plexus pathology

Diabetic Cranial and Peripheral Mononeuropathies*General Characteristics*

1. Cranial Nerve involvement:
 - a. VIIth nerve is most commonly involved
 - b. IIIrd nerve palsy:
 - i. Pupil is usually not involved
 - ii. Light-near dissociation occurs
 - iii. The ptosis may be more severe than that seen with an aneurysm compressing the IIIrd nerve
 - c. VIth nerve palsy
 - d. Rarely the IVth nerve is involved
 - e. V and VII cranial nerves may be involved concomitantly from ischemia of the lateral trunk of the external carotid artery
 - f. Diabetic pseudotabes
 - i. Severe symmetric loss of cutaneous and deep pain sensation including proprioception
 - ii. Tabetic gait, positive Romberg sign
 - iii. Absent reflexes
 - iv. Foot ulcers and arthropathy
2. Diabetic patients are vulnerable to pressure and chemotherapy. Most of the mononeuropathies that are seen occur in a background of DSPN. The most common mononeuropathies occur:
 - a. Median nerve at the carpal tunnel

- b. Lateral femoral cutaneous nerve (compressed under the femoral ligament in the groin and associated with meralgia paresthetica)
- c. Peroneal nerve at the fibular head
- d. Rarely, the sciatic nerve at the level of the piriformis muscle
- e. Plantar nerve in the tarsal tunnel

Hypoglycemic Neuropathy*General Characteristics*

1. Hypoglycemic neuropathy has been associated with early stages of treatment for DM or persistent hypoglycemia from an insulinoma
2. Hypoglycemia is common in type one diabetes mellitus
 - a. 1 of 6 patients has at least one severe episode/year
3. The incidence rate of hypoglycemia is higher in patients with:
 - a. Previous severe hypoglycemia
 - b. Existing peripheral neuropathy
 - c. Long duration of DM (>20 years)
 - d. Polypharmacy

Clinical Manifestations

1. Progressive numbness and paresthesias of the hands and feet
2. Distal muscle weakness evolves over time. Multiple episodes occur prior to anterior horn cell involvement
3. Decreased muscle stretch reflexes
4. Classic triad of an insulinoma:
 - a. Progressive encephalopathy
 - b. Intractable seizures
 - c. Peripheral neuropathy
5. Isolated VIth nerve palsy has been reported

Neuropathology

1. Wallerian-like axonal degeneration that is initiated at the nerve terminal and spreads to the proximal axon; motor axons may be more affected than sensory axons
2. Nerve biopsy:
 - a. Axonal degeneration primarily of large myelinated fibers

Laboratory Evaluation

1. EMG:
 - a. Reduced amplitude or absent SNAPs; CMAPs are slightly reduced
 - b. Conduction velocities may be mildly decreased
2. Needle EMG:
 - a. Positive sharp waves and fibrillation in potentials
 - b. In reinnervating muscles, there is decreased recruitment of large polyphasic MUAPs

Acromegaly*General Characteristics*

1. 35% of patients suffer CTS which is often apparent at presentation

- a. 35% to 45% have a sensorimotor peripheral neuropathy
2. CTS may be the presenting complaint
3. Enlarged sinuses, cardiac failure, severe arthropathy, myelopathy and radiculopathy (due to bony encroachment of the foraminal exit canals) may be concomitant medical complications
4. The pituitary gland is usually not enlarged as the morphological facial features of the endocrinopathy may lead to an early diagnosis. The optic neuropathy is usually a result of surgery and X-RT

Clinical Manifestations

1. Patients with generalized neuropathy:
 - a. Have paresthesias of the hands and feet; legs are more affected than the hands
 - b. Decreased light touch, vibration, and proprioception
 - c. Rare distal muscle wasting
 - d. Absent or reduced muscle stretch reflexes
 - e. Concomitant proximal myopathy
 - i. Type 2 fiber atrophy
 - f. Severe CTS often precedes the diagnosis
 - g. Rare compression of the optic chiasm or nerve; usual involvement is from surgery and X-RT
 - h. Tarsal tunnel syndrome

Neuropathology

1. Bone overgrowth may narrow the spinal canal with consequent spinal cord compression
2. Similarly, there may be encroachment from bone overgrowth in the exit foramina of nerve roots with consequent radiculopathy
3. Nerve biopsy:
 - a. Increase of endoneurial and subperineurial connective tissue
 - b. Loss of myelinated and unmyelinated nerve fibers
4. Acromegaly occurs in 20% of patients with the McCune-Albright syndrome (poly/monostotic fibrous dysplasia, café-au-lait spots, and hyperfunctioning endocrinopathies)

Laboratory Evaluation

1. EMG (in patients with the generalized neuropathy):
 - a. Reduced amplitudes of SNAPs with prolonged distal latencies and slow conduction velocity
 - b. CMAPs are frequently normal but may demonstrate reduced amplitudes and prolonged distal latencies
 - c. Slightly slowed motor nerve conduction velocities
2. Increased insulin-like growth factor
3. Growth hormone > 1.0 ng/dl
4. Increased somatostatin C

Hypothyroidism

General Characteristics

1. Concurrent hypothyroid myopathy (Hoffman's Syndrome)

- a. Pseudohypertrophy; proximal weakness
2. Hyperexcitability of the sarcolemmal membrane (lumping phenomenon with mechanical percussion of its muscle)
3. Associated central nervous system signs and symptoms:
 - a. Decreased mentation
 - b. Cranial nerve V involvement (pain)
 - i. Laryngeal sensory neuropathy
 - c. Sensorineural hearing loss from VIIIth nerve involvement
 - d. Cerebellar ataxia (Purkinje cell dysfunction)
4. Peripheral neuropathy manifestations:
 - a. Distal sensory loss (all modalities)
 - b. Burning and lancinating distal pain
 - c. Leg muscle cramps
 - d. Distal leg muscle weakness
 - e. Concomitant CTS with hand paresthesias
 - f. Delayed relaxation phase of the ankle muscle stretch reflex as well as other reflexes
 - g. Hoarseness (mucopolysaccharide deposition in the vocal cords)

Neuropathology

1. Sural nerve biopsy:
 - a. Myelinated fiber loss: large > small fibers
 - b. Axonal degeneration with segmental demyelination
 - c. Occasional "onion bulb" formation

Laboratory Evaluation

1. Hemoglobin of 12 grams; monocytic anemia
2. CSF
 - a. Increased protein; without pleocytosis
3. TSH levels (thyrotropin)
 - a. Euthyroidism:
 - i. Thyrotropin (TSH) levels 0.45–4.49 mIU/L with normal thyroxine levels
4. EMG:
 - a. Carpal tunnel NCS is the most common abnormality
 - b. Patients with generalized neuropathy
 - i. Reduced SNAP amplitudes with slightly prolonged distal latencies
 - ii. CMAPs may have slightly reduced amplitude
 - iii. Slowing of conduction velocities and slight prolongation of distal latencies

Hyperthyroid Neuropathy

General Characteristics

1. CNS neurologic dysfunction predominates:
 - a. Cognitive dysfunction
 - b. Apathetic hyperthyroidism (associated with slow atrial fibrillation)
 - c. Davidoff syndrome:
 - i. Nystagmus
 - ii. Hyperactive muscle stretch reflexes
 - iii. Babinski signs

2. Proximal myopathy
 - a. Iliopsoas often severely involved; wasting of the rhomboid muscles
3. Thyroid storm
 - a. Fever to 105° Fahrenheit, atrial fibrillation; wide pulse pressure; hypotension; most are associated with increased T4; rarely increased T3 with a normal T4

Clinical Manifestations

1. Neuropathy:
 - a. Sensory loss is mild
 - b. Proprioceptive large myelinated > small fiber phenotype
2. Basedow's paraplegia:
 - a. Proximal and distal leg weakness
 - b. Hypotonia
 - c. Areflexia in the legs
3. Thyroid ophthalmopathy
4. Associated with (other diseases):
 - a. Myasthenia gravis
 - b. Hypokalemic periodic paralysis

Neuropathology

1. Nerve biopsy
 - a. Not well defined
2. Muscle biopsy
 - a. Denervation of distal muscles

Laboratory Evaluation

1. EMG
 - a. NCS slightly slow motor and sensory conduction velocities

Nutritional Deficiencies and Neuropathy

Overview

Dietary nutritional deficiency in the developed world is most often secondary to alcoholism, patients with chronic illness, those with restricted or unusual diets, malabsorption syndromes, gastrectomy and obesity surgery, sprue and intestinal surgery. Medications may interfere with vitamin metabolism that occurs with B6 deficiency (isoniazid). In cases of malnutrition and those patients with malabsorption, multiple vitamin deficiencies occur.

Thiamine Deficiency (Vitamin B1)

General Characteristics

1. Occurs in the setting of starvation, alcoholism, prolonged vomiting, post-gastric stapling, dialysis and a diet of carbohydrates without vitamin supplementation
2. Vitamin B1 is absorbed in the small intestine by passive diffusion and active transport; it is phosphorylated in the jejunum to thiamine pyrophosphate
3. Vitamin B1 is involved in the decarboxylation of alpha-keto acids that are metabolized to alpha ketols
4. It may develop with total parenteral nutrition

Clinical Manifestations

1. Presents in two forms:
 - a. Wet beriberi:
 - i. The neuropathy is associated with congestive heart failure and significant peripheral edema most severe in the lower extremities
 - b. Dry beriberi patients have no congestive heart failure
2. Presents as a symmetrical sensorimotor neuropathy
3. Evolves over weeks to months; it may rarely develop over several days
4. A subgroup of patients develops a small fiber phenotype
5. Patients frequently complain of paresthesia of the extremities; all sensory modalities are affected
6. Associated Wernicke-Korsakoff syndrome
7. Distal weakness with loss of ankle motor stretch reflexes
8. Rare involvements:
 - a. Vagus and recurrent laryngeal nerves
 - b. Tongue and facial weakness
9. Central and centrocecal scotoma may develop

Neuropathology

1. Sural nerve biopsy:
 - a. Primarily loss of large myelinated fibers
 - b. Autopsy evaluation:
 - i. Chromatolysis of anterior horn cells
 - ii. Loss of DRG cells
 - iii. Axonal degeneration with secondary demyelination of the posterior columns
 - c. Thiamine deficiency:
 - i. Decreases thiamine-dependent enzymatic activity
 - ii. Alters mitochondrial function
 - iii. Impairs oxidative metabolism
 - iv. Selective neuronal death
 - v. No defined mutations in three thiamine carrier genes:
 1. SLC19A2
 2. SLC19A3
 3. SLC25A19
 - vi. Two patients have demonstrated an increase of vascular endothelial growth factor in the serum

Laboratory Evaluation

1. Erythrocyte transketolase activity and the percentage increase of activity after the addition of thiamine pyrophosphate is an accurate assay
2. EMG:
 - a. Absent or reduced SNAP amplitudes
 - i. Minimally affected distal sensory latencies and conduction velocities
 - b. Motor NCS is normal or demonstrates slightly reduced CMAP amplitudes

Vitamin B6

General Characteristics

1. Associated with:

- a. Polynutritional deficiencies
- b. Isoniazid
- c. Hydralazine
- d. Duodenal infusion of levodopa in severe Parkinson's disease:
 - i. Low B12 levels
 - ii. High homocysteine and methylmalonic acid are associated
 - iii. The levodopa infusion has been reported to cause an acute GBS syndrome
- 2. Toxic doses of B6 are >200 mg/day
- 3. Inhibits the conversion of pyridoxal phosphate

Clinical Manifestations

- 1. May be seen in patients on peritoneal dialysis
- 2. Malnutrition of chronic alcoholism
- 3. Peripheral neuropathy:
 - a. Distal burning paresthesias in the feet and hands
 - b. Severe deficiency has been associated with sensory ataxia
 - c. Sensory > motor polyneuropathy

Neuropathology

- 1. Axonal degeneration

Laboratory Evaluation

- 1. EMG:
 - a. Features of an axonal sensorimotor neuropathy
- 2. B6 levels can be determined by direct assay

Cobalamin (Vitamin B12) Deficiency

General Characteristics

- 1. B12 deficiency is common in patients over the age of 65 years
 - a. Possible prevalence of 10 to 20% but only 5–10% are symptomatic
- 2. The main causes of cobalamin deficiency are pernicious anemia and food-cobalamin malabsorption
- 3. Characteristics of food-cobalamin malabsorption:
 - a. A disorder in which there is an inability to release cobalamin from food or its binding proteins
 - b. The syndrome is most often caused by atrophic gastritis that is related or unrelated to *Helicobacter pylori* infection, long-term ingestion of antacids and biguanides
- 4. Mutations in genes that encode endocytic receptors that are involved in ileal absorption and uptake of cobalamin are responsible for some patients with hereditary megaloblastic anemias
- 5. Cobalamin is in meat, fish, and dairy products but not in fruits, vegetables and grains:
 - a. It requires the transport molecule – intrinsic factor which is synthesized and secreted by gastric parietal cells for its absorption
 - b. Intrinsic factor deficiency may be caused by:
 - i. Autoimmune destruction of gastric parietal cells
 - ii. Gastrectomy

- 6. Other causes of vitamin B12 deficiency include:
 - a. Vegan diet (lack of intake)
 - b. Inflammatory bowel disease (malabsorption)
 - c. Blind loop syndrome (*diphyllobothrium latum* overgrowth)
 - d. Nitrous oxide anesthesia (acute)
 - e. In association with another autoimmune disease (parietal cell antibodies)
 - f. Severe steatorrhea (malabsorption)
 - g. Infestation of the fish tapeworm
 - h. May accompany folic acid deficiency; if the folate deficiency is treated without B12 replacement, hematologic abnormalities may clear, but neurologic deficits may be exacerbated

Clinical Manifestations

- 1. Both CNS and PNS neurological deficits occur with B12 deficiency which may or may not be associated with megaloblastic anemia and pancytopenia
- 2. Peripheral neuropathy:
 - a. It is an active large fiber neuropathy that may be initiated with paresthesias and burning in the hands and feet
 - b. Sensory ataxia may occur due to the loss of proprioceptive sense in the nerve and dorsal column degeneration
 - c. Romberg sign may be present
 - d. Due to associated spinal cord involvement, the hands may be more affected than the feet
 - e. Spasticity with distal muscle weakness
 - f. Muscle stretch reflexes may be lost at the ankle (from the neuropathy) and increased throughout due to the myelopathy
 - g. Babinski sign is present
 - h. CNS signs and symptoms include:
 - i. Cranial I and II involvement
 - ii. Characteristic myelopathy:
 - 1. Spasticity
 - 2. Posterior column dysfunction
 - 3. Bilateral Babinski sign
 - iii. Frontal lobe dysfunction
 - 1. Euphoria
 - 2. Psychiatric manifestations
 - iv. Cerebellar ataxia

Neuropathology

- 1. Nerve biopsy:
 - a. Loss of large diameter myelinated fibers
 - b. Axonal degeneration
 - c. Secondary segmental demyelination
- 2. Cobalamin is necessary for the demethylation of methyl-tetrahydrofolate; the tetrahydrofolate produced is required for the synthesis of folate coenzymes pivotal for DNA synthesis. Other possible mechanisms include:

- a. Decreased methylation of myelin phospholipids
- b. Accumulation of methylmalonic and propionic acids that may be substrate for fatty acid synthesis that causes aberrant myelination
- 3. White matter demyelination in many brain areas including projections to the frontal lobe
- 4. Autopsy material
 - a. Degeneration of cortical spinal tracts and the dorsal columns

Laboratory Evaluation

- 1. Vitamin B12 may be directly assayed but is not sensitive
- 2. Large hypersegmented neutrophils; low platelets and a macrocytic anemia that may be severe (<2 grams/dl) may develop gradually
- 3. Increased urinary methylmalonic acid concurrently with increased homocysteine
- 4. Detection of intrinsic factor and parietal cell antibodies
- 5. Schilling test is utilized to detect pernicious anemia
- 6. Elevated gastrin and antiparietal cell antibody are specific and sensitive for pernicious anemia
- 7. EMG:
 - a. SNAP amplitudes are reduced or absent
 - b. CMAPs amplitudes may be normal or only slightly reduced
 - c. Minimal abnormalities of motor and sensory distal latencies and conduction velocities
- 8. Somatosensory-evoked potentials and transcranial magnetic stimuli often reveal slowed central conduction times

Clinical Points

- 1. Nitrous oxide anesthesia:
 - a. Inactivates methylcobalamin
 - b. Causes both neuropathy and subacute combined degeneration of the spinal cord
 - c. Generally appears more quickly than the progression of the natural disease
 - d. Primarily affects patients with low or borderline B12 levels
 - e. Similar in all spheres to B12 deficiency
- 2. High vitamin B12 levels (350–1,200 pmol/L) are associated with hematological and hepatic disorders as well as malignancy
- 3. Intestinal (duodenal infusion of levodopa) has been associated with B12 deficiency

Folate Deficiency

General Characteristics

- 1. Folate is in fruit, vegetables, and liver
- 2. Folate is absorbed in the proximal jejunum
- 3. Isolated deficiencies occurs:
 - a. Rarely
 - b. In the elderly that are malnourished
 - c. Alcoholic malnutrition

- d. Partial gastrectomies
- e. Duodenojejunal resections
- f. Celiac disease
- 4. Cerebral folate deficiency:
 - a. Definition:
 - i. A neuropsychiatric condition associated with low CSF N5-methyl tetrahydrofolate (MTHF) with normal folate levels outside of the CNS
 - b. Caused by serum autoantibodies of the blocking type that are directed against folate receptor-alpha (FR-alpha) that are attached to the plasma side of choroid plexus epithelial cells:
 - i. The blocking FR antibodies inhibit MTHF transport across the choroid plexus
 - ii. Progressive dystonia or schizophrenic syndromes develop during adolescence

Clinical Manifestations

- 1. Characteristics of the peripheral neuropathy:
 - a. Slowly progressive polyneuropathy predominant lower extremity involvement
 - b. Sensory > motor with large fiber rather than small fiber phenotype
- 2. Other neurologic deficits are similar to those seen with B12 deficiency:
 - a. Subacute combined degeneration of the spinal cord
 - b. Psychiatric disease

Neuropathology

- 1. Other drugs that can interfere with folate metabolism are:
 - a. Phenytoin
 - b. Phenobarbital
 - c. Sulfasalazine
 - d. Colchicine
- 2. Sural nerve biopsy
 - a. Large fiber-predominant axonal degeneration without segmental demyelination
- 3. Low serum folate levels
- 4. Megaloblastic anemia
 - a. Rare for hemoglobin levels to drop below 10 g/dl
- 5. EMG:
 - a. Consistent with an axonal neuropathy
 - b. Sensory and motor NCS may be similar to B12 deficiency

Vitamin E Deficiency Neuropathy

General Characteristics

- 1. Vitamin E is found in vegetable oils and wheat germ
- 2. Vitamin E is most often in the alpha-tocopherol form
- 3. It is a lipid-soluble antioxidant that is present in the lipid bilayer of the cell membrane
- 4. There are three major mechanisms that cause vitamin E deficiency:
 - a. Fat malabsorption:

- i. Cystic fibrosis
- ii. Short bowel syndrome
- iii. Chronic cholestasis and hepatobiliary disorders
- iv. Intestinal lymphangiectasia
- b. Alteration of fat transport:
 - i. Abetalipoproteinemia (Bassen-Kornzweig disease)
 - ii. Hypobetalipoproteinemia
 - iii. Normotriglyceridemic abetalipoproteinemia
 - iv. Chylomicron retention disease
- c. Genetic forms of the disease:
 - i. Alpha-tocopherol transfer protein gene mutations on chromosome 8q13
 - ii. The majority of patients are homozygous for the 744 del A mutation

Clinical Manifestations

1. May occur several years after the onset of the deficiency
2. A common presentation is difficulty walking and poor coordination of fine movements in the hands
3. Severe loss of proprioception and vibration sensibilities
4. Limb ataxia
5. Truncal ataxia with head titubation
6. Resembles a spinocerebellar ataxia with a polyneuropathy
7. Ophthalmoparesis and dysarthria
8. A subset of patients has dystonia and bradykinesia
9. Generalized diminution or absence of muscle stretch reflexes
10. Proximal muscle weakness
11. Pigmentary retinopathy with visual loss
12. Rare patients may have an isolated polyneuropathy while in a Tunisian cohort 50% of patients had no neuropathy (a hereditary form)

Neuropathology

1. Sural nerve biopsy:
 - a. Loss of large diameter myelinated fibers
 - b. Axonal degeneration with regenerating clusters
 - c. Rare vacuoles of the myelin sheath and disruption of Schmidt-Lanterman incisures
2. Autopsy material:
 - a. Swelling and degeneration of axons in the dorsal columns and spinocerebellar pathways
 - b. Neuronal loss in posterior column nuclei
3. After absorption from the small intestine, alpha-tocopherol is incorporated into chylomicrons and is transported to the liver where it is incorporated into low-density lipoproteins
4. In the hereditary form, autosomal recessive, there are mutations in the TTPA gene that encodes the alpha-TTP protein. Its putative function is intracellular alpha-tocopherol transport
5. Vitamin E is an important free radical scavenger and appears to be important in cell membrane physiology

Laboratory Evaluation

1. Vitamin E levels can be measured in the serum; hyperlipidemia may cause erroneous readings
2. EMG:
 - a. Absent SNAPs and reduced amplitudes in those that are obtainable
 - b. Sensory nerve conduction velocities may be normal or are only slightly slow
 - c. Motor NCS are normal
3. Somatosensory evoked potentials
 - a. Slowing of central conduction

Copper Deficiency

General Characteristics

1. Copper is an essential trace element involved in multiple enzymatic processes throughout the body
2. Almost 90% of patients have combined hematologic and neurologic signs and symptoms at presentation; approximately 20% may present with only hematologic dysfunction
3. A significant number of patients have high serum zinc concentrations ($>18 \mu\text{m/L}$) from zinc-containing dental fixatives
4. Deficiency may occur from the duodenal switch operative procedure and Roux-en-Y gastric bypass procedures

Clinical Manifestations

1. Weakness, spasticity, gait difficulties from a myelopathy
2. Bilateral Babinski signs
3. Large fiber proprioceptive and vibratory sensibility loss
 - a. Some patients also lose components of light touch, pinprick and temperature sensibility concurrently
4. Reflexes are increased (due to the myelopathy)

Neuropathology

1. Sural nerve biopsy
 - a. Axonal degeneration
2. Other causes of copper deficiency include:
 - a. Malnutrition
 - b. Prematurity
 - c. Total parenteral feeding
 - d. Copper chelating agents
3. Zinc (a component of dental fixtures) upregulates enterocyte metallothionein which decreases copper absorption from the stomach and proximal jejunum

Laboratory Evaluation

1. Anemia, thrombocytopenia, and neutropenia; microcytic anemia
2. Low serum copper levels; high zinc levels in those with zinc dental fixatives
3. Bone marrow biopsy:
 - a. Multilineage dysplasia
 - b. Excess blasts

- c. A subset of patients with myelodysplasia
- 4. CSF:
 - a. Normal or minimally elevated protein
 - b. Some patients demonstrate an increased immunoglobulin synthesis rate
- 5. EMG:
 - a. Consistent with a sensorimotor axonal polyneuropathy
- 6. Somatosensory evoked potentials
 - a. Decreased conduction in central pathways
- 7. MRI:
 - a. Multifocal T2 hyperintense signal foci in subcortical white matter
 - b. Atrophy of the cerebrum and cerebellum
 - c. Signal change in the posterior columns of the cervical and thoracic cord

Bariatric Surgery

General Characteristics

1. In the USA approximately 150,000 bariatric procedures are performed annually
2. Approximately 5% of patients suffer neurologic complications from the procedure which are seen at all levels of the neuroaxis
3. The most common deficiencies from the surgery include:
 - a. Thiamine
 - b. B12
 - c. Copper
 - d. Folate
 - e. Zinc
 - f. Vitamins A and E

Clinical Manifestations

1. Characteristics of the peripheral neuropathy:
 - a. Usually, occurs in a setting of significant weight loss or recurrent prolonged vomiting
 - b. The sensory loss may be acute or subacute
 - c. Burning feet associated with distal weakness
 - d. GBS-like syndrome
 - e. Mononeuropathy
 - f. Radiculoplexus neuropathy
 - g. The neuropathy usually occurs within the first 1½ years following surgery
 - i. The latency has been documented for months or years in some patients operated on for total or partial gastrectomy due to ulcer or cancer
 - h. Wernicke-Korsakoff syndrome may occur concomitantly

Neuropathology

1. Sural nerve biopsy:
 - a. Active axonal degeneration
 - b. Some perivascular, endoneurial and epineurial inflammatory cell infiltrate

Laboratory Evaluation

1. EMG:
 - a. Most often consistent with an axonal neuropathy
 - b. Patients with GBS demonstrate a demyelination pattern
2. Deficits and laboratory values reflect the specific vitamins that have been malabsorbed

Hypophosphatemia

General Characteristics

1. Intravenous glucose administration is the most common cause of hypophosphatemia in hospitalized patients. It usually is asymptomatic
2. Major other causes of hypophosphatemia include:
 - a. Severe diabetic ketoacidosis
 - b. Parenteral alimentation
 - c. Burn patients
 - d. Antacids
 - e. Diuretics
 - f. Steroids
 - g. Biphosphonates
3. Severe hypophosphatemia is a serum phosphorus less than or equal to 0.48 mmol/L or ≤ 1.5 mg/dl
4. Often neurological recovery obtains with rapid restoration of phosphorous concentrations

Clinical Manifestations

1. Characteristics of the neuropathy:
 - a. Hypophosphatemia may be associated with a subacute severe sensorimotor peripheral neuropathy
 - b. Patients first note paresthesias in the feet which ascend to affect the entire body
 - c. Patients suffer generalized weakness
 - d. Decreased sensation to all modalities
 - e. Ataxia
 - f. Loss or depression of muscle stretch reflexes
 - g. The weakness may be severe enough to cause respiratory embarrassment that requires mechanical ventilation

Neuropathology

1. Sural nerve biopsy (one patient):
 - a. Mild axonal degeneration
 - b. Moderate subperineurial edema
 - c. Phosphatonins are being investigated as a mechanism that regulates phosphorus metabolism along with parathormone and vitamin D. Fibroblast growth factor 23 (FGF-23) may be pivotal

Laboratory Evaluation

1. A phosphorus level of < 1.5 mg/dl
2. EMG:
 - a. Absent SNAPs; reduced CMAP amplitudes with slightly slow conduction velocities
 - b. Some patients have absent F-waves

Alcoholic Neuropathy

General Characteristics

1. Alcoholic neuropathy occurs in 10 to 30% of hospitalized patients and is seen in >80% of patients with Wernicke-Korsakoff syndrome
2. Men and women are equally susceptible
3. It usually requires 100 grams daily for a prolonged period of time
4. The neuropathy may occur in a setting of severe weight loss over the preceding several months

Clinical Manifestations

1. The usual presentation is a slowly progressive, generalized sensorimotor peripheral neuropathy
2. Rarely, a more acute GBS-like presentation has been described
3. Loss of all sensory modalities; the insidious onset of numbness, paresthesias and burning pain in the feet
4. There are mild distal leg weakness and atrophy; strength in proximal muscles and the upper extremities is usually maintained
5. Alcoholic myopathy may occur with proximal muscle weakness
6. Distal loss of motor stretch reflexes in the ankles that progresses proximally
7. Autonomic dysfunction is often subtle
8. Central nervous system manifestations:
 - a. Dementia
 - b. High incidence of chronic subdural hematoma and chronic traumatic brain encephalopathy
 - c. "Marionette" gait occurs from anterior vermal atrophy (trunk is held in extension; stiff legged)
 - d. Central pontine myelinolysis

Neuropathology

1. Sural nerve biopsy:
 - a. Loss of large diameter and thinly myelinated fibers
 - b. Wallerian degeneration and secondary segmental demyelination
2. Skin biopsy:
 - a. Decreased end nerve fiber densities (ENFD)
3. Ethanol may be directly neurotoxic via its metabolite acetaldehyde and may induce oxidative stress in peripheral nerves
4. May activate protein kinase C epsilon in primary afferent nociceptors which lowers their firing threshold
5. May cause cytoskeletal dysfunction and inhibits antegrade and retrograde axonal transport
6. Is also frequently seen in association with deficiencies of B vitamins and folate

Laboratory Evaluation

1. EMG:
 - a. Characteristics of a generalized axonal sensory or sensorimotor polyneuropathy

2. QST

- a. Phenotype of a small fiber neuropathy with altered pain and temperature thresholds
- b. Decreased RBC transketolase activity

Tumors of Peripheral Nerves

Overview

Peripheral nerve tumors are rare types of soft tissue tumors. In a large series of 397 peripheral neural sheath tumors, 91% were benign. A large subgroup of patients with benign lesions was in the brachial plexus: 54 schwannomas (38%) and 87 neurofibromas (62%). In the breakdown of the neurofibromas, 63% were solitary, and 37% were type I (NF-1 associated neurofibromas); a supraclavicular location was predominant. A much smaller subgroup of patients had benign peripheral nerve sheath tumor in the pelvic plexus, 62% of which were neurofibromas and 38% were schwannomas. Twenty-eight of the 397 peripheral neural sheath tumors were malignant. Approximately 7% comprised neurogenic sarcomas in 28. In 36 others, tumors included fibro, spindle cell, synovial and perineurial types.

In general, the majority of tumors were benign peripheral nerve sheath tumors originating in the brachial plexus area. Neurofibromas in all locations comprised the majority of peripheral nerve sheath tumors (PNST); the predominant form being a solitary tumor. Neurofibromas are primarily in the upper extremity whereas schwannomas were distributed equally between upper and lower extremities.

The most common symptoms include:

1. Tumor mass (100%)
2. Tinel's sign (sensitivity to a mechanical stimulus) in 95% of patients
3. Paresthesias (over 90%)
4. Sensory deficit (approximately 90%)
5. Motor deficit in approximately 40% of patients

Tumors occurred almost equally in major peripheral nerves and small nerve branches. The mass may be displaced at right angles to the course of the nerve. The tumor's mechanosensitivity is demonstrated by paresthesias when it is mechanically compressed. It is not possible to distinguish clinically between a neurofibroma, schwannoma, or malignant tumor.

Schwannoma (Neurilemmoma)

General Characteristics

1. Schwannomas are benign tumors derived from nerve sheath Schwann cells
2. They occur between the third to fifth decades
3. There is no racial or gender difference
4. They usually develop as a solitary mass of 1.5 to 3 cm diameter at presentation. They are rarely large and multiple
5. Schwannomas are located in the upper extremity in 12 to 19% of patients and the lower extremity in 13.5 to 17.5% of patients

6. They are well encapsulated and have a non-infiltrating growth pattern

Clinical Manifestations

1. Positive Tinel's sign (paresthesias elicited by mechanical stimulation of the tumor in the distribution of the affected nerve) is often elicited
2. Rarely, presents as a neurologic deficit of the affected nerve
3. Most common nerves affected are:
 - a. Supra- greater than infraclavicular components of the brachial plexus
 - b. Axillary and musculocutaneous nerves may rarely be affected
 - c. The tibial nerve is more often affected than the sciatic nerve in the thigh
 - d. Median > ulnar > radial nerve are affected; the proximal portions of the nerve are more often affected than the distal

Neuropathology

1. A well encapsulated growth that displaces adjacent nerve fascicles laterally
2. Antoni Type A (hypercellular compact or palisading regions) is the predominant pathology
3. A plexiform Schwannoma is a rare variant that accounts for 5% of all Schwannomas; it can be associated with neurofibromatosis type 2 or Schwannomatosis
4. Sox-10 is a marker for Schwannian and melanocytic neoplasms

Neuroimaging

1. Well circumscribed mass by MRI neurography
2. Intermediate signal intensity on T2-weighted sequences
3. Ultrasonography can adequately delineate the tumor
4. Differentiation of malignant soft tissue tumors from a peripheral Schwannoma
 - a. In Schwannomas:
 - i. Split fat sign
 - ii. Bright rim sign
 - iii. Lobular shape and peritumoral edema are more common with malignant soft tissue tumors

Variant Schwannomas

Cellular Schwannoma

General Characteristics

1. Comprise approximately 10% of schwannomas
2. Primarily located in paravertebral paraspinal locations in association with autonomic or spinal nerves
3. Slightly more prevalent in females 1.4 to 1.6:1
 - a. Usually occur in the fifth decade

Clinical Manifestations

1. Mass in a paravertebral location
2. Pain in affected root distribution
3. Rare intracranial locations compress associated structures

Neuropathology

1. Variable hemorrhage
2. High cellularity Antoni type A pattern
3. Antoni type B zones are seen in 2/3 of tumors
4. Dense pericellular reticulin staining and strong S100 protein immunoreactivity

Neuroimaging

1. MRI:
 - a. Inhomogeneous T2-weighted signal in areas of cystic change
 - b. T1-weighted sequences demonstrate well encapsulated lobular mass

Melanotic Schwannoma

General Characteristics

1. The melanotic schwannoma is the least common variant
2. The age at presentation is a mean of 35 years with a female to male ratio of 1.2:1
3. Approximately 50% are associated with the Carney complex: myxomas, spotty pigmentation and nodular adrenocortical disease (Cushing's syndrome), pituitary adenoma (acromegaly) and large cell calcifying sertoli tumors
4. Tumors may involve the GI tract, retroperitoneum, liver, bone, chest wall and soft tissue of the chest and trunk

Clinical Manifestations

1. May involve spinal nerve root with accompanying weakness, sensory loss or pain
2. Rare involvement of the Vth nerve

Neuropathology

1. Tumor cells may be extremely melanotic
2. Cytoarchitecture includes:
 - a. Spindled and dendritic forms
 - b. Fusiform cells
 - c. Epithelioid cells

Neuroimaging

1. MRI:
 - a. 20% of patients have multiple tumors
 - b. Low signal T1-weighted sequence calcified bodies that resemble psammoma bodies
 - c. Circumscribed, lobulated tumors
 - d. High intensity signal in areas of cystic degeneration on T2-weighted sequences

Neurofibromas

General Characteristics

1. Solitary neurofibromas are the most common tumor of peripheral nerves
2. Tumors develop from the second to fourth decade; cutaneous forms may occur in childhood and adolescence
3. Cutaneous nerves, deep nerves, and visceral autonomic fibers are the most often affected; spinal nerve roots are

frequently affected; intracranial sites are rare (as opposed to schwannomas)

4. Neurofibromas may undergo malignant transformation which occurs in 5 to 10% of the plexiform variant; patients with neurofibromatosis type 1 (NF1) have a 10% lifetime risk of developing a malignant nerve sheath tumor

Neurofibroma Not Associated with Von Recklinghausen's Disease

General Characteristics

1. Females are affected more than males
2. Occur as localized mass; may involve a long segment of the nerve
3. Most often there is no cleavage plane; total removal may require nerve section

Clinical Manifestations

1. Arise from the motor more often than the sensory portion of the nerve
2. The nerve can be displaced side to side but not longitudinally
3. More painful than Schwannomas
4. Fusiform > plexiform
5. Tinel's sign is nearly universal
6. R > L side of the body
7. Location:
 - a. Supraclavicular > infraclavicular brachial plexus compartments 4:1
 - b. Axillary nerve > the radial nerve
 - c. Pelvic plexus > sciatic nerve in the thigh
 - d. Sciatic nerve in the buttock, peroneal and tibial nerve have equal incidences
 - e. Painful particularly if partially resected

Neuropathology

1. A classification divides neurofibromas into intraneural and diffusively infiltrative variants
2. Intraneural lesions are solitary, fusiform or less commonly multinodular with involvement of many branches
 - a. A plexiform growth pattern is pathognomonic of neurofibromatosis type I
3. Histopathologic features:
 - a. Spindle shaped, wavy Schwann cells that are arranged in loose bundles
 - b. Matrix of collagen and mucopolysaccharide
 - c. There are scattered perineurial cells and fibroblasts
 - d. Myelinated and non-myelinated nerve fibers are within the tumor
 - e. Arise from the perineurial fibroblast

Neuroimaging

1. Irregular T2-weighted and gadolinium enhanced signals
2. The tumors are usually not encapsulated and grow into adjacent tissue; rarely a tumor is confined beneath the epineurium

3. Solitary tumors diffusely expand into endoneurial spaces across perineurial lines; they appear as globoid masses with a fusiform enlargement of the affected nerve and diffusely spread individual nerve fibers
4. Plexiform neurofibromas:
 - a. Involve multiple nerve fascicles with thickening of nerve branches

Neurofibromas Associated with Von Recklinghausen's Disease

General Characteristics

1. Autosomal dominant with full penetrance; chromosome 17 mutation; 50% are new mutations
2. Incidence of 1/3000 persons; often patients have few symptoms
3. Tumors are found in nerve endings in the skin as well as proximal nerves
4. An approximate 10% chance of malignant degeneration

Clinical Manifestations

1. Patients present at an earlier age than those with isolated neurofibromas
2. Both motor and sensory symptoms
3. There is anesthesia in the center of a small neurofibroma whose origin is from a small intraepidermal nerve
4. Painful Tinel's sign is usually present in affected nerves location:
 - a. Supraclavicular > infraclavicular in the brachial plexus at 3:1
 - b. Axillary nerve > musculocutaneous nerve
 - c. Ulnar > median > radial nerve involvement
 - d. Tibial > peroneal > saphenous nerve involvement
 - e. Radicular signs and symptoms

Neuropathology

1. Similar to that of an isolated neurofibroma
2. Plexiform neurofibroma is diagnostic of NF-1

Neuroimaging

1. Tumors of the CNS:
 - a. Optic nerve glioma
 - b. Gliomas and astrocytomas
 - i. Midline location
 - c. Non-tumoral white matter lesions:
 - i. Unidentified bright objects (UBO)
 - ii. Typical location is the basal ganglia and posterior fossa structures
 - iii. The lesions are most prevalent in childhood and fade with age; a rare malignant transformation has been documented
 - d. Plexiform variants most frequently involve the lumbosacral plexus
 - e. Hydrocephalus

- f. Neurofibromas are homogeneous oval or nodular tumors that may extend into the spinal canal (intradural extramedullary spinal compartment)
- g. Dural sac abnormalities may be associated with meningocele formation
- h. Neurofibrosarcoma:
 - i. May develop de novo
 - ii. Sarcomatous degeneration of a pre-existing plexiform neurofibroma occurs
 - iii. A large heterogeneous tumor that invades adjacent structures
- i. Osseous lesions with NF-1 include:
 - i. Thoracic scoliosis
 - ii. Vertebral anomalies (posterior scalloping)
 - iii. Long bone anomalies with bowing of the tibia; may cause pseudoarthrosis
 - iv. Rib anomalies (ribbon ribs)
- j. Vasculopathy that may be associated with aneurysm formation and hypertension

Intraneural Perineuroma

General Characteristics

1. There are two major forms of perineuroma:
 - a. Intraneural
 - b. Extranural
2. It is a benign neoplasm composed exclusively of well-differentiated whorls of perineural cells surrounding nerve fibers well circumscribed within the confines of a peripheral nerve
3. Extranural perineuroma is also composed of perineural cells which are found in soft tissue and skin
4. Perineural cells surround nerve fascicles and constitute a component of the blood-nerve barrier
5. They create tight junctions in association with endothelial cells
6. One patient had a clonal expansion associated with chromosome 22 abnormalities

Clinical Manifestations

1. Median age of onset of neurological symptoms was 14 years (6 months to age 55)
2. Chief complaint on presentation is weakness and atrophy; a few patients (<10%) have numbness and pain as the presenting symptom
3. Motor weakness in the distribution of the affected nerves has been detected in almost all patients
4. Approximately 2/3 of patients have sensory loss in the distribution of the affected nerve
5. Muscle stretch reflexes are diminished or absent in the affected nerve
6. The most common nerves affected are the sciatic nerve or its branches
7. Other affected nerves and plexuses include:
 - a. Brachial plexus

- b. Radial nerve
- c. Ulnar nerve
- d. Median nerve
- e. Femoral nerve
- f. Trigeminal nerves
- g. Lumbosacral plexus
- 8. Most common pattern of involvement is a mononeuropathy; approximately 15% have plexopathy; rare to have bilateral disease

Neuropathology

1. Perineural cells are immunoreactive for EMA (epithelial membrane antigen), CD34, Glut1 and claudin-1 which are diagnostic markers
2. Nerve biopsy:
 - a. The tumor cells form a whirling arrangement into a fasciculated or laminated pattern
 - b. The cytoarchitecture of the tumor cell is a fusiform shape with bipolar cellular processes and a spindled nucleus
 - c. Layers of spindle shaped cells surround a central nerve fiber

Laboratory Evaluation

1. The majority of patients have a normal CSF protein. There is no pleocytosis and a few patients demonstrate slight increase of protein
2. EMG:
 - a. Axonal degeneration is the characteristic finding
 - b. Needle EMG:
 - i. Fibrillation potentials and large motor unit potentials
 - c. In a majority of patients, there is reduction or absence of SNAPs
3. QST:
 - a. Increased thresholds to all modalities in affected nerves

Neuroimaging

1. MRI:
 - a. Fusiform nerve enlargement
 - b. Isointense on T1-weighted sequences; avid enhancement with gadolinium

Differential Diagnosis of Rare Benign Neural Sheath Tumors

1. Hybrid peripheral nerve sheath tumors:
 - a. Demonstrate hybrid features of more than one cell type:
 - i. Schwannoma/perineuroma
 - ii. Neurofibroma/perineuroma
 - iii. Granular cell tumor/perineuroma
2. Neurothekeoma:
 - a. Occurs in patients less than 30 years of age
 - b. Commonly misdiagnosed as Schwannoma

- c. Soft mobile tumor of the dermis
 - d. Schwann cell or perineural origin
 - e. Tumor cells in fascicles circumscribed by a myxoid stroma
3. Nerve sheath myxoma:
- a. Myxoma may have a superficial resemblance to a neurofibroma
 - b. Occurs on the face and upper extremities of young women
 - c. A loose aggregation of spindle, stellate and ovoid cells in a myxomatous matrix

Differential Diagnosis of Benign Non-Neural Sheath Tumors

- vii. Normal fatty tissue; genetic HMGA2 rearrangement is characteristic of soft tissue lipoma
6. Lipohamartoma:
- a. Intrinsic to nerve
 - b. Involves the median nerve at the wrist or in the palm and causes its dysfunction
 - c. Composed of normal fatty tissue that may envelope the nerve
7. Hemangiopericytoma:
- a. Most often arises in the cerebellum often in the setting of Von Hippel-Lindau syndrome
 - b. Rarely arises at peripheral sites
 - c. May arise from spinal nerves and within a nerve
 - d. Usually arises in the mediastinum and may compress the brachial plexus
 - e. All tumors have a complex network with large thin-walled vessels
 - f. Tumors express neurospecific endolase, S100 protein GLUT-1
8. Hemangioma:
- a. They are benign neoplasms that closely resemble normal tissue
 - b. May be found in all organs of the body
 - c. High or low flow characteristics by MR angiography
 - d. May be intrinsic to peripheral nerves
9. Ganglions:
- a. In most instances they arise from joints and may compress contiguous nerves
 - b. They often present as pain and paresthesias of the affected nerve
 - c. Compress adjacent nerves at the following levels:
 - i. Thenar sensory branch of the median nerve
 - ii. Ulnar palmar branch
 - iii. Median and ulnar major trunks
 - iv. Radicular junction (posterior interosseous nerve)
 - v. Knee (peroneal nerve)
 - vi. Ankle (posterior tibial nerve)
 - vii. Shoulder (brachial plexus); suprascapular nerve at the scapular notch
 - viii. Elbow > radial > median > ulnar nerves
 - ix. Ganglions without joint connections
 - 1. Intraneural ganglions:
 - a. Extend great distances with the nerves
 - b. Cause motor and sensory nerve deficits
10. Epidermoids cysts:
- a. Congenital epidermoid cysts are common in aberrant spinal cord closure (dysraphisms)
 - b. Often they are associated with filum terminal defects and lipomas; they may occur in many areas of the neuraxis and intracranially
 - c. Acquired epidermoid cysts may occur following lumbar puncture
 - d. In peripheral nerve compression the sciatic nerve is affected at the sciatic notch and in the posterior popliteal fossa

Malignant Peripheral Nerve Sheath Tumors (MPNST)

Overview

Malignant peripheral nerve sheath tumors are spindle cell sarcomas that arise from a nerve or a pre-existing benign nerve sheath tumor. They may be a sarcoma that demonstrates nerve sheath differentiation. Most MPNSTs are malignant degenerations of neurofibromas. Malignant transformation of a schwannoma is extremely rare. Malignant degeneration of neurofibroma in patients with NF-1 is 4.0 to 4.6% (usually from the plexiform variant). There is a slight male predominance in NF-1. Approximately 10% of all soft tissue sarcomas are MPNST. Malignant peripheral nerve tumors may occur following X-RT. They may, as noted, rarely arise from malignant transformation of Schwannomas and ganglioneuromas.

The tumors are most often associated with major nerve trunks. They are most often located in the proximal extremities, trunk, and occasionally in the head and neck. Extremely rarely, they will affect a cranial nerve. NF-1 associated tumors tend to be centrally located. Multifocal tumors are also rare. The clinical presentation is one of an expanding mass that is painful and is associated with motor and sensory deficits of the affected nerve. The tumor may be firmer than benign neural sheath tumors and is often adherent to adjacent structures. There is a rapid increase in size. Patients may present with metastases to lung, bone or the liver. The recurrence rate after treatment with X-RT and chemotherapy is high. The five-year survival rate with tumors arising in the setting of NF-1 is approximately 16% versus 53% in those that are sporadic.

The histologic features vary although the majority of patients demonstrate densely cellular fascicles of spindle cells (herringbone or storiform patterns). Necrosis is common. Patients with NF-1 may demonstrate heterologous differentiation that includes rhabdomyosarcomatous features (malignant triton tumor): these include skeletal muscle, bones, cartilage, epithelial and neuroendocrine components.

MPNST with Rhabdomyoblastic Differentiation (Malignant Triton Tumors)

General Characteristics

1. Malignant triton tumor defines those that demonstrates rhabdomyoblastic differentiation
2. Approximately 70% of these tumors are seen in patients with NF-1

Clinical Manifestations

1. Occur in young patients
2. May arise anywhere in the peripheral somatic nervous system including the head, neck, and trunk
3. Rarely occur in cranial nerves; the most frequent nerve involved is VIII
4. A poor five years survival rate of 12%

Neuropathology

1. The distinctive feature of the tumor is rhabdomyoblast distribution throughout the tumor
2. There are areas of necrosis
3. Immunohistochemical stains are positive for desmin and myoglobin within the rhabdomyoblasts
4. S100 protein is positive within the normal Schwann cells

Epithelioid MPNST

General Characteristics

1. More common in superficial sites
2. MPNST that arises from pre-existing Schwannoma are epithelial in type

Clinical Manifestations

1. Similar to that of Schwannoma but less often arise from nerve trunks
2. Deficits of motor and sensory function of the involved peripheral nerve

Neuropathology

1. Epithelioid cells have granular abundant eosinophilic cytoplasm that is arranged in nests or cords
2. The tumors express S100 protein
3. The differential diagnosis of epithelioid MPNST tumor includes melanoma, clear cell sarcoma, epithelioid sarcoma, and carcinoma

Differential Diagnosis of MPNST

1. NF-1
2. Schwannoma
3. Variety of sarcomas
4. Adult-type fibrosarcoma
5. Synovial sarcoma
6. Rhabdomyosarcoma
7. Leiomyosarcoma
8. De-differentiated liposarcoma
9. Clear cell sarcoma

Traumatic and Compressive Neuropathies

Overview

1. Peripheral nerve injuries occur in 2 to 3% of patients admitted to level 1 trauma centers; the addition of root and plexus injuries increases this figure to 5%
2. Definitions for injuries:
 - a. Neuropraxia: axons are intact but fail to conduct action potentials due to focal demyelination or loss of ion channels and paranodal proteins
 - b. Axonotmesis: transection of axons but the nerve trunk is intact
 - c. Neurotmesis: a transected nerve trunk

3. Sunderland Classification of Peripheral Nerve Injury
 - a. First degree: disruption of the myelin sheath with intact axon and stroma
 - b. Second degree: transection of axons with intact stroma
 - c. Third degree: transection of axons and the endoneurium; the perineurium is intact
 - d. Fourth degree: transection of the axons, endoneurium, and perineurium; fascicular transection occurs; the epineurium is intact
 - e. Fifth degree: transection of the nerve trunk
4. Prognosis after peripheral nerve injury depends upon:
 - a. The degree of injury
 - b. Distance from the muscle and area of sensory innervations
 - c. Activation of the genetic pathways that control the process of Wallerian degeneration and repair

Dorsal Scapular Nerve

General Characteristics

1. Arises directly from the C5 spinal nerve after it exits the intervertebral foramen. It courses between the middle and posterior scalene muscle to innervate the major and minor rhomboid muscles and the levator scapulae
2. The rhomboids adduct the scapula to the midline; the levator scapulae lift and slightly rotate the scapula forward

Clinical Manifestations

1. The superior portion of the scapula is deviated laterally; the shoulder sags (levator involvement)
2. Interscapular pain

Neuropathology

1. Usually a compression injury from improper backpack loading
2. Rarely trauma

Long Thoracic Nerve

General Characteristics

1. Derived from the C5, C6, C7 spinal nerves prior to the origin of the brachial plexus
2. Innervates the serratus anterior muscle

Clinical Manifestations

1. Paralysis of the serratus anterior muscle with scapular winging (primarily the ventral and tip of the scapula)
2. Shoulder stabilization is decreased
3. There is no cutaneous innervation
4. The inferior scapular border is rotated medially; the vertebral border is more prominent when the arm is extended against resistance

Differential Diagnosis

1. Neuralgia amyotrophica:

- a. Probable viral origin that may damage the nerve or its component roots in isolation
 - b. Severe shoulder pain for days to weeks
 - c. Difficulty with shoulder movement (destabilization and pain)
2. Intercostobrachial nerve damage from the medial cord of the brachial plexus:
 - a. This is a purely sensory nerve that innervates the lateral and upper anterior chest wall and radiates under the breast to the midline
 3. Limb-girdle muscular dystrophy
 - a. Muscle disease is almost always symmetrical (congenital forms)
 4. The long thoracic nerve is a major component of scapular winging that may be caused by:
 - a. Injury (usually traction)
 - b. Periscapular and soft tissue abnormalities
 - c. Brachial plexus injury
 - d. Facioscapulohumeral dystrophy and other myopathies
 - e. The long thoracic nerve may be injured during first rib resection
 - f. Subscapular osteochondroma
 - g. Rupture of the rhomboid and trapezius muscles
 5. The long thoracic nerve may be injured in isolation due to breast cancer surgery or cosmetic breast surgery (implants)

Suprascapular Nerve

General Characteristics

1. C5–C6 are its roots of origin; it arises from the upper trunk of the brachial plexus and traverses the suprascapular notch
2. Rarely, anomalous branches may contribute to innervations of axillary nerve territory

Clinical Manifestations

1. Impingement at the suprascapular notch causes shoulder pain
2. There are no cutaneous innervations; sensory innervations are in the deep tissues (muscles of the capsule of the glenohumeral joint)
3. There may be deep throbbing pain along the superior border of scapula toward the shoulder (exacerbated by stretching the adducted arm across the chest)
4. If there is entrapment in the suprascapular notch there is a weakness of both supra- and infraspinatus muscles; if an injury occurs at the lateral border of the spine, the infraspinatus muscle is involved in isolation
5. Weakness of the first 30 degrees of abduction occurs with supraspinatus weakness; external rotation of the arm is compromised with infraspinatus weakness
6. Infraspinatus injury at the spinoglenoid notch is painless and may only involve this muscle
7. Pain may be severe at the suprascapular notch

Differential Diagnosis

1. Entrapment usually occurs at the suprascapular notch; rarely the nerve may be compromised at the spinoglenoid notch
2. Repetitive overhead movements (baseball pitchers; meat cutters)
3. Ganglion cysts
4. Sarcoma
5. Metastatic disease
6. Positioning during surgical procedures (knee-chest position)
7. Weightlifting (shoulder abduction and protraction)
8. Volleyball, dancing, baseball pitchers (the injury is distal often at the spinoglenoid notch)
9. Associated with neuralgia amyotrophica (along with other shoulder girdle nerves)

Differential Diagnosis of Supra- and Infrascapular Nerve Lesions

1. Musculoskeletal pain around the shoulder that is generated from:
 - a. Subacromial bursitis
 - b. Bioccipital tendonitis
 - c. Acromioclavicular joint arthritis or separation (typical football injury)
 - d. Pericapsular fibrosis
 - e. Rotator cuff injury (no weakness)
 - f. C5, C6 radiculopathy; refers pain to the deltoid cap (C5); C6 (thumb and lateral forearm); often pain in this instance radiates to the upper arm; weakness of the biceps, depressed biceps, and brachioradialis muscle stretch reflexes
 - g. Brachial neuritis (Parsonage-Turner syndrome; neuralgia amyotrophica)
 - i. Abrupt onset of pain and weakness of other muscles innervated by the plexus; may be bilateral
2. Brachial plexus traction injury (neuropraxic):
 - a. Tinel's sign at the supra- and infraclavicular fossa
 - b. Mechanical allodynia of the neurovascular bundle when compressed against the humerus
 - c. Tinel's signs at the Arcade of Frohse and pronator canal
 - d. Positive Roos abduction stretch maneuver (the arms are held in a surrender position) which induces trunk and cord sensory loss and weakness

Nerve to the Subclavius Muscle*General Characteristics*

1. Arises from the C5 root or upper trunk of the brachial plexus
2. Innervates the small subclavius muscle between the clavicle and the first rib
3. One of the destinations of the C4 ventral ramus that forms the prefixed brachial plexus

Clinical Manifestations

1. Variation of the subclavius muscle
 - a. Attaches medially to the first rib by a tendon and to the clavicle by fibrous bands
 - b. Possible component of thoracic outlet syndrome

Medial Pectoral Nerve*General Characteristics*

1. The spinal nerves innervating the muscles are C8 and T1; it arises from the medial trunk of the brachial plexus to innervate the pectoralis major and pectoralis minor muscles
2. The nerve innervates the pectoralis major and minor muscles that are a component of adduction flexion and extension and medial rotation of the shoulder joint
3. The muscle also contributes to the stabilization of the glenohumeral joint

Clinical Manifestations

1. Loss of muscle functions as noted; if the muscle is denervated the shoulder is abducted, laterally rotated, retracted and elevated (compensatory from antagonistic muscles)

Differential Diagnosis

1. The nerve is injured during mastectomy (modified radical mastectomy) and during breast reconstruction
2. The nerve may be injured during breast augmentation surgery
3. Severe trauma (motor vehicle accidents; contact sports)
4. In association with brachial plexus pathology
5. The pectoral nerves may be used as donors to the musculocutaneous, axillary long thoracic and spinal accessory nerves during reconstruction procedures

Lateral Pectoral Nerves (LPN)*General Characteristics*

1. Arise primarily from the lateral cord of the brachial plexus; it may arise from the anterior division of the upper and middle trunk prior to the formation of the lateral cord
2. It is innervated by C5–C7 spinal nerves
3. The medial and lateral pectoral nerves are most frequently connected distally to the thoracoacromial artery by the ansa pectoralis
4. The LPN supplies the upper portions of the pectoralis major muscle

Clinical Manifestations

1. Major functions that are compromised by injury are protraction and depression of the scapula
2. The nerve may be injured by:
 - a. Direct trauma
 - b. Hypertrophic muscle compression
 - c. Axillary node dissection
 - d. Breast surgery for cancer and reconstruction
 - e. Cosmetic breast surgery
 - f. Utilized for nerve transfers

Spinal Accessory Nerve

General Characteristics

1. The component of the nerve from the medulla supplies the soft palate; the cranial component merges with the vagal nerve
2. In the majority of people, the spinal component originates in the upper cervical spinal cord to C5
3. The spinal component has a long course as it ascends between the dentate ligament and posterior spinal nerve roots to enter the skull foramen and exits through the jugular foramen; the nerve descends posterior to the digastric and stylohyoid muscles to innervate the sternocleidomastoid and trapezius muscles

Clinical Manifestations

1. The ability to tip the head and rotate the cranium contralaterally is decreased or lost with a sternocleidomastoid injury
2. The trapezius muscle has several scapular functions that include elevation of the shoulder. It also is a component of arm abduction
3. The nerve may be surgically injured from medical procedures (surgery) of the head and neck. A common procedure that injures the nerve is a simple posterior triangle lymph node biopsy. The distal part of the nerve is most often injured
4. Lymphoma, neck cancers and severe trauma (spinal cord injury) injure the nerve

Phrenic Nerve

General Characteristics

1. The major spinal nerve comprising the phrenic nerve is C4. It receives contributions from C3 and C5
2. The nerve descends obliquely in association with the internal jugular vein across the anterior scalene muscle deep to the prevertebral layer of the deep cervical fascia and across the transverse cervical and suprascapular arteries. On the left side, it crosses the initial part of the subclavian artery while on the right, it crosses the anterior scalene muscle and traverses the second component of the subclavian artery. Bilaterally it is posterior to the subclavian vein and passes anteriorly to the root of the lung. It lies between the fibrous and parietal layers of the pericardium. The nerve passes through the vena cava hiatus at the level of T8
3. The motor components of the phrenic nerve innervate the diaphragm while sensory fibers innervate the fibrous pericardium, mediastinal pleura, and the diaphragmatic peritoneum

Clinical Manifestations

1. Rapid respiratory failure is accompanied by:
 - a. Anxiety
 - b. Tachypnea

- c. Tachycardia
 - d. Diaphoresis
2. Paradoxical respiration may occur:
 - a. The abdominal wall retracts during inspiration due to the inability of the diaphragm to contract while a negative intrathoracic pressure is generated by the intercostals and accessory muscles of respiration
 - b. Respiratory alternans may occur, in which the diaphragm descends only on alternate breaths (most often seen with airway obstruction)
 - c. These patterns of respiration are seen in acutely ill patients when the vital capacity is approximately 10% of normal (500 ml in an average-sized man)
 3. Patients with weakness of respiratory muscles may have $p\text{CO}_2 > 40$ torr (in acute respiratory failure $p\text{CO}_2$ may be > 70 torr) which can cause:
 - a. Daytime somnolence
 - b. Early morning headache
 - c. Rarely papilledema
 4. Patients with only one diaphragm affected are most often normal at rest but become dyspneic too easily with exertion
 5. Irritation of the phrenic nerve often initiates the hiccup reflex:
 - a. A hiccup is a spasmodic contraction of the diaphragm that causes inhalation of air against the closed folds of the larynx
 6. The phrenic nerve may be injured during various surgical procedures that include:
 - a. Open heart surgery
 - b. Abdominal surgery
 - c. First rib removal (thoracic outlet surgery)
 - d. Cancer surgery of the neck
 - e. The right phrenic nerve may be injured by the vena cava clamp during liver transplantation

Differential Diagnosis of Neuromuscular Diseases That May Present with Subacute Respiratory Failure

1. Manifest as dyspnea and exercise intolerance:
 - a. Motor neuron disease
 - b. Myasthenia gravis
 - c. Lambert-Eaton syndrome
 - d. Polymyositis/dermatomyositis
 - e. Acid maltase
 - f. Mitochondrial myopathy
 - g. AIDP
 - h. All processes that affect the neuromuscular junction

Subscapular Nerves

General Characteristics

1. The upper and lower subscapular nerves arise from the posterior cord in the axilla
2. The subscapularis muscle fills the subscapular fossa and inserts into the lesser tubercle of the humerus, anterior to the capsule of the shoulder joint

3. Its major function is to rotate the head of the humerus medially when the arm is raised; it also pulls the humerus forward and downward
4. It is the most powerful muscle of the rotator cuff and stabilizes the glenohumeral joint
5. The lower subscapular nerves supply the teres major

Clinical Manifestations

1. There are multiple variations in the origin of the lower subscapular nerve, which is important for surgical procedure in the axilla:
 - a. It may take origin from the axillary nerve in 40–50% of patients
2. Injuries to the subscapular nerves occur in:
 - a. Surgical procedures of the axilla
 - b. Scapular fractures
 - c. Shoulder dislocations
 - d. Infraclavicular brachial plexus blocks

Thoracodorsal Nerve

General Characteristics

1. The thoracodorsal nerve takes origin from the posterior cord to innervate the latissimus dorsi muscle
2. Anatomic variations include origins from the radial or axillary nerves
3. The major spinal nerve is C7 with contributions from C5 and C6

Clinical Manifestations

1. The latissimus dorsi muscle is a functional component for:
 - a. Extension adduction and transverse extension (horizontal adduction)
 - b. Flexion from an extended position
 - c. Internal rotation of the shoulder joint
 - d. It has a synergistic role in extension and lateral flexion of the lumbar spine
2. The nerve may be injured by:
 - a. High-velocity trauma such as motor vehicle accidents (MVA), including motorcycle accidents
 - b. Brachial plexus pathologies
 - c. Rotator cuff surgery

Medial Cutaneous Nerve of the Arm

General Characteristics

1. It arises from the medial cord of the brachial plexus
2. It is composed of spinal nerves C8 and T1
3. It traverses the axilla, behind and then medial to the axillary vein
4. It communicates with the intercostobrachial nerve

Clinical Manifestations

1. The nerve provides sensation to the medial upper arm above the elbow
2. The nerve is injured:

- a. During axillary dissection for lymph nodes
- b. Mastectomy
- c. Brachial plexus injury
- d. Maybe injured in concert with injuries to the intercostobrachial nerve

Medial Cutaneous Nerve of the Forearm

General Characteristics

1. Usually, arises from the medial cord; a variation is its origin from the medial cutaneous nerve of the arm
2. It is derived from the 8th cervical and first thoracic nerves medial to the axillary artery
3. It gives off a branch near the axilla that supplies the integument that covers the biceps brachii
4. Divides into a volar and ulnar branch
5. Supplies sensation from the medial forearm to the wrist
6. Injuries of the nerve:
 - a. Steroid injection for epicondylitis
 - b. Venipuncture
 - c. Open fracture fixation
 - d. Tumor excision
 - e. Elbow arthroscopy
 - f. Rare subcutaneous lipoma

Musculocutaneous Nerve

General Characteristics

1. The musculocutaneous nerve arises from the lateral cord of the brachial plexus
2. It is derived from spinal nerves C5, C6, C7
3. Its usual course is through the coracobrachialis muscles to the biceps brachiale and the brachialis; it pierces the deep fascia lateral to the tendon of the biceps brachii. It continues into the forearm as the lateral cutaneous nerve of the forearm
4. Variations:
 - a. May not penetrate the coracobrachialis
 - b. The median nerve may project to join the nerve
 - c. May pass through the biceps brachii
 - d. May project a filament to the pronator teres
 - e. May supply the dorsal surface of the thumb when the superficial branch of the radial nerve is absent
 - f. In approximately 5% of the population, the nerve originates from the anterior division of the upper trunk; in this situation, the lateral component to the median nerve takes origin from the middle trunk
5. The nerve innervates:
 - a. The coracobrachialis
 - b. Biceps brachii
 - c. Brachialis
 - d. Terminals of the lateral cutaneous nerve of the forearm form sensory innervation of the lateral aspect of the forearm from the elbow to the wrist

Clinical Manifestations

1. Weakness of elbow flexion and supination of the forearm

2. Decreased sensation on the lateral side of the forearm
3. Decreased biceps and brachioradialis reflexes

Neuropathology

- a. The nerve is usually injured in association with upper brachial plexus injuries
- b. Entrapment due to hypertrophy or compression between the biceps aponeurosis and the brachialis fascia
- c. Neuropractic injury during surgery
- d. It is injured at the coracobrachialis level due to stretch or from repetitive movements above the horizontal
- e. Distal to the coracobrachialis:
 - i. Injuries may be due to weight lifting
 - ii. Benign humeral exostosis

Axillary Nerve

General Characteristics

1. Arises from the posterior cord, and is derived from spinal nerves C5 and C6
2. It lies behind the axillary artery and in front of the subscapularis muscle in company with the posterior humeral circumflex artery to traverse the quadrilateral space
3. The quadrilateral space:
 - a. Is bounded above by the subscapularis muscle, below by the teres major muscle, medially by the long head of the triceps brachii muscle, and laterally by the neck of the humerus beneath the deltoid muscle. It divides into:
 - i. The anterior branch:
 1. Innervates the deltoid muscle
 2. Cutaneous branches to supply the skin overlying the deltoid muscle
 - ii. Posterior branch:
 1. Innervates the teres minor and posterior fascicles of the deltoid muscle
 2. Continues as the superior (upper) lateral cutaneous nerve of the arm to supply the skin over the lower 2/3 of the muscle and the long head of the triceps brachii
 - iii. A motor branch to the long head of the triceps
 - iv. The trunk of the axillary nerve gives off an articular collateral branch to the shoulder joint

Clinical Manifestations

1. Weakness of abduction (15–90 degrees) and external rotation of the shoulder
2. Slight weakness of shoulder extension
3. Paralysis of the deltoid and teres minor muscles results in a flat shoulder deformity
4. Quadrilateral space syndrome:
 - a. Compression of the axillary artery and at times the posterior circumflex humeral artery (PCHA)
 - i. Caused by fibrous bands between the teres major and the long head of the triceps tendon

Clinical Manifestations of Quadrilateral Space Syndrome

1. Point tenderness in the quadrilateral space
2. Poorly localized posterior shoulder pain and paresthesia that are exacerbated by humeral abduction and external rotation; patients present with pain from performing overhead tasks
3. The pain can also radiate in a non-dermatomal pattern and may be associated with teres minor and deltoid muscle atrophy

Pathogenesis of Injuries to the Radial Nerves

1. Dislocation and fracture of the shoulder
2. Fracture of the humerus
3. Surgical positioning
4. Entrapment in the quadrilateral space

Laboratory Evaluation

1. EMG:
 - a. Denervation of the deltoid and teres minor
2. MRI:
 - a. Suspected quadrilateral space patients
 - i. Selective fatty infiltration of the teres minor with atrophy; atrophy of the deltoid muscle
 - ii. Increased signal intensity on T2-weighted images of the axillary nerve
3. MRA to evaluate compression of the posterior circumflex humeral artery
4. Ultrasound guided technique for a diagnostic quadrilateral space block

Differential Diagnosis

1. Orthopedic shoulder conditions
2. C5–C6 radiculopathy
3. Brachial plexus traction injury
4. Neuralgia amyotrophica
5. Suprascapular neuropathy

Radial Nerve

General Characteristics

1. The primary spinal nerves that comprise the radial nerve are C5–C8; in approximately 10% of people, there is a contribution from T1
2. It is the continuation of the posterior cord
3. Its branches innervate the dorsal arm muscles (the triceps brachii and the anconeus) as well as the extrinsic extensors of the wrist and hand
4. It provides most of the cutaneous innervations to the back of the hand. It is most often damaged in the upper arm and axilla but is the least involved of the nerves of the arm
5. In the axilla, it gives off the posterior cutaneous nerve that innervates the posterior aspect of the upper arm to the elbow
6. In the proximal upper arm, it descends medial to the humerus through the triangular space between the medial and long heads of the triceps muscles along the spiral groove of the humerus

7. In the upper arm, it innervates the long medial and lateral heads of the triceps brachii and the anconeus muscle
8. After exiting the spiral groove it innervates:
 - a. Brachioradialis
 - b. Extensor carpi radialis longus
 - c. Brachialis
 - d. Supinator
9. Four centimeters proximal to the lateral epicondyle, the nerve bifurcates into the superficial sensory nerve and the posterior interosseous nerve
 - a. The superficial radial sensory nerve supplies the dorso-lateral hand, the lateral part of the thumb, and the proximal phalanges of the index, middle, and ring fingers; it lies under the brachioradialis
 - b. The superficial radial nerve traverses the upper forearm on the underside of the brachioradialis muscle and the side of the radial tunnel. In the mid forearm, it lies superficially. Once past the wrist it innervates sensation for:
 - i. Extensor surface of the hand and fingers except for the distal finger tips (supplied by the median and ulnar nerves); and the dorsum of the medial aspect of the hand and medial fingers that are supplied by the dorsal ulnar cutaneous nerve
 - c. The posterior interosseous nerve is purely motor and innervates:
 - i. Extensor carpi radialis
 - ii. Extensor carpi ulnaris
 - iii. Extensor communis
 - iv. Abductor pollicis longus
 - v. Extensor digitorum communis (EDC)
 - vi. Extensor pollicis longus and brevis
 - vii. Extensor indicis proprius
 - viii. Supinator
 - d. The posterior interosseous nerve traverses the radial tunnel that is bounded by:
 - i. The radius
 - ii. The capsule of the radiocapitular joint
 - iii. The medial wall is formed by the tendons of the brachialis and the biceps brachii tendons
 - iv. The lateral and anterior walls are formed by the brachioradialis, extensor carpi radialis, and the extensor carpi ulnaris muscles
 - v. The radial tunnel terminates at the fibrous band around the superficial head of the supinator muscle known as the Arcade of Frohse
 - e. The posterior interosseous nerve descends under the Arcade of Frohse after traversing the radial tunnel
 - f. The posterior interosseous nerve innervates the interosseous membrane and joint between the radius and ulna

Radial Nerve Injury in the Axilla

General Characteristics

1. Often from compression

Clinical Manifestations

1. Wrist and finger drop
2. Weakness of supination
3. Loss of wrist and finger extension
4. Weakness of arm extension
5. Loss of sensation in the lateral arm, posterior forearm, lateral 1/2 of the dorsal aspect of 3 1/2 digits (excluding the tips of the fingers)
 - a. There is normal deltoid and thoracodorsal nerve function, which rules out a posterior cord lesion of the brachial plexus

Pathogenesis of the Injury

1. Crutch injury (long arm crutches)
2. Axillary surgery (hyperabduction; lymph node dissection)
3. Lymphoma or metastatic tumor
4. Transaxillary first rib resection for thoracic outlet syndrome

Laboratory Evaluation

1. EMG:
 - a. Focal slowing of the radial nerve in the upper arm (motor and sensory NCVs)
 - b. Denervation of radial nerve innervated muscles in the forearm
 - c. The triceps may be spared if the lesion is beyond the axilla

Radial Nerve Injury at the Spinal Groove

General Characteristics

1. Abuts the spinal groove in the mid-shaft of the humerus

Clinical Manifestations

1. Wrist and finger drop
2. Mild weakness of supination (loss of supinator muscle)
3. Slight weakness of elbow flexion (brachioradialis)
4. Spared elbow extension (C7 innervated muscles (triceps) comes off more proximally)
5. Loss of sensation in the posterior forearm; radial half of the dorsum of the hand and the dorsal 3 1/2 digits excluding the fingertips (superficial radial sensory nerve)

Pathogenesis of Nerve Injury

1. Fracture of the mid-shaft of the humerus (2 to 16% occur through the spiral groove)
2. Compression (Saturday night palsy)
3. Vasculitic infarction
4. Strenuous repetitive exercise
5. Multifocal neuropathy with conduction block
6. Compression by the lateral head of the triceps or by a fibrous band

Posterior Interosseous Nerve

General Characteristics

1. Pathology most often occurs just distal to the elbow

2. Injury to the deep branch of the radial nerve that pierces the radial head
3. There is no sensory loss; pain emanates from the innervations of the interosseous ligament

Clinical Manifestations

1. Following injury, patients complain of pain in the elbow and proximal forearm for a few days
2. Pain can be elicited by compression of the nerve distal to the radial head (extensor carpi radialis brevis)
3. Wrist extensor weakness with radial deviation; the extensor carpi ulnaris is weaker than the extensor carpi radialis
4. No extension of the fingers at the MCPs (metacarpal-phalangeal joints)
5. Loss of thumb extension at the MCP joint; no radial thumb abduction; weak extension of the thumb
6. Interphalangeal joints (IP joints) of the intrinsic hand muscles are innervated by the median and ulnar nerves
7. If there is partial paralysis of the nerve:
 - a. There is decreased extension of the MCP joint at digits IV and V; intact extension of the proximal interphalangeal digits (PID) and the distal interphalangeal digits (DIP) because they are innervated by the median ulnar nerves
8. Rare patterns of partial posterior interosseous nerve injury:
 - a. Weakness of MCP extension of the thumb
 - b. Weakness of extension of V

Pathogenesis of Nerve Injury

1. Fracture of neck of the brachialis
2. Elbow dislocation or fracture
3. Tight cast
4. Rheumatoid nodules
5. Injections for tennis elbow
6. Injury of the deep branch of the radial nerve that pierces the radial head (causes the posterior interosseous syndrome)
7. Ganglion cyst
8. Nerve sheath tumors
9. Entrapment under the Arcade of Frohse
10. Open reduction of the fractures at the proximal radius with plating
11. Tenderness band in the supinator muscles

Laboratory Evaluation

1. EMG:
 - a. Focal slowing of motor NCV across the Arcade of Frohse
 - b. Prolonged distal latency from the elbow to the FDC
 - c. The supinator muscle and the extensor carpi radialis are normal (supplied by more proximal components of the nerve)
 - d. Cutaneous branches of the superficial radial nerve are normal

Radial Tunnel Syndrome

General Characteristics

1. The true neurogenic syndrome requires weakness of posterior interosseous innervated muscles

Clinical Manifestations

1. Lateral elbow pain
2. Dull ache deep on extension of the muscle mass of the forearm
3. Night pain with distal and proximal radiations
4. Increased pain with resisted active supination of the forearm
5. Weakness of all posterior interosseus innervated muscles

Pathogenesis of the Nerve Injury

1. Fibrous, tendinous band at the Arcade of Frohse
2. Recurrent fan of aberrant muscles
3. Compression by the tendon of the extensor carpi radialis

Laboratory Evaluation

1. EMG:
 - a. Denervation of the EDC
 - b. ECR should be spared

Superficial Radial Nerve Injury

General Characteristics

1. In the past, this injury has been called Wartenberg's syndrome
2. Entrapment of the superficial radial nerve beneath the tendinous insertion of the brachioradialis muscle

Clinical Manifestations

1. The sensory deficits depend on the lateral antebrachial cutaneous nerve
2. Numbness, tingling and paresthesia in the radial half of the dorsum of the hand and the dorsal radial 3½ digits excluding the distal digits
3. There are no motor deficits
4. In Wartenberg's syndrome patients have wrist pain that is often confused with De Quervain's tenosynovitis (in which Finkelstein's test is often positive)

Pathogenesis of the Nerve Injury

1. Compression by handcuffs, bandages, and watch bands
2. Wartenberg's syndrome:
 - a. Compression beneath the tendinous insertion of the brachioradialis muscle
 - b. Surgical procedures for De Quervain syndrome
 - c. Tight casts
 - d. Joint degenerative arthritis
 - e. Scaphoid fracture
 - f. Accessory brachioradialis muscle compression

Differential Diagnosis of Radial Neuropathy

1. Most patients present with a wrist drop

2. A radiculopathy at C7:
 - a. This is the major spinal nerve that innervates the muscles of extension of the wrist and fingers; C5–C6 roots make major contributions and therefore the loss of extension with this root injury is never as severe as with a radial nerve injury
 - b. The sensory loss from C7 is in the third finger
3. Brachial neuropathy from injury at the spiral groove or axilla: Involves the brachioradialis muscle (C5–C6 spinal nerves) which is not affected by a C7 spinal nerve lesion; the triceps is spared but would be affected by a C7 spinal nerve injury
4. If the C7 spinal nerve is damaged, the pronator teres and radial nerve innervated muscles are weak
5. A posterior cord brachial plexus lesion would involve the subscapular thoracodorsal and the axillary nerve, as well as other radial nerve innervated muscles
6. An embolus from the internal carotid artery (central sulcal branch of the superior division of the middle cerebral artery) to the motor cortex may present with a wrist drop (pseudoradial palsy). Finger flexion is involved, and rarely individual fingers may be affected
8. In the mid forearm, the anterior interosseous nerve branches from the nerve. It is a pure motor nerve and innervates:
 - a. Flexor digitorum profundus 1+2
 - b. Flexor pollicis longus
 - c. Pronator quadratus
9. At the wrist:
 - a. Prior to entering the carpal tunnel, the median nerve gives off the palmar cutaneous branch which innervates the thenar eminence
 - b. The carpal tunnel is bounded by the carpal bones medially and laterally with the transverse ligament superiorly. The median nerve is accompanied in the carpal tunnel by the flexor tendons to the fingers
 - c. Either within or just distal to the carpal tunnel, the median nerve gives origin to the recurrent branch that innervates:
 - i. Abductor pollicis brevis
 - ii. The superficial head of the flexor pollicis brevis
 - iii. Opponens pollicis
 - d. The terminal branches of the median nerve supply:
 - i. The first and second lumbrical muscles
10. Digital branches are the sensory innervations of the volar aspects (and the nail beds) of the thumb, index, and middle fingers

The Median Nerve

General Characteristics

1. The median nerve is composed of components of the lateral and medial cords of the brachial plexus
2. Its contributions are from the ventral roots of C5, C6 and C7 (lateral cord) and C8 and T1 of the medial cord
3. The nerve enters the arm from the axilla at the inferior margin of the teres major muscle and courses with the brachial artery on the medial side of the arm. It lies between the biceps brachii and the brachialis muscles and lies anterior to the elbow joint. In the cubital fossa, it is medial to the brachial artery, anterior to the insertion of the brachialis, and deep to the biceps. Immediately proximal to the elbow joint it may give off a branch to the pronator teres muscle
4. Motor fibers to the nerves arise from spinal nerves C6–T1 while sensory innervation is from C6–C7 spinal segments. Rarely the C5 spinal nerve is a component of the median nerve
5. Sensory fibers traverse the upper and middle trunks to the lateral cord. Motor fibers access all trunks and the medial and lateral cords
6. Distal to the elbow, the nerve traverses through the two heads of the pronator teres muscle, and then between the flexor digitorum superficialis and profundus muscles to the wrist
7. While in the forearm the median nerve innervates:
 - a. Pronator teres
 - b. Flexor carpi radialis
 - c. Palmaris longus
 - d. Flexor digitorum superficialis muscles

High Median Nerve Compression in the Region of the Shoulder or Proximal Humerus

General Characteristics

1. Lesions involving the nerve at this level are uncommon and usually traumatic

Clinical Manifestations

1. Deficit of forearm pronation from paralysis of the pronator teres and pronator quadratus
2. Weak wrist flexion with ulnar hand deviation due to weakness of the flexor carpi radialis
3. Paralysis of:
 - a. Flexor pollicis longus
 - b. Flexor digitorum superficialis of the digits (therefore, absence of flexion of the distal interphalangeal joints and proximal interphalangeal joint of the index finger)
 - c. Weakness of grip of the 3th and 5th digits (flexor digitorum superficialis)
 - d. Slight weakness of the flexor digitorum profundus with consequent weakness of distal interphalangeal flexion
4. Paralysis of the thenar muscles
5. Decreased sensation to the thenar eminence and median nerve innervated digits

Pathogenesis of Median Nerve Injury

1. Anterior dislocation of the shoulder
2. Compression in the axilla from long arm crutches
3. Hanging the arm over hard objects
4. Aneurysms of the brachial or axillary arteries
5. Trauma to the upper arm

*Median Nerve Injury in the Forearm***General Characteristics**

1. In approximately 0.7 to 2.7% of the population there is a supracondylar process that arises five centimeters above the medial epicondyle. There is a fibrous band that passes from this supracondylar process that attaches to the medial epicondyle of the elbow. The median nerve and brachial artery and vein course under the ligament of Struthers
2. In the antecubital fossa the median nerve courses adjacent to the brachial artery and then in the forearm continues below a thick fibrous band known as the lacertus fibrosus (originates from the biceps tendon and attaches to the forearm flexor musculature)
3. The median nerve gives off two branches in the forearm:
 - a. The anterior osseous nerve:
 - i. Courses with the anterior interosseous artery
 - ii. Innervates the deep group of muscles of the anterior compartment except the medial half of the flexor digitorum profundus and the flexor carpi ulnaris (supplied by the ulnar nerve; this branch ends with innervations of the pronator quadratus muscle)
 - iii. The distal median forearm nerve passes deep to the flexor digitorum sublimis muscle and its aponeurotic tendinous edge, known as the sublimis bridge
 - a. Lacertus fibrosus site:
 - i. Forced supination and elbow flexion
 - b. Pronator teres:
 - i. Forced pronation and elbow flexion
 - c. Sublimis bridge:
 - i. Flexion of the proximal interphalangeal joint of the middle finger
2. All three sites of entrapment cause:
 - a. Weakness of FPL and the APB; rarely the FDP
 - b. Paresthesias of the median nerve innervated digits
 - c. Aching of the proximal forearm
 - d. Tenderness over the pronator teres muscle
 - e. Clumsiness and weakness of the hand
3. At the level of the lacertus fibrosus, the median nerve passes through a tunnel; the bottom is the medial trochlea of the humerus; the lateral wall is the brachialis muscle; the medial wall is the pronator muscle and the roof is the lacertus fibrosus
4. The organization of the median nerve in this proximal location is important for surgical considerations:
 - a. At the lacertus tunnel level; the branches to the pronator teres and the FCR are anterior and those to the FPL and FDP are medial
 - b. At the level of the superficialis arcade, the anterior and superficial branches innervate the FDS and sensation to the hand

Pathogenesis of Median Nerve Injury in the Forearm

1. Trauma: casting, direct injury, venipuncture, tumor or hematoma
2. Neuralgia amyotrophica
3. Neuropathy with sensitivity to pressure palsy (chromosome 17)
4. Dislocation of the elbow
5. Persistent median artery

*Ligament of Struthers Compression***Clinical Manifestations**

1. Pain in the volar forearm
2. Paresthesias in the median nerve innervated digits
3. The sensory symptoms are exacerbated by forearm supination and extension at the elbows
4. Palpation of the distal spur on the medial humerus (approximately 5.5 cm proximal to the medial epicondyle)
5. Weakness of the pronator teres is greater than other median nerve innervated muscles

*The Pronator Syndrome***General Characteristics**

1. The pronator syndrome or proximal median nerve entrapment at the level of the elbow occurs at three sites:
 - a. Lacertus fibrosus site
 - b. Pronator teres muscle
 - c. Sublimis bridge

Clinical Manifestations

1. Evocative maneuvers:

Laboratory Evaluation

1. EMG:
 - a. The electrodiagnostic evaluation is abnormal in a minority of patients
 - b. Focal motor nerve conduction at the elbow
 - c. Denervation of median nerve forearm and hand muscles
2. Imaging by MR neurography and high resolution ultrasound
 - a. MRI:
 - i. Ability to sample nerve T2 signal over large areas allows the detection of individual nerve fascicles
 - ii. Diffusion tensor MR neurography provides quantitative estimates of fiber structure which correlates with focal entrapment
 - b. High resolution ultrasound provides localization of symptomatic nerve entrapment:
 - i. Fascicular hypoechogenicity is the ultrasound correlate of nerve T2 signal lesions

Differential Diagnosis of the Pronator Teres Syndrome

1. Entrapment in the carpal tunnel
2. Cervical radiculopathy:
 - a. C6 or C7 spinal nerve injury may cause vague forearm pain
 - b. There may be sensory loss in the thumb, index and 3rd finger
 - c. There may be a positive Spurling's sign at the nerve root exit; foraminal pressure causes mechano-allodynia

- elicited from the spinal nerve; lateral rotation of the neck causes paresthesias in the thumb and index finger as well as pain down the spinous processes of the neck
- d. There is weakness of the biceps (C6) and the triceps muscle (C7)
- e. Decreased biceps reflex (due to injury of C5–C6 spinal nerves) and the triceps reflex is decreased from involvement of the spinal nerves at C7
- 3. Brachial plexus neuropractic injury (upper trunk and lateral cord)
- 4. Musculoskeletal disease at the elbow that includes:
 - a. Sprains of the flexor and pronator muscles
 - b. Vascular anomalies:
 - i. Aneurysm of the median artery
 - c. AV shunt placement for renal dialysis
 - d. Fistula due to trauma (knife > bullet)
 - e. Minimum or no sensory loss

Anterior Interosseous Nerve

General Characteristics

1. The nerve arises from the median nerve 5 to 8 cm distal to the lateral epicondyle
2. Innervates the flexor pollicis longus, flexor digitorum profundus to the index and long finger and the pronator quadratus
3. There are no surface cutaneous innervations; there are proprioceptive and pain afferents to the wrist joint
4. Anomalous innervations:
 - a. The anterior interosseous nerve may supply all of the flexor digitorum profundus (patient would be unable to flex any distal joints); and all median hand
 - b. The flexor digitorum profundus to the index or long finger may be spared (innervated by the ulnar nerve)
 - c. 50% of Martin-Gruber anastomosis arise from the anterior interosseous nerve

Clinical Manifestations

1. Inability to flex the distal phalanx of the thumb and index finger; weak forearm pronation (pronator quadratus)

Pathogenesis of the Nerve Injury

1. Trauma from casting
2. Repetitive elbow flexion and pronation
3. Open reduction of forearm fractures
4. Anatomic anomalies:
 - a. Tendinous origin of the deep head of the pronator teres muscle
 - b. Tendinous compression of the flexor digitorum superficialis of the 3rd finger

Laboratory Evaluation

1. EMG:
 - a. Decreased distal motor latencies from the elbow to the pronator quadratus

- b. Denervation of the flexor digitorum profundus, FPL and pronator quadratus
- c. Fascicular/partial nerve lesions in spontaneous neuropathies have been difficult to delineate with electrodiagnostic methods
- 2. Magnetic resonance neurography (MRN)
 - a. Fascicular lesions with a strict somatotopic organization can be identified in the upper arm median nerve trunks in patients with AIN (anterior interosseous nerve) in non-traumatic instances which supports:
 - i. AIN is a multifocal mononeuropathy that selectively involves the motor fascicles of the median nerve

Differential Diagnosis of Anterior Interosseous Nerve Lesions

1. Paralytic brachial neuritis with concomitant AIN involvement (associated other components of the brachial plexus are involved and pain may last for days or weeks)
2. Vascular anomaly of the lateral cord of the brachial plexus (may have no motor involvement, which is predominant with AIN)
3. Rheumatoid arthritis which may cause rupture of the FPL and FDT tendons
4. Cervical radiculopathy (there is sensory loss with biceps, triceps weakness and loss of motor stretch reflexes)

Median Nerve Injury at the Wrist

General Characteristics

1. Injury at this level is traumatic

Clinical Manifestations

1. Weakness of flexion of the index, long finger and thumb
2. Loss of abduction and opposition of the thumb
3. A simian hand deformity at rest due to hyperextension of the index finger and thumb with thumb adduction
4. Benediction sign when attempting to form a fist due to flexion weakness of the thumb index and long finger
5. Loss of sensation in the first 3½ digits (splits the 4th finger; ulnar side of the finger is insensate; the thenar eminence and the nail beds are affected)

Pathogenesis of the Nerve Injury

1. Laceration
2. Industrial accidents

Carpal Tunnel Syndrome

General Characteristics

1. The carpal bones comprise the floor and side of the carpal tunnel; the transverse carpal ligament forms the roof
2. Proximal to the wrist and the carpal tunnel, the palmar cutaneous branch arises from the median nerve to innervate the thenar eminence
3. In the palm the motor branch arises to innervate the thumb and first and second digits; the recurrent thenar motor

branch supplies the opponens pollicis, APB (abductor pollicis brevis), the superficial head of the flexor pollicis brevis

4. A sensory branch innervates the medial thumb, index, long finger and the radial side of the 4th finger

Clinical Manifestations

1. Numbness of the thumb, index, middle finger and radial side of the 4th finger; a large percentage of patients complain of paresthesia of all fingers (suggested that there may be compression concomitantly of the ulnar nerve)
2. Nocturnal paresthesias that may awaken the patient from sleep; the hand may be held in a dependent posture as a position of comfort
3. Activities that elicit pain or paresthesias:
 - a. Writing
 - b. Computer keyboards
 - c. Driving
 - d. Holding a phone or book
4. Pain is often felt in the hand and forearm:
 - a. Very rarely radiates to the antecubital fossa, but has been reported in the shoulder
 - b. Wrist flexion exacerbates distal and proximal pain radiations (Phalen's sign; usually flexion needs to be maintained for 1 to 2 minutes to elicit pain)
 - c. Tinel's sign (mechanically induced hypersensitivity of the nerve) may be elicited over the carpal tunnel (not specific as it may be elicited in normal people)
5. Weakness or tiredness of the hand during writing; spontaneous dropping of objects
6. Weakness of flexion of the index, 3rd and a component of the 4th finger; weakness of abduction and opposition of the thumb
7. Hyperesthesia in the median nerve distribution (3½ digits including the nail beds) but excluding the thenar eminence which is supplied by the palmar cutaneous branch; unlike the sensory loss that occurs with laceration of the nerve at the wrist, there is no sensory loss of the central palm (palmar cutaneous branch courses above the flexor retinaculum). The tip of the index finger is the earliest and most severe area of sensory loss. Two-point discrimination is affected prior to pin prick and temperature loss. The radial split of the 4th finger is characteristic
8. Raynaud's phenomenon and autonomic dysregulation of the hand may occur (the median nerve supplies the bulk of the sympathetic innervations to the hand)

Pathogenesis of Carpal Tunnel Syndrome

1. A congenitally narrow carpal tunnel
2. Most common in middle-aged women 3:1 female to male incidence; often bilateral; the dominant hand is most often more severely affected
3. Fibrosis of the transverse carpal ligament
4. Repetitive flexion and extension of the wrist
5. Diabetes mellitus

6. Scleroderma
7. Rheumatoid arthritis
8. Acromegaly
9. Amyloidosis
10. Lyme's disease
11. Sarcoid
12. Colles fracture
13. Pregnancy
14. Hemodialysis
15. Anomalous flexor tendons
16. Flexor tendon synovitis (rare)
17. Gout
18. Double crush: associated with cervical spine or brachial plexus pathologies (controversial)

Laboratory Evaluation

1. EMG:
 - a. Median sensory or mixed nerve conduction study
 - b. Median motor conduction study
 - c. Needle examination of the APB
 - d. Ulnar and/or radial motor and sensory NCS (to exclude a peripheral neuropathy)
 - e. Needle EMG of muscles innervated by C5 to T1 roots (to exclude a cervical radiculopathy)

Supplementary Tests Include

1. Comparison of the median motor nerve distal latency (second lumbrical) to the ulnar motor nerve distal latency
2. Inching
3. Median motor terminal latency index
4. Median nerve conduction between the wrist and the palm
5. MRI: neurography
6. High resolution ultrasound

Differential Diagnosis of Carpal Tunnel Syndrome

1. Generalized neuropathy
2. Brachial plexopathy (lateral cord)
3. Cervical radiculopathy ("double crush")
4. Median neuropathy at the elbow:
 - a. Sensory loss of the thenar eminence, which is not found with Carpal Tunnel syndrome (CTS)
 - b. Weakness of distal thumb flexion and arm pronation

Ulnar Nerve

General Characteristics

1. Second most common nerve entrapment of the arm (less than CTS)
2. The major spinal nerves contributing to the ulnar nerve are C8 and T1; C7 fibers may contribute in from 43 to 93% of patients
 - a. The C7 component of the nerve derives from the lateral cord and innervates the flexor carpi ulnaris muscle
3. Proximally the nerve is anterior to the teres major and latissimus dorsi muscles and descends in the posterior

compartment of the upper arm to the ulnar groove at the elbow

4. The ulnar groove at the elbow is formed by the medial epicondyle of the humerus and the olecranon process of the ulna; the ulnar collateral ligament is the floor
5. 1–2.5 cm distal to the ulnar groove the nerve courses under a fibrous aponeurosis arch; the ulnar groove and this arch form the cubital tunnel. The ulnar nerve gives off no branches proximal to the elbow. It enters the forearm between the humeral and ulnar heads and lies under the aponeurosis of the flexor carpi ulnaris next to the ulna. It descends between the flexor carpi ulnaris and flexor digitorum profundus to the wrist. In the forearm it innervates:
 - a. Flexor carpi ulnaris
 - b. Flexor digitorum profundus III and IV muscles
 - c. The dorsal ulnar cutaneous nerve (innervates the dorsum of the medial hand and the 4th and 5th fingers)

Guyon's Canal

Prior to entering Guyon's canal at the wrist, the nerve gives branches to the hypothenar eminence (palmar branch) and innervates the palmaris brevis muscle.

1. Guyon's canal at the wrist is formed by:
 - a. Radially by the hook of the hamate bone
 - b. The pisiform bone on the ulnar side
 - c. The pisohamate ligament is the floor
 - d. The transverse carpal ligament is the roof
2. Either in Guyon's canal or slightly distal to it, it gives off a superficial sensory terminal branch that innervates the palmar aspect of the 5th finger; it also provides sensation dorsally to these digits

The deep motor branch (given off in Guyon's canal or slightly distal to it) innervates:

1. The muscles of the hypothenar eminence:
 - a. Opponens digiti minimi
 - b. Abductor digiti minimi
 - c. Flexor digiti minimi brevis
2. In the hand it innervates:
 - a. The 3rd and 4th lumbrical muscles
 - b. Dorsal interossei
 - c. Palmar interossei
 - d. The deep head of the flexor pollicis brevis
 - e. Adductor pollicis
3. The ulnar nerve is the most commonly injured nerve at the elbow

Clinical Manifestations

1. Injury from the axilla to the upper elbow:
 - a. As there are no branches of the ulnar nerve in the upper arm, proximal lesions cause deficits similar to those that occur from lesions at the elbow

Pathogenesis of Proximal Ulnar Neuropathy

1. Trauma
2. Compression (sleep, operative positioning, coma)

3. Soft tissue or peripheral nerve tumors
4. AV fistula
5. Vasculitis
6. Multifocal motor neuropathy
7. Multifocal acquired demyelinating motor and sensory neuropathy

Laboratory Evaluation

1. EMG:
 - a. Reduced ulnar and dorsal ulnar nerve SNAPs amplitude
 - b. The lateral antebrachial cutaneous SNAP is normal
 - c. Ulnar CMAP demonstrates reduced amplitude without focal slowing or conduction block across the elbow
 - d. Denervation of ulnar innervated muscles of the hand and forearm
 - e. Demonstration of a focal conduction block or slowing of CV of the ulnar CMAP between the axilla and above the elbow areas
2. High resolution ultrasound
3. MRI neurography

Ulnar Neuropathy at the Elbow

General Characteristics

1. Anatomical variant of the cubital tunnel (dense fibrous band)
2. Epitrochleoanconeus muscle may occur between the medial epicondyle and the olecranon process in the ulnar groove
 - a. Tardy ulnar palsy is defined as a neuropathy that occurs following bone injuries at the elbow

Clinical Manifestations

1. Motor deficits include:
 - a. Weakness of flexion of the hand at the wrist
 - b. Loss of flexion of the 4th and 5th digits
 - c. Loss of spreading of the fingers and their opposition (interossei)
 - d. Loss of grip strength
 - e. Weakness of flexion of the little finger at the distal interphalangeal joint is the most sensitive test of forearm muscle weakness
 - f. Patients may present with intrinsic hand muscle atrophy; lateral displacement and loss of control of the 5th finger
 - g. Claw hand deformity (late manifestation)
2. Sensory deficits:
 - a. Initially, there is intermittent hyperesthesia in the ulnar nerve distributions that is exacerbated by elbow flexion; symptoms abate with elbow extension; rarely symptoms may be restricted to the hand
 - b. Decreased sensation of the ulnar aspect of the palm, the volar surface of the 5th digit and the ulnar side of the 4th digit. The dorsal sensory branch supplies the dorsal $\frac{1}{2}$ of the 4th finger and the entire 5th digit

- i. Tactile deficit is greater than that to pinprick loss; both may be lost over the distal two phalanges of the 5th finger
3. Ulnar nerve innervation stops at the skin crease of the wrist (it may extend above the wrist in a small triangular area)
 - a. Proximally the innervation of the forearm is from the antebrachial cutaneous nerve of the forearm and not the ulnar nerve
4. Pathogenesis of ulnar neuropathy at the elbow:
 - a. Tardy ulnar palsy:
 - i. Deformities of the elbow (not allowing full extension or changing the angle of extension) that are related to old fractures of the humerus or trauma to the joint
 - ii. Bone spur at the distal end of the humerus
 - iii. Malalignment after supracondylar fracture of the humerus with valgus deformity
 - iv. Subluxation of the ulnar nerve:
 1. 10 to 20% are asymptomatic
 2. Congenital laxity of the aponeurosis
 3. Direct trauma
 4. Repetitive flexion and extension of the elbow
 5. Controversial:
 - a. That repeated subluxation may cause a clinically significant ulnar palsy
 - v. Compression by the arcade of Struthers (medial intramuscular symptoms)
 - vi. Compression by an aponeurotic band between the heads of the flexor carpi ulnaris
 - vii. Compression by a retrocondylar ligament or fibrous band
 - viii. Soft tissue tumor
 - ix. Leprosy
 - x. Associated with diabetes mellitus
 - xi. Lesions within the cubital tunnel:
 1. Osteophytes from an old fracture or arthritis
 2. Synovitis associated with rheumatoid arthritis
 3. Tumors of the elbow joint
 4. Epitrochleoanconeus ligament
 5. Chondromatosis
 6. Ganglion of the ulnar nerve sulcus

Laboratory Evaluation

1. EMG:
 - a. Ulnar and dorsal ulnar cutaneous SNAP amplitude reduction
 - b. Slow CV between above and below the elbow; conduction block may be demonstrated
 - c. Inching method to determine the site of pathology (the nerve is stimulated every 1–2 cm from 5 cm below to 5 cm above the elbow)
 - d. In neuropraxia or demyelinating lesions, there may be just reduced recruitment of MUAPs
 - e. Short segment nerve conduction studies (SSNCS)
 - f. Conduction slowing and conduction block

2. High resolution ultrasound:
 - a. Changes increase sectional area (CSA) and swelling ratio measurements are equally sensitive
3. MRI neurography

Ulnar Neuropathy at the Wrist/Hand

General Characteristics

1. Guyon's canal:
 - a. The proximal border is the pisiform bone; distally, the hook of the hamate bone
 - b. Floor of the canal:
 - i. Transverse carpal ligament; hamate triquetral bones
 - c. Roof:
 - i. The pisohamate ligament that extends from the hook of the hamate to the pisiform bone
2. Sites of Damage
 - a. Guyon's canal (or slightly proximal to it)

Clinical Manifestations

1. There is damage to the superficial sensory and deep motor branches of the distal ulnar nerve:
 - a. Weakness of all ulnar innervated hand muscles with consequent loss of flexion of the 4th and 5th digits; deficient abduction and adduction of the digits (interossei); particularly noticeable atrophy of the first dorsal interosseous muscle; loss of flexion of the metacarpal phalangeal joint of the 4th and 5th digit)
 - b. Loss of function of the hypothenar muscles
 - c. Sensory loss of the volar aspect of the medial 4th finger and the entire 5th finger; more proximal lesions spare the dorsal ulnar cutaneous nerve that supplies the dorsum of the hand
 - d. There is normal strength of the flexor carpi ulnaris and flexor digitorum profundus III and IV

Pathogenesis of Nerve Injury in Guyon's Canal

1. Ganglion of the triquetral hamate joint
2. Fracture of the metacarpal bones
3. Lipoma
4. Pisohamate arthritis
5. Dislocation of the pisiform bone
6. Dislocation of the distal ulnar bone
7. Degenerative arthritis
8. Rheumatoid arthritis
9. Diabetes mellitus

Laboratory Evaluation

1. EMG:
 - a. The ulnar SNAP may demonstrate a prolonged distal latency or reduced amplitude; the dorsal ulnar cutaneous SNAP is normal (branches off prior to the canal)
 - b. Reduced CMAPs of the abductor digiti minimi and the first dorsal interosseous
 - c. Denervation of the first dorsal interosseous and abductor digiti minimi with normal flexi carpi ulnaris and flexor digitorum profundus III and IV

*Compression Just Proximal to Guyon's Canal***Clinical Manifestations**

1. The superficial branch of the ulnar nerve is affected with:
 - a. Loss of sensation in the ulnar $\frac{1}{2}$ of the palm and half of the 4th finger and the entire 5th finger; dorsal hand is moved
 - b. Motor function is normal
2. Pathogenesis of the nerve injury
 - a. Laceration

Laboratory Evaluation

1. EMG:
 - a. Decreased amplitude and prolonged latency of the ulnar SNAP

Compression in the Hand*Clinical Manifestations*

1. Injury is distal to the branching of the superficial sensory branch
2. Sensation is spared
3. Partial damage to the ulnar innervated intrinsic hand muscles

Pathogenesis of the Nerve Injury

1. Prolonged pressure in the palm of the hand (bike riding, industrial tools)
2. Trauma
3. Laceration

Laboratory Evaluation

1. EMG:
 - a. The ulnar SNAPS are normal
 - b. The CMAPs of the first dorsal interosseous and the digiti minimi are decreased in amplitude and the muscles are denervated

Compression Distal to the Branch Innervating the Hypothenar Eminence*Clinical Manifestations*

1. The interossei and adductor pollicis muscle are affected; a more distal lesion can separately affect the adductor pollicis or the first dorsal interosseous muscle

Pathogenesis of the Nerve Injury

1. Sustained palmar pressure
2. Laceration
3. Trauma

Laboratory Evaluation

1. EMG:
 - a. Ulnar SNAPS and CMAPs of the abductor digiti minimi are normal; the CMAP from the dorsal interosseous muscle would be abnormal
 - b. Denervation of the dorsal interossei and adductor pollicis muscles
2. High resolution ultrasound
3. MRI neurography

Digital Nerve Entrapment in the Hand*General Characteristics*

1. Compression neuropathy in the palm and digits is much less common than proximal compression

Clinical Manifestations

1. Hyperesthesia in the finger or fingers is the most common symptom
2. The proper digital nerve innervates the lateral and medial side of each digit; rarely pain rather than paresthesia is the presenting symptom
3. May be associated with digital Raynaud's syndrome
4. Positive Tinel's sign over the entrapped nerve
5. Digital nerve involvement in the palmar causes numbness in the adjacent side of the digit

Pathogenesis of Nerve Injury

1. Acute external blunt trauma to the palm or digit
2. Dislocation or fracture
3. Bowler's thumb; pain on the ulnar side of the base of the thumb
4. Neuroma-in-continuity associated with perineural and intraneural fibrosis:
 - a. Tinel's sign with lancinating digital pain
5. Cysts of the flexor tendon sheath (proximal flexion crease)
 - a. Volar and lateral extension is painful
6. Degenerative arthritis of the digit
7. Tumors:
 - a. Periosteal chondroma
 - b. Lipoma (from the flexor tenosynovium)
 - c. Schwannoma of the digital nerve
 - d. Fibrosarcoma
8. Rheumatoid flexor tenosynovitis (may compress the common or proper digital nerve within the lumbrical canal)
9. Dupuytren's contracture

Entrapment Neuropathies of the Lower Extremity**Sciatic Nerve***General Characteristics*

1. Originates from the L4–S3 spinal segments; the L4–L5 segments join the nerve from the lumbosacral trunk
2. The nerve is formed by the merger of the superior and inferior gluteal nerves; its lateral division is the peroneal nerve, and the medial division is the tibial nerve
3. The peroneal nerve has minimal innervations from S3 whereas there is minimal L4 contribution of the tibial nerve
4. Prior to the formation of the sciatic nerve, there are two major branches that arise from the upper sacral spinal nerves:
 - a. The pudendal nerve:
 - i. Arises from S2–S4 spinal nerves

- ii. The posterior cutaneous nerve of the thigh from S1–3 spinal nerves
 - iii. The merger of S1–S3 segments and the lumbosacral trunk is the beginning of the sciatic nerve which occurs lateral and anterior to the sacrum
5. The two major sciatic nerve branches in the pelvis are the superior and inferior gluteal nerves:
 - a. The superior gluteal nerve originates from L4–S1 roots
 - b. The inferior gluteal nerve originates from L5–S1 roots
6. The superior gluteal nerve:
 - a. Exits the sciatic notch above the piriformis muscle (originates from the front of the ramus, the gluteal surface of the ilium and the anterior capsule of the sacroiliac joint; it inserts on the greater trochanter)
 - b. Innervates:
 - i. Gluteus medius and minimus
 - ii. Tensor fascia lata
 - c. Abducts the thigh at the hip and internally rotates the thigh:
 - i. Gluteus minimus (small contribution to thigh flexion)
 - ii. Posterior component of the gluteus medius contributes to external rotation of the thigh
7. The inferior gluteal nerve:
 - a. Innervates the gluteus maximus
 - i. The primary thigh extensor
 - ii. Contribution to external thigh rotation
8. There is no sensory component to either the superior or inferior gluteal nerves

The Pudendal Nerve

General Characteristics

1. Originates from spinal segments S2–S4
2. Leaves the pelvis in the caudal component of the sciatic notch proximate to the sacrococcygeal junction
3. The three branches of the pudendal nerve are:
 - a. Inferior rectal
 - b. Perineal
 - c. Dorsal nerve of the penis/clitoris
4. Inferior rectal branch:
 - a. Innervates the external and internal sphincter
 - b. Provides sensation to the distal anal canal and perineal areas
5. The perineal nerve:
 - a. Innervates the muscles of the pelvic floor, the external urethral sphincter and the erectile tissue of the corpus cavernosa of the penis
 - b. It's sensory territory includes the perineum ventral to the rectum, the scrotum, and labia. The dorsal nerve of the penis is a purely sensory branch that supplies sensation to the penis and/or labia and clitoris

The Posterior Cutaneous Nerve of Thigh

1. Origin is spinal segment S1–S3
2. Leaves the pelvis through the lower sciatic notch

3. Lies beneath the gluteus maximus
4. It gives off clinical branches at the level of the gluteal crease that innervates the inferior buttock
5. Its perineal branches innervate:
 - a. Skin and fascia of the lateral perineum
 - b. The proximal medial thigh
 - c. Posterior areas of the scrotum/labia and root of the penis/clitoris
 - d. The terminal branch innervates:
 - i. The posterior thigh and in some individuals the proximal portion of the posterior calf

At the Sciatic Notch

General Characteristics

1. The sciatic nerve passes under the piriformis muscle in approximately 70% of individuals. There is variation in whether the peroneal nerve passes along, through or above the muscle. Rarely the entire nerve passes through the muscle
2. In general, the sciatic nerve divides into the common peroneal and tibial nerve in the upper angle of the popliteal fossa. It may divide in the back of the thigh or, rarely, in the pelvis. The nerve has been described as dividing into its two major divisions at various levels from the sacral plexus to the lower thigh. The nerve descends lateral to the Ischial tuberosity and medial to the greater trochanter of the proximal femur
3. The tibial component of the sciatic nerve (medial trunk) innervates:
 - a. The semitendinosus muscle
 - b. The semimembranosus muscle
 - c. The long head of the biceps femoris
 - d. Sends a branch to the adductor magnus muscle
4. Lesions of the sciatic nerve proximal to the knee cause loss of sensation to the entire foot and the distal half of the lateral surface of the leg. The medial lower leg sensory supply is from the saphenous nerve that derives from the L4 spinal segment
5. The blood supply to the sciatic nerve derives from the inferior gluteal artery and popliteal arteries. This creates a watershed between the two arteries at the mid-thigh level that is significant in atherosclerosis and vasculitic processes
6. In the leg:
 - a. The common peroneal nerve bifurcates into the deep and superficial divisions below the fibular head
 - b. The deep peroneal nerve:
 - i. Innervates the anterior compartment of the lower leg, which includes the following muscles:
 1. Tibialis anterior
 2. Extensor hallucis longus
 3. Extensor digitorum longus
 - ii. In the foot it innervates the extensor digitorum brevis (EDB)
 - iii. The function of the muscles innervated by the deep peroneal nerve is to dorsiflex the foot at the ankle and the toes at the metatarsal-phalangeal joints

- c. The superficial peroneal nerve:
 - i. Innervates the lateral compartment of the leg, which includes the following muscles:
 - 1. Peroneus longus muscle
 - 2. Peroneus brevis muscle
 - ii. The function of these muscles is to evert the foot at the ankle
 - iii. The sensory innervation of the deep peroneal nerve is the interdigital space between the first and second digits; the superficial peroneal nerve supplies cutaneous sensation to the dorsum of the foot and the distal lateral leg
- d. The tibial nerve:
 - i. Arises from L5–S3 nerve roots and is the continuation of the medial cord of the sciatic nerve
 - ii. After dividing from the peroneal nerve in the distal thigh:
 - 1. It transverse the popliteal fossa and enters the leg anterior to the heads of the gastrocnemius muscle
 - 2. In the thigh it innervates:
 - a. Semitendinosus
 - b. Semimembranosus
 - c. Long head of the biceps femoris
 - 3. In the leg it innervates:
 - a. The posterior compartment
 - b. Both heads of the gastrocnemius muscle
 - c. Soleus
 - d. Tibialis posterior
 - e. Flexor digitorum longus
 - f. Flexor hallucis longus
 - 4. In the foot it innervates:
 - a. All intrinsic foot muscles except the EDB (superficial peroneal nerve)
 - 5. Functions of the muscle supplied by the posterior tibial nerve:
 - a. Flexes the leg at the knee
 - b. Plantar flexes and inverts the foot at the ankle
 - c. Flexes, abducts and adducts the toes
 - 6. The three cutaneous components of the tibial nerve branch at the medial malleolus and include:
 - a. The medial and lateral plantar nerves:
 - i. Supply the medial and lateral plantar surfaces of the anterior 2/3 of the sole
 - b. Calcaneal nerve
 - i. Supplies the heel
 - 7. The sural nerve:
 - a. Arises from the common peroneal and tibial nerves in the popliteal fossa
 - b. Its origin is primarily the S1 spinal root
 - c. It has two branches:
 - i. Medial cutaneous branch, which arises from the tibial nerve
 - ii. Lateral cutaneous from the common fibular nerve

- d. Courses down the posterior lateral side of the leg and enters the foot posterior to the lateral malleolus below the fibularis tendon sheath
- e. Provides sensation to the posterior lateral portion of the distal leg and the lateral foot as well as the fifth digit

Clinical Manifestations

- 1. Paresthesias, pain and sensory loss in its cutaneous distributions

Pathogenesis of Nerve Injury

- 1. Entrapment due to fascial thickening
- 2. Ganglion
- 3. Lipoma
- 4. Heel straps
- 5. Repetitive ankle sprains
- 6. Ankle fractures
- 7. Gastrocnemius muscle injury

Laboratory Evaluation

- 1. EMG:
 - a. Increased distal latency and decreased SNAP of the nerve
- 2. High resolution ultrasonography
- 3. MRI neurography

Piriformis Syndrome

General Characteristics

- 1. Controversial; it is suggested that the sciatic nerve can be compressed at the pelvic outlet by the piriformis muscle
- 2. There are anomalous relationships between the sciatic nerve and the piriformis muscle which often do not correlate clinically
- 3. Some patients (women > men) demonstrate an anomalous band or vessel in the sciatic notch in proximity to the sciatic nerve

Clinical Manifestations

- 1. Buttock pain and tenderness without sciatic nerve pain radiations
- 2. Sciatic notch point tenderness
- 3. The pain is exacerbated by sitting and rarely by bending at the waist
- 4. Pain may also be produced by maneuvers that require hip adduction and internal rotation; the pain may be relieved by standing and walking
- 5. Positive Trendelenburg sign
- 6. No weakness, reflex change or hand sensory loss
- 7. Leg may be slightly externally rotated with walking
- 8. Rarely, positive Freiberg, Pace and Beatty tests:
 - a. Pain on adduction, internal rotation and flexion of the thigh
- 9. Rarely mild wasting of the gluteus maximus

Pathogenesis of Nerve Injury

1. Myofascial band between the bicep femoris and the adductor magnus (compresses the nerve)
 - a. Distal thigh pain above the posterior popliteal fossa
2. Muscle spasm with piriformis compression of the nerve caused by rheumatic disease, bursitis or trochanteric disease at its insertion
3. Minimal trauma to the buttock
4. Sciatic nerve compression from muscle fibrosis (pentazocine infections)

Laboratory Evaluation

1. EMG:
 - a. NCVs are usually normal
 - b. Denervation in both peroneal and tibial divisions; peroneal branch usually is more affected
 - c. The short head of the biceps is less affected than other hamstring muscles
 - d. Flexor digitorum longus and medial and lateral gastrocnemius muscles may show fibrillation potentials
2. Botulinum toxin injection into the muscle:
 - a. Relieves spasm
 - b. Blocks pain afferents
3. MRI neurography
4. Diagnostic and therapeutic analgesic block of the muscle
 - a. Percutaneous lidocaine and depomedrol injection under fluoroscopic guidance

Sciatic Nerve Injury at the Hip or Thigh**General Characteristics**

1. The lateral greater than the medial division of the nerve is affected due to the difference of the fasciculi pattern of the nerve and its course in the epineurium

Clinical Manifestations

1. Foot drop; the peroneal component of the nerve is more affected than the tibial
2. Slight weakness of the hamstrings, gastrocnemius, and posterior tibial muscles
3. Rarely, a high sciatic lesion may manifest as a pure peroneal palsy
4. Depressed or absent ankle jerk
5. Decreased sensation on the side and lateral foot; sensation is spared around the medial malleolus (saphenous nerve cutaneous territory)
6. Instability of the foot
7. The gait is impaired due to knee and ankle instability

Pathology of the Nerve Injury at the Hip and Thigh Level

1. Sciatic mononeuropathy is uncommon; most diseases affect the L4–S3 nerve roots; these processes usually compromise only one or two roots and include:
 - a. Disc disease
 - b. Lumbar spondylosis

- c. Spondylolisthesis
- d. Intervertebral osteophytes in the nerve exit foramina
- e. Metastatic disease
2. Hip replacement surgery:
 - a. 1 to 3% of patients injure the nerve during hip joint replacement surgery (much higher percentage by EMG criteria)
 - b. Higher incidence of sciatic nerve damage in:
 - i. Total hip revisions
 - ii. Surgery requiring limb lengthening
 - iii. Congenital dysplasia or dislocation:
 1. Usually noted following surgery
 2. Most often a neuropraxic (stretch) injury
3. Rarer causes of surgical injury:
 - a. Methylmethacrylate leakage
 - b. Traction dislocation
 - c. Migrating traction wire
 - d. Hemorrhage
 - e. Prosthetic dislocation
4. Hip fracture and femur fracture
 - a. Injury occurs during internal fixation or closed reduction
5. External compression of the nerve:
 - a. Coma
 - b. Poor positioning during anesthesia:
 - i. Gluteal or posterior thigh compartment syndrome
 - ii. "Toilet seat" compression
 - iii. Lotus position (yoga)
 - iv. Operative sitting procedures
 - c. Malignant or benign tumors
 - d. Heterotopic ossification following trauma
 - e. Enlargement of the lesser trochanter
 - f. Persistent sciatic artery
 - g. Severe direct trauma; gunshot or stab wounds
 - h. Improper injections (often only the peroneal component is affected)
 - i. May be delayed due to fibrosis
 - i. Hemorrhage within the gluteal compartment:
 - i. Anticoagulation
 - ii. Hemophilia (rare; usually bleeding is into joints)
 - iii. Following hip surgery
 - iv. Rupture of an iliac artery aneurysm
 - j. Endometriosis:
 - i. Catamenial sciatica
 - ii. Starts prior to menstruation and ceases with its end
 - k. Ischemic Nerve Injury
 - i. Watershed between the descending inferior gluteal artery and the ascending popliteal artery in the mid-thigh
 1. Inflammation and occlusion of the vasa vasorum (autoimmune vasculitis)
 2. Atherosclerosis
 3. Iliac or femoral artery occlusion
 4. Prolonged catheter in the femoral artery for interventional procedures
- l. Congenital Lesions

- m. Hereditary neuropathy with liability to pressure palsies (HNPP) deletion on chromosome 17

Differential Diagnosis of Sciatic Nerve Injury

1. Peroneal nerve lesion at the fibular neck:
 - a. Tinel's sign over the nerve at the fibular neck
 - b. Foot pain is rare
 - c. No back pain or L4–S3 radiations
 - d. Negative stretch maneuvers (straight leg raising test)
 - e. Normal ankle jerk
 - f. Intact inversion, plantar and toe flexion
 - g. Sensory loss between the great toe and first digit
2. Herniated Lumbar Disc:
 - a. Usually long standing back pain (may be acute)
 - b. Position of comfort is flexed knee in recumbency
 - c. Cough, sneezing, laughing are all painful as are all valsalva maneuvers (extrude the disc dorsolaterally into the exit foraminal canal)
 - d. Monoradicular symptoms: S1 > L5 > L4 radiations
 - e. Proximal pain is primarily in the buttocks or posterior thigh
 - f. Often bilateral asymmetric symptoms (loss of maintenance of the foraminal exit canal and foramina on the involved and uninvolved side)
3. Spinal stenosis:
 - a. L4–L5 > L5–S1 levels; may involve mid-lumbar to mid-sacral levels; primarily epidural compression; common in elderly patients with degenerative osteoarthritis
 - b. Progressive calf and foot pain induced by walking and relieved by rest (usually patients are able to walk further than patients suffering from arterial intermittent claudication)
 - c. Frequent calf neurogenic cramps (often misdiagnosed as vascular claudication)
4. Vascular monomelic neuropathy:
 - a. Primarily occurs in diabetic or those with severe atherosclerosis
 - b. Often has an acute onset (over several days)
 - c. Leg muscle wasting may be prominent
 - d. No back pain; the pain in the calf is more burning (protons activating acid sensors on C-fibers; rather than the deep "charlie horse" pain of neurogenic cramps)
 - e. Sciatic symptoms are mixed with those of the femoral or saphenous nerves
 - f. Prior history of leg ischemia
 - g. The sensory loss is "stocking"; with sciatic lesions, the saphenous territory is spared
5. Malignancy of the Spinal Cord
 - a. Intraspinal tumor:
 - i. The gastrocnemius is more severely involved than the anterior tibialis or extensor hallucis longus
 - b. Lymphoma:
 - i. The tumor has a tendency to incase the lumbosacral cord and roots (by MRI)

- ii. Often involves the lower sacral roots
- c. Myeloma:
 - i. There may be root compression by fracture and displacement of vertebral bones
 - ii. Loss of marrow signal at multiple spinal levels on MRI

The Peroneal Nerve

General Characteristics

1. A motor branch exits near the gluteal fold to innervate the short head of the biceps femoris
2. In the popliteal fossa:
 - a. Exit of the lateral cutaneous nerve of the calf (upper 1/3 of the lateral leg)
 - b. Gives off a branch to join a branch from the tibial nerve to form the sural nerve
3. The common peroneal nerve passes through the fibular tunnel (tendon of the peroneus longus muscle and the fibula) and then divides into deep and superficial branches:
 - a. Anterior peroneal nerve (the deep peroneal branch)
 - i. Courses in the anterior compartment of the leg and innervates:
 1. Tibialis anterior
 2. Extensor hallucis longus
 3. Extensor digitorum longus
 4. Peroneus tertius
 - b. Under the extensor retinaculum nerve the nerve divides into:
 - i. The lateral motor branch that innervates the extensor digitorum brevis (EDB)
 - ii. A medial sensory branch that supplies cutaneous sensation to the web spaces between the great and second toe

Clinical Manifestations

1. Foot drop with steppage gait
2. Weakness of the tibialis anterior, extensor hallucis longus and extensor digitorum longus
3. Sensory loss of the web space between the great and second toe
4. Distal deep peroneal lesions (traction injuries from an ankle sprain) cause selective weakness of the toe extensors with normal ankle dorsiflexion

Pathology of the Nerve Injury

1. Fracture and sprains of the lower leg
2. Prolonged squatting
3. Pneumatic compression
4. Knee arthroplasty
5. High tibial osteotomy
6. Synovial cysts
7. Schwannoma and other tumors (particularly nerve sheath tumors)
8. Distal tibial osteochondroma
9. Femoral distal extension osteotomy

Laboratory Evaluation

1. EMG:
 - a. Reduced CMAPs amplitudes in the tibialis anterior extensor digitorum longus, and extensor digitorum brevis
 - b. Normal superficial peroneal SNAP
2. High resolution ultrasound
3. MRI neurography

Superficial Peroneal Nerve*General Characteristics*

1. Innervates the peroneus longus and brevis muscles of the lateral compartment
2. In the distal leg, it becomes the superficial peroneal sensory nerve:
 - a. It is subcutaneous 40 cm proximal to the lateral malleolus
 - b. Its intermediate and medial cutaneous branches innervate this skin of the lower 2/3 of the leg and the dorsum of the foot except for the web space between the first and second toe
3. Accessory or deep peroneal nerve:
 - a. Occurs in approximately 20% of people and arises as a continuation of the muscular branch of the superficial peroneal nerve and innervates the peroneus brevis muscle proximally
 - b. Distally it innervates part of the extensor digitorum brevis (EDB), the ankle joint and its ligament

Clinical Manifestations

1. Weak eversion of the foot
2. Sensory loss of the lower lateral leg and dorsum of the foot that is exacerbated with walking or running
3. Tinel's sign at 10 cm proximal to the lateral malleolus (where the nerve becomes subcutaneous)
4. Pain in the distal anterolateral leg
5. Ankle pain with or without numbness over the dorsum of the foot if the nerve is affected at the ankle; increased pain with plantarflexion or inversion

Pathogenesis of Nerve Injury

1. Iatrogenic causes:
 - a. Arthroscopy
 - b. Local anesthetic block
 - c. Surgical approach to the fibula
 - d. Open reduction and internal fixation of lateral malleolar fractures
 - e. Application of external fixators
 - f. Elevation of a fasciocutaneous or fibular flaps for grafting
 - g. Surgical decompression of neurovascular structures:
 - i. Blunt trauma
 - ii. Lipoma
 - iii. Boot or shoe straps
 - iv. Neuroma

Laboratory Evaluation

1. EMG:

- a. Decreased amplitude, prolonged latency or absence of superficial peroneal SNAPs

Common Peroneal Nerve at the Fibular Neck*General Characteristics*

1. It courses between the tendon of the biceps femoris and lateral head of the gastrocnemius muscle and then passes around the neck of the fibula between the peroneus longus and the bone; it divides into its superficial and deep branches beneath the muscle
2. It gives off articular branches, which course with the superior and inferior genicular arteries to the knee
3. The recurrent articular branch is given off at the division of the nerve; it ascends with the anterior tibial artery through the tibialis anterior muscle to supply sensation to the front of the knee
4. It innervates the short head of the biceps close to the gluteal cleft
5. Men are affected more than women 3:1
6. Right side and left are affected equally; it is bilaterally affected in 10% of patients

Clinical Manifestations

1. The symptoms and signs occur from the pathology of its branches
2. If the superficial branch is more affected:
 - a. Weakness of foot eversion; the invertors of the foot and toe and foot plantar flexion are spared
 - b. Sensory loss is noted in the lower 2/3 of the lateral leg
3. Rarely Tinel's sign is positive at the fibular neck
4. The ankle jerk is intact

Pathogenesis of Nerve Injury

1. Bed rest of long duration
2. Hyperflexion of the knee
3. Pressure in obstetrical stirrups
4. Compression from habitual leg crossing
5. Blunt trauma

Laboratory Evaluation

1. EMG
2. High resolution ultrasonography
3. MRI neurography

Acute Peroneal Palsy at the Fibular Neck*General Characteristics*

1. Few or no sensory symptoms

Clinical Manifestations

1. Foot drop; loss of function of the deep peroneal branch is more often seen than that of the superficial branch

Pathogenesis of the Nerve Injury

1. Compression:
 - a. Poor positioning during anesthesia

2. Coma
3. Habitual leg crossing
4. Weight loss
5. Positional (yoga; childbirth)
6. Casts
7. Lithotomy position with stirrups
8. Pneumatic compression devices
9. Trauma:
 - a. Blunt and direct trauma
 - b. Tibial plateau fracture
 - c. Dislocation of the knee
 - d. Knee joint ligament rupture
 - e. Arthroscopic knee surgery
 - f. Knee joint replacement

Differential Diagnosis of Deep Peroneal Neuropathy at the Fibular Neck

1. L5 radiculopathy
 - a. There is normal ankle inversion and toe flexion in peroneal palsy; it is weakened in L5 radiculopathy
2. Anterior compartment syndrome:
 - a. Follows contusion or fracture; hemolytic toxin snake envenomation
 - b. Strenuous exercise
 - c. The anterior compartment contains:
 - i. Anterior tibialis
 - ii. Extensor digitorum longus
 - iii. The extensor digitorum brevis is outside the compartment
 - iv. All muscles of the compartment are weakened; the EDB may be denervated when the peroneal nerve is involved
 - d. Differential points favoring an anterior compartment syndrome versus deep peroneal nerve palsy:
 - i. Severe pain (peaks 1–3 days in anterior compartment syndrome after the inciting event)
 - ii. Exacerbation of pain on toe and planar flexion of the ankle
 - iii. Swelling and heat over the compartment
 - iv. Tissue pressure above 60 mm Hg is diagnostic at the ankle (in compartment syndrome)
3. Forcible inversion of the foot may cause hemorrhage into the nerve trunk
4. Prolonged squatting position (the tendon of the posterior border of the peroneus longus at the fibular head or the tendon of the biceps femoris of the distal thigh may compress the nerve)
5. Rarely the nerve may be compressed between the fibular and the tendinous edge of the peroneus longus muscle

Mass Lesions That Compress the Deep Peroneal Nerve

1. Ganglia from the superior tibia-fibular joint (originate from the synovial membrane)
2. Baker's cyst
3. Osteochondroma
4. Giant cell tumor
5. Pseudoaneurysm (genicular artery)

Laboratory Evaluation

1. EMG:
 - a. Denervation of the anterior tibialis, extensor hallucis longus (EHL), extensor digitorum longus, extensor digitorum brevis, and the extensor hallucis brevis
 - b. Need to rule out proximal common peroneal mononeuropathy by demonstrating no denervation of the short head of the biceps femoris and normal conduction studies of the common peroneal nerve
2. High resolution ultrasonography
3. MRI neurography

Sciatic Mononeuropathy Affecting the Lateral Division (Peroneal Component)

General Characteristics

1. In high- or mid-sciatic nerve injury, the lateral (peroneal division) is affected more frequently than the medial (tibial division)
2. The peroneal division has fewer and larger nerve fascicles with less supportive tissue
3. The peroneal nerve is fixed at the sciatic notch and fibular neck (more taut than the tibial nerve)

Clinical Manifestations

1. Similar to a lesion at the fibular neck, but with subtle tibial nerve (medial division) involvement that includes:
 - a. Slight weakness of the anterior tibialis muscle
 - b. Weak ankle inversion
 - c. Sensory loss in the upper lateral third of the leg (territory of the lateral cutaneous nerve of the calf that takes origin from the common peroneal nerve proximal to the fibular neck)

Pathogenesis of the Nerve Injury at the Sciatic Level

1. Hip trauma
 - a. Fracture/dislocation (femur)
 - b. Hip joint replacement
 - c. Abnormal positioning
2. Gluteal injection (penicillin; iron)
3. Gluteal compartment syndrome

Laboratory Evaluation

1. Denervation of the short head of the bicep femoris (the only hamstring muscle innervated by the peroneal nerve)
2. High resolution ultrasound
3. MRI neurography

Deep Peroneal Neuropathy at the Ankle (Anterior Tarsal Tunnel Syndrome)

General Characteristics

1. The floor is the fascia overlying the talus and tarsal bones; the roof is the inferior extensor retinaculum
2. The entrapment is of the distal segment of the deep peroneal nerve

Clinical Manifestations

1. May be unilateral or bilateral
2. More common in women than men
3. Numbness and paresthesias in the deep peroneal sensory distribution (web space between the great and second toe)
4. Wasting of the EDB
5. Ankle and foot pain is often worse at night

Pathogenesis of the Nerve Injury

1. Pressure from straps, shoe rims
2. Ganglion cysts
3. Pes cavus
4. Osteophytes of the talonavicular bones
5. Plantar flexion of the foot with extension of the toes (high heels)
6. Extreme inversion of the foot as occurs in dystonia or spasticity

Laboratory Evaluation

1. EMG:
 - a. Neurogenic MUAP of the distal segment of the peroneal nerve
 - b. Prolonged latency of the distal peroneal branch to EDB
 - c. Denervation of EDB
2. High resolution ultrasonography
3. MRI neuropathy

Differential Diagnosis of Unilateral Foot Drop

1. Hereditary sensory motor neuropathy/Charcot-Marie-Tooth
 - a. Pes cavus; usually atrophy of all muscles below the knee
 - b. Approximately 10% of patients have a flat foot ("rocker bottom")
 - c. There is foot and ankle weakness in all fields of movement
 - d. Weakness of ankle and toe dorsiflexion with intact plantar flexion is a true foot drop
 - e. HSMN/CMT are overwhelmingly bilateral
2. Deep peroneal neuropathy
3. Common peroneal palsy at the fibular neck
4. L4 and L5 radiculopathy (usually not as severe as with the nerve injury)
5. Poliomyelitis
6. Post-polio syndrome:
 - a. Often associated with pain
 - b. Occurs after a period of stability
7. Cerebrovascular disease:
 - a. Anterior cerebral artery infarction:
 - i. The shoulder is often involved
 - ii. All muscles of the foot are involved
 - iii. Dense sensory loss of cortical pattern in the lower leg and foot
 - iv. Loss of ankle jerk acutely

- b. Lacunar infarction of the corona radiata (penetrating medullary artery)
 - c. Lacunar infarction of the ventral pons (lateral area)
8. ALS:
 - a. Painless foot drop may be a common presentation
 - b. Fasciculations in diffuse muscles
 - c. Hyperactive reflexes
 9. Anterior compartment syndrome:
 - a. Severe swelling and pain
 - b. All muscles of the compartment are involved
 - c. In the face of excessive repetitive movements, snake envenomation, rhabdomyolysis
 10. Lumbosacral plexopathy:
 - a. Weak toe and weak plantarflexion
 11. Hereditary neuropathy with sensitivity to pressure palsy (deletion of chromosome 17):
 - a. Concomitant involvement of other nerves or past involvement of other nerves with recovery
 12. Mononeuritis multiplex:
 - a. Setting of autoimmune disease
 13. Multifocal motor neuropathy with conduction block:
 - a. GM1 ganglioside antibodies
 - b. Usually, the upper extremities are affected first
 14. Parasagittal meningioma:
 - a. Usually, presents with a seizure
 15. L5 radiculopathy
 - a. Greater weakness of EHL than the anterior tibialis muscle
 - b. Ankle jerk is intact as it is primarily innervated by the S1 root
 - c. The usual cause of L5 radiculopathy is a herniated nucleus pulposus with pain radiations that include:
 - i. Lower back and posterior thigh; hip pain, great toe, and dorsum of the foot
 16. Posterior tibial nerve neuropathy:
 - a. Inversion weakness of the foot

Differential Diagnosis of Bilateral Foot Drop

1. Neuropathies:
 - a. GBS (subacute; usually with numbness)
 - b. CIDP (depressed reflexes throughout)
 - c. MMNCB (GM1 antibody, asymmetric; upper extremity often affected first)
 - d. Bilateral peroneal lesions (autoimmune pathologies)
 - e. Bilateral sciatic compressive lesions
 - f. Bilateral lumbosacral plexopathies (metastasis, lymphoma, retroperitoneal hemorrhage)
2. Anterior horn cell:
 - a. ALS (usually unilateral; weakness at onset; associated upper motor neuron signs and symptoms)
 - b. Spinomuscular atrophy (SMA)
 - c. Poliomyelitis
 - d. Leukemia and lymphoma
 - e. Radiculopathies:
 - i. Cauda equina syndrome (disc; spondylolisthesis)

- ii. Conus medullaris (the bowel and bladder symptomatology is predominant over motor loss; cancer; glioma; syrinx)
- iii. If the S1 root is more involved than the L5 root, the process is more suggestive of an intraspinal lesion
- f. Myopathies:
 - i. Myotonic dystrophy (concomitant masseter, neck and distal extremity weakness)
 - ii. Facioscapulohumeral muscular dystrophy (severe facial involvement)
 - iii. Scapuloperoneal dystrophy (upper shoulder girdle is concomitantly involved)
 - iv. Distal congenital myopathies:
 - 1. Welander
 - 2. Markesbery-Griggs
 - 3. Nonaka
 - 4. Laing

Tibial Nerve

General Characteristics

1. Innervates all of the hamstring muscles except the short head of the biceps femoris (innervated by the common peroneal nerve)
2. The sural branch is given off in the upper popliteal fossa
 - a. In 80% of the population, the common peroneal nerve gives off a medial branch that joins the sural nerve
3. In the upper calf the tibial nerve lies under the tendinous arch of the soleus muscle to innervate the flexor digitorum pollicis (FDP), the flexor hallucis longus (FHL), gastrocnemius, soleus and tibialis posterior muscles
4. At the ankle, it passes posterior to the medial malleolus in the tarsal tunnel
5. Its terminal branches are:
 - a. A calcaneal branch
 - b. Medial plantar nerve
 - c. Lateral plantar nerve
6. Interdigital branches arise from the medial and lateral plantar nerves on the soles of the foot

Clinical Manifestations

1. High tibial nerve injury:
 - a. Foot pain and numbness; increased by dorsi and plantar flexion of the foot
 - b. Tenderness and positive Tinel's sign in the posterior popliteal fossa
 - c. Weakness of plantar and toe flexion and inversion of the foot
 - d. Absent ankle muscle stretch reflex

Pathogenesis of the Nerve Injury

1. Most often the nerve is injured at or near the popliteal fossa
2. Synovial cyst or superior tibial-fibular ganglion cyst
3. Fibrous band or aponeurotic arch of the soleus muscle
4. Knee surgery
5. Schwannoma and neurofibromas

Laboratory Evaluation

1. EMG:
 - a. Low amplitude or absent MUAP of the abductor hallucis and abductor digiti minimus
 - b. Sural nerve SNAP amplitude is decreased or absent depending on the location of the origin of the nerve in the popliteal fossa
2. MRI neurography
3. High resolution ultrasonography

Tibial Nerve Injury at the Ankle: The Tarsal Tunnel Syndrome

General Characteristics

1. Usually an insidious onset
2. Women have a greater incidence than men
3. In 10 to 20% of patients it is bilateral
4. Anatomy:
 - a. The roof is the laciniate ligament that extends between the medial malleolus and the calcaneum. The floor of the tunnel is the fascia overlying the navicular bones
5. The medial calcaneal nerve branches from the posterior aspect of the posterior tibial nerve in 75% of individuals and from the lateral plantar nerve in 25%
6. The medial calcaneal nerve terminates as a single branch in 80% of individuals and in numerous terminal brands in the remainder
7. There are three well defined tough fascial septae in the sole of the foot that may entrap individual branches of the nerve
8. The tunnel also contains the posterior tibial artery and the tendons of the tibialis posterior, FDL and FHL muscles

Pathogenesis of the Nerve Injury

1. Repetitive movement injures the nerves in runners and dancers
2. Rheumatoid arthritis
3. Diabetes mellitus
4. Acromegaly
5. SLE
6. Hyperlipidemia
7. Hypothyroidism
8. Ganglion cyst
9. Lipoma
10. Schwannoma
11. Varicose veins
12. Varus and valgus deformities
13. Hypertrophic or anomalous abductor hallucis muscles
14. Mobile pes planus

Clinical Manifestations

1. Burning pain and numbness on the sole of the foot and heel; the pain may radiate to the calf
2. Nocturnal pain
3. Increases with rest after activity

4. May be exacerbated by walking and jogging
5. Tinel's sign is positive over the tunnel; a component of the triple compression test (compression of the tarsal tunnel while flexing and inverting the foot)
6. In approximately 40% of patients, the calcaneal branch may be spared as it may arise proximal to the retinaculum
7. 25% of patients have the sensory loss only in the medial branch; 10% are affected only in the lateral branch
8. There may be weakness of the flexor hallucis brevis (FHB), flexor digitorum brevis (medial plantar nerve), quadratus plantae; interossei (lateral plantar nerve); these deficits impair the pushing off phase of walking and plantar flexion of the lateral toes

Laboratory Evaluation

1. EMG:
 - a. Decreased motor nerve conduction of the posterior tibial nerve; prolonged distal latency
 - b. Decreased SNAPs amplitudes and slowed NCVs of the medial and lateral plantar nerves
 - c. Rare denervation of the abductor hallucis and abductor digiti quinti
2. Ultrasonography
3. MRI neurography

Differential Diagnosis of the Tarsal Tunnel Syndrome

1. Plantar fasciitis (the entire sole is equally involved)
2. Stress fractures (lateral metatarsals, particularly the Vth)
3. Bursitis (insertion of the posterior tibial muscle)
4. Chronic regional pain syndrome type two (CRPS II); (severe allodynia, mechanical hyperalgesia, impaired foot movement and autonomic dysregulation)
5. Rheumatoid arthritis (severe joint deformities)
6. Proximal tibial mononeuropathy (compression by the tendinous arch of the soleus muscle); plantar foot flexion weakness; decreased ankle muscle stretch reflex
7. Tibial component nerve sheath tumor
8. S1 and S2 radiculopathy (concomitant weakness of the roots innervated by these muscles; associated back pain)
9. Peripheral neuropathy (usually bilateral)
10. Entrapment of the medial plantar nerve (area of the insertion of the posterior tibial nerve which originates from the calcaneus; or in the fascial canal of the sole of the foot)
11. Burning in the sole and aching in the arch of the foot; compression of the medial plantar nerve against the tuberosity of the navicular bone

Differential Diagnosis of Injury to the Medial Plantar Nerve

1. Bunion surgery
2. Pes cavus
3. Synovial cyst of the first metatarsal phalangeal joint
4. Schwannoma
5. Running and dancing
6. Prolonged standing
7. Entrapment in the sole of the foot

Differential Diagnosis of Lateral Plantar Nerve Injury

1. Trauma (particularly the Vth metatarsal fractures)
2. Schwannoma
3. Entrapment in the sole of the foot (fascial septae)

Joplin's Neuroma

General Characteristics

1. Compression neuropathy of the plantar proper digital nerve to the hallux

Clinical Manifestations

1. Pain primarily on the medial aspect of the great toe
2. Tinel's sign at the first metatarsophalangeal joint

Pathogenesis of Nerve Injury

1. Bunion surgery
2. Ill-fitting shoes
3. Trauma

Laboratory Evaluation

1. EMG
2. Ultrasonography
3. MRI neurography

Morton's Neuroma

General Characteristics

1. Anatomy:
 - a. Metatarsal tunnels are between the deep and transverse metatarsal superficial ligaments that connect the metatarsal heads
 - b. A Morton's neuroma generally refers to an interdigital neuropathy between the 3rd and 4th toes but may occur between the web space of all toes
 - c. The medial plantar nerve branches, arteries, and veins traverse the metatarsal tunnels of the first, second, third toes
 - d. The lateral plantar nerve branches supply the IVth and Vth toes
 - e. Chronic compression of the interdigital nerve between the metatarsal head or hyperextension of the metatarsal joint exacerbates the angulation of the nerve

Clinical Manifestations

1. Lancing electric-like pain in the territory of the involved interdigital nerve
2. The pain is triggered by pressure between the III and IVth metatarsal head (classic)
3. Hypoesthesia in the distribution of the involved digital nerve
4. Arch pain
5. Exacerbated by standing and walking
6. Web space compression test is positive

Pathogenesis of Nerve Injury

1. Distortion of the metatarsophalangeal joints

2. Repetitive trauma (high heels)
3. Fractures
4. Subluxation of the joint
5. Rheumatic inflammatory disease
6. Synovial cysts
7. Hyperextension of the toes narrows the canals and compresses the nerves
8. Flexion contraction of the hip and knees causes toe hyperextension
9. Dystonia and spasticity

Laboratory Evaluation

1. EMG:
 - a. Decreased sensory NCV's of the interdigital nerves
 - b. High resolution ultrasound demonstrates an ovoid hypoechoic lesion non-parallel to the long axis of the metatarsal bone
 - c. MRI neurography

Sural Nerve

General Characteristics

1. A branch of the distal sciatic nerve from both of its divisions that forms in the posterior popliteal fossa
2. The formation and topography of the nerve is anatomically variable. In approximately 30% of patients, it is formed in the distal leg

Clinical Manifestations

1. Pain and paresthesias in the lateral ankle and foot as well as the distal lateral leg
2. Tinel's sign over its emergence 20 to 25 cm above the foot
3. Normal ankle muscle stretch reflex and gastrocnemius strength differentiate it from an S1 radiculopathy

Pathogenesis of Nerve Injury

1. Entrapment of the sural nerve may occur from compression and fixation caused by fascial thickening
2. Sural neuralgia may occur in 5% of patients after surgical procedures and biopsy (neuroma formation)
3. Ganglion
4. Lipoma
5. Positioning
6. Heel straps
7. Repetitive ankle sprains
8. Fractures of the ankle (Vth metatarsal)
9. The "superficial sural" aponeurosis may be thickened which forms a fibrous tunnel at the fascial opening in the leg at the site of entrapment
10. Vein stripping
11. Vasculitis
12. Arthroscopy
13. Baker's cyst

Laboratory Evaluation

1. EMG

- a. Low amplitude or absent SNAP
2. Ultrasound
3. MRI neuropathy

Femoral Nerve

General Characteristics

1. Formed by the posterior division of the ventral rami of L2, L3, L4
2. Innervates the psoas muscle
 - a. Passes between the psoas and iliacus muscle where it is covered by the iliacus fascia (roof of the iliacus compartment)
3. Passes under the inguinal ligament and innervates the iliacus muscle (4–5 cm proximal to the ligament)
4. After the ligament it innervates:
 - a. Four heads of the quadriceps muscle and the sartorius muscle
 - b. Gives rise to the medial and the intermediate cutaneous nerve of the thigh (innervates the anterior thigh) and the saphenous nerve
 - c. The saphenous nerve is posteromedial in the femoral triangle and passes through the adductor canal:
 - i. It is the origin of the infrapatellar branch that innervates the skin of the anterior patella
 - ii. The saphenous nerve becomes subcutaneous 10 cm proximal and medial to the knee (pierces the fascia between the sartorius and gracile muscles); crosses the pes anserinus bursa at the upper medial tibia
 - iii. In the lower 1/3 of the leg, it divides into the two terminal branches that innervate the medial surface of the knee, leg, medial malleolus and the medial arch of the foot

Clinical Manifestations

1. Usually, the nerve is injured unilaterally
 - a. The exception is the lithotomy position with concomitant pressure on the adductor canal (during delivery or GYN surgery)
2. Acute thigh weakness
3. Weakness and atrophy of the quadriceps muscle
4. Sensory loss over the anterior thigh and the medial lower leg
5. Hip flexor weakness (L1–L3) suggests lumbar plexus involvement
6. An unstable leg:
 - a. The knee buckles when partially flexed
 - b. The patients suffer frequent falls
7. Acute groin and thigh pain; later deep thigh pain
8. Femoral nerve involvement from retroperitoneal hematoma is associated with severe back, abdominal, groin, buttock and anterior thigh pain
 - a. The position of comfort is lying in bed with a flexed thigh
9. Hip flexion weakness (iliopsoas involvement with an intrapelvic lesion); is spared if the lesion is at the inguinal ligament (lithotomy position)

10. A positive reverse straight leg raising test (particularly with proximal lesions)
11. Depressed or absent knee muscle stretch reflex

Pathogenesis of Nerve Injury

1. The nerve is most often injured during surgical or diagnostic procedures
 - a. Retractors compress the nerve against the pelvic wall
2. Pelvic injury:
 - a. Abdominal hysterectomy
 - b. Prostatectomy
 - c. Renal transplantation
 - d. Colectomy
 - e. Inguinal herniorrhaphy
 - f. Lumbar sympathectomy
 - g. Tubal ligation
 - h. Aortic aneurysm surgery
3. Retroperitoneal bleeding:
 - a. Pressure under the fascia; blood is trapped over the iliopsoas muscle beneath the femoral triangle and under the fascia
 - b. Renal transplantation (bleeding)
 - c. Hemophilia
 - d. Anticoagulation
 - e. Coagulopathy
 - f. Ruptured abdominal aneurysm
 - g. Femoral artery catheterization
 - i. Approximately 0.5% of femoral artery catheterization for coronary artery disease bleed; often there is concomitant use of anticoagulation; approximately 1/3 of these patients have a lumbar plexopathy or femoral nerve injury
 - h. Large hemorrhages extend into the psoas muscle and the retroperitoneal space which compromises the lumbosacral plexus
4. Compression at the inguinal ligament:
 - a. Prolonged lithotomy position (hip flexion with external leg rotation):
 - i. Associated with vaginal delivery
 - ii. Vaginal hysterectomy, prostatectomy and laparoscopy
 - iii. Inguinal hematoma
5. Total hip replacement:
 - a. Nerve injury may occur in up to 2–3% of patients
 - b. Anterior acetabular retraction compresses the nerve
 - c. The most common setting for injury occurs with revisions and complicated reconstruction of the hip
6. Lymphadenopathy at the inguinal area
7. Pelvic mass lesions:
 - a. Lymphoma
 - b. Metastatic tumor (ovary, prostate, colon)
 - c. Abscess
 - d. Aortic or iliac aneurysm
8. Neuropraxia (stretch injury)
9. Radiation therapy

10. Laceration (blood drawing and catheterization)
11. Diabetic femoral neuropathy or as a nerve involved with autoimmune mononeuritis multiplex
12. Femoral nerve tumors (neurofibroma, schwannoma and neurogenic sarcoma)

Laboratory Evaluation

1. EMG:
 - a. Slowing of motor nerve conduction at the inguinal ligament
 - b. Decrease SNAP amplitude of the saphenous nerve
 - c. Denervation of femoral nerve innervated muscles
2. High resolution ultrasound
3. MRI neurography

Differential Diagnosis

1. L2, L3, L4 radiculopathy (rare disc disease)
2. Lumbar plexopathy; if the thigh adductors are denervated the lesion is proximal to the femoral nerve (obturator nerve)
3. Weakness of ankle dorsiflexion (L4 and L5) from the peroneal nerve suggests an L4 radiculopathy or lumbar plexopathy; back buttock and leg pain with a positive straight leg raising test favors radiculopathy

Lateral Femoral Cutaneous Nerve

General Characteristics

1. Arises from the sensory fibers of the dorsal rami of the L2 and L3 spinal roots
2. The nerve passes within or under the inguinal ligament anterior or medial to its insertion at the anterior superior iliac spine. There are significant anatomical variations of its passage
3. It pierces the tensor fascia lata to innervate the lateral thigh

Clinical Manifestations

1. Numbness and paresthesias in the lateral thigh (often a burning sensation); never below the knee
2. Hyperesthesia as well as dynamic and static mechanallodynia may occur
3. The abnormal sensation may be exacerbated by standing, walking or turning and may be relieved by hip flexion
4. The “wind-up” phenomenon may be demonstrated; increased dysesthesia with temporal summation

Pathogenesis of Nerve Injury

1. Entrapment of the LFCN as it passes through or under the inguinal ligament:
 - a. Diabetes mellitus
 - b. Pregnancy
 - c. Obesity
 - d. Constricting belts
2. Direct injury:
 - a. Iliac bone graft

- b. Injections
- c. Renal transplantation
- d. Gastric bypass surgery
- e. Herniorrhaphy
- f. Intrapelvic retraction injury
- g. Abnormal positioning (hip flexion)
- h. Blunt trauma (seat belt; avulsion of the anterior superior iliac spine)
- i. Metastasis to the iliac crest
- j. Abdominal aortic aneurysm

Laboratory Evaluation

1. EMG:
 - a. Decreased amplitude of the SNAP and nerve conduction velocity
2. High-frequency ultrasound:
 - a. The LCFN is most easily identified if the intermuscular space between the tensor fascia lata muscle and the sartorius is the initial sonographic landmark
3. MRI neurography

Differential Diagnosis of Lateral Femoral Cutaneous Nerve Injury

1. Lumbar radiculopathy:
 - a. Not as well circumscribed sensory loss with radiculopathy
 - b. Associated back and often groin pain (S1 root)
2. Femoral neuropathy:
 - a. Numbness involves the anterior thigh; may extend medially and to the leg
3. Lumbar plexopathy:
 - a. Anterior thigh pain
 - b. Weakness of the quadriceps and often the iliopsoas
 - c. Loss of knee muscle stretch reflex
4. Lumbar spinal stenosis:
 - a. “Simian” forward flexed posture when walking
 - b. Weakness is primarily in the L4–S1 distributions
 - c. Loss of AJ at times; others have increased knee jerks and ankle jerks due to concomitant cervical stenosis
5. Tensor fascia lata bursitis:
 - a. Lateral thigh pain often with specific point tenderness (usually after compression during recovery from surgical procedure)

Saphenous Nerve

General Characteristics

1. Courses through the adductor canal; penetrates the fascia above the knee
2. Supplies the cutaneous sensation to the medial calf, medial malleolus and medial arch of the foot

Clinical Manifestations

1. Pain or numbness in the distribution of the nerve; the medial calf is most noticeable

2. Tinel’s sign over the site of entrapment
3. Entrapment often occurs at the exit from Hunter’s canal (10 cm above the medial femoral condyle)
4. Knee pain is common
5. Infrapatellar branch entrapment causes anterior anteromedial or anterolateral knee pain; this branch involvement is also a common cause of chronic regional pain syndrome (CRPS II)

Pathogenesis of Nerve Injury

1. Stripping of the long saphenous vein as well as harvesting the vein for coronary bypass surgery
2. Superficial femoral thromboendarterectomy
3. Meniscectomies (knee joint)
4. Arthroscopic procedures (knee)
5. The infrapatellar branch may be entrapped behind the sartorius tendon
6. Medial knee trauma

Laboratory Evaluation

1. EMG:
 - a. Low amplitude or absent SNAP of the nerve
 - b. High resolution ultrasound
 - c. MRI neurography

Ilioinguinal Nerve

General Characteristics

1. The ilioinguinal nerve is a branch of the first lumbar nerve (L1):
 - a. There may be a contribution from T12
 - b. The nerve separates from the first lumbar in association with the iliohypogastric nerve
2. It has both motor and sensory components
 - a. The muscular branches innervate the lowest portions of the transverse abdominal muscle and the internal oblique muscle and fascia
3. After emerging from the lateral border of the psoas major inferior to the iliohypogastric nerve:
 - a. It courses obliquely across the quadratus lumborum and the iliacus muscles, perforates the transverse abdominis muscle near the anterior iliac crest, and associates with the iliohypogastric nerve
 - b. It pierces and innervates the internal oblique muscle and courses with the spermatic cord through the superficial inguinal ring
 - c. It innervates the upper and medial thigh as well as:
 - i. In males (“anterior scrotal nerve”) innervates the root of the penis and upper scrotum
 - ii. In females it innervates (“anterior labial nerve”) the mons pubis and labium majora
 - iii. It does not enter the deep inguinal ring and thus passes through a part of the inguinal canal
 - iv. Entrapment occurs slightly medial to the anterior iliac spine

Clinical Manifestations

1. Burning pain in the lower abdomen; inner portion of the upper thigh; base of the scrotum; labia majora
2. Bulging of the lower abdominal wall from weakness of the internal oblique and transversalis muscles
3. Pain is exacerbated with extension of the thigh or hip; position of comfort is a flexed hip
4. Tinel's sign may be elicited medial to the anterior iliac spine (if this is the point of entrapment)

Pathogenesis of Nerve Injury

1. Laparoscopy
2. Hernia repair
3. Appendectomy
4. Bladder suspension
5. Pfannenstiel incision
6. Blunt trauma
7. Entrapment
8. Parturition
9. Bone harvesting from the iliac crest
10. Nephrectomy

Laboratory Evaluation

1. EMG:
 - a. Denervation of lower abdominal muscles
2. High resolution ultrasound
3. MRI neurography

Differential Diagnosis of Ilioinguinal Nerve Injury

1. High lumbar radiculopathy (L1 or L2)
2. Genitofemoral neuropathy

Iliohypogastric Nerve*General Characteristics*

1. Originates most commonly from L1 with a contribution from the T12 spinal segment
2. It crosses the psoas and quadratus lumborum muscles, passes through and innervates the transverse abdominis and internal oblique muscles
3. The nerve has two terminal cutaneous branches that innervate a portion of the lateral buttock (lateral branch) and the anterior branch that innervates a high portion of the pubis

Clinical Manifestations

1. Pain and sensory loss above the symphysis pubis
2. Rarely weakness of the lower abdominal wall
3. A strip of numbness in the lateral buttock

Pathogenesis of Nerve Injury

1. The nerve is frequently injured in association with the ilioinguinal nerve
2. Surgical procedures:
 - a. Lower quadrant, abdominal surgery that includes:
 - i. Appendectomy

- ii. Nephrectomy
- iii. Retroperitoneal tumors
- iv. Hernia repair
- v. Pfannenstiel incision
- vi. Abdominoplasty

Laboratory Evaluation

1. EMG:
 - a. Denervation of the lower abdominal muscles
 - b. Anesthesia; ultrasound guided iliohypogastric nerve block
 - c. MRI neurography

Differential Diagnosis of Iliohypogastric Nerve Injury

1. Ilioinguinal neuropathy
2. Genitofemoral neuropathy
3. L1 and L2 radiculopathy

Genitofemoral Nerve*General Characteristics*

1. The nerve originates from the L1 and L2 spinal roots and passes through the psoas muscle; it divides into the femoral and genital branches at the inguinal ligament
2. The femoral branch innervates a small area of the anterior thigh; the genital branch innervates the scrotum and labia majora
3. It innervates the cremasteric muscle

Clinical Manifestations

1. Pain in the medial inguinal area, scrotum or labia majora
2. The sensory loss may overlap with that of the ilioinguinal nerve
3. Absent cremasteric reflex

Pathogenesis of Nerve Injury

1. Psoas abscess
2. Appendectomy
3. Inguinal herniorrhaphy
4. Nephrectomy
5. Cesarean section
6. Abdominal trauma
7. Adhesion and scarring from abdominal surgeries (delayed presentation)
8. Concomitant genital branch and ilioinguinal nerve injury that occurs at the inguinal ligament

Laboratory Evaluation

1. EMG:
 - a. No NCS have been reported from this nerve
 - b. Ultrasound guided diagnostic nerve block
 - c. MRI neurography

Differential Diagnosis of Genitofemoral Nerve Injury

1. L1–L2 radiculopathy
2. Ilioinguinal neuropathy
 - a. No anterior femoral distribution

Posterior Cutaneous Nerve of the Thigh*General Characteristics*

1. Its origin is the S1–S3 spinal roots
2. Exits the pelvis with the inferior gluteal nerve through the sciatic notch under the piriformis muscles
3. It supplies cutaneous innervations of the lower buttock, posterior thigh, popliteal fossa and at times the proximal 1/3 of the calf; it has perineal, scrotal and labia majora branches
4. The nerve may be injured with the sciatic and inferior gluteal nerves

Clinical Manifestations

1. Paresthesias of the lower buttock and posterior thigh; exacerbated by sitting or the supine posture

Pathogenesis of Nerve Injury

1. Gunshot and laceration wounds
2. Colorectal tumors
3. Venous malformations
4. Bicycle riding; specific compressions
5. Intramuscular injections

Laboratory Evaluation

1. EMG:
 - a. Decreased or absent SNAP of the nerve
2. Ultrasound guided anesthetic block
3. MRI neurography

Differential Diagnosis of PCNT Injury

1. S1 or S2 radiculopathy (rarely purely sensory)
2. Sacral plexopathy:
 - a. The above root lesions would be accompanied by a depressed or absent ankle jerk; sciatic nerve lesions would have concomitant hamstring or gastrocnemius muscle weakness

Obturator Nerve*General Characteristics*

1. The nerve originates from the ventral divisions of the second, third and fourth lumbar nerves of the lumbar plexus
2. It descends through the psoas muscle and emerges from its medial border at the brim of the pelvis
 - a. It traverses behind the common iliac arteries and progresses along the lateral wall of the pelvis to the upper portion of the obturator foramen
3. It enters the thigh through the obturator canal and divides into an anterior and posterior branch
4. Its sensory innervation is the medial thigh
5. Its motor innervation includes:
 - a. Adductor muscles of the lower extremity:
 - i. External obturator
 - ii. Adductor longus
 - iii. Adductor magnus
 - iv. Gracilis
 - v. Pectineus

Clinical Manifestations

1. The initial symptom is usual pain in the groin, anterior or medial thigh (often in athletes or associated with an obturator hernia)
2. Adductor muscle weakness may cause destabilization of the hip joint; difficulty with walking; wide-based gait
3. Pain may radiate to the medial calf and is exacerbated by extension or lateral leg movement

Pathogenesis of Nerve Injury

1. Lumbar plexopathy
2. Pelvic trauma (fractures)
3. Hip surgery:
 - a. Retractor blade
 - b. Cement extrusion
 - c. Fixation screws
4. Aortofemoral bypass
5. Oophorectomy
6. Laparoscopic lymphadenectomy
7. Vaginal delivery (forceps)
8. Obturator hernia
9. Endometriosis
10. Pelvic malignancy
11. Entrapment under the adductor fascia
12. Schwannoma
13. Sacroiliac lesion may impinge on the nerve
14. Tumors:
 - a. Transitional cell cancer of the bladder
 - b. Cervical carcinoma
 - c. Lymphoma
 - d. Prostatic cancer
 - e. Sarcoma
15. Parturition
16. Surgical tourniquets
17. Myositis ossificans

Laboratory Evaluation

1. EMG:
 - a. Adductor muscle denervation
 - b. Large MUAP and fibrillation potentials in muscles that are innervated by the nerve
 - c. Ultrasonographically guided nerve block
 - d. MRI microneurography

Differential Diagnosis of Obturator Nerve Injury

1. L3–L4 radiculopathy
2. Lumbar plexopathy:
 - a. Diabetes mellitus
 - b. Infection
 - c. Malignancy
 - d. Collagen vascular disease

The above are ruled out by iliopsoas, quadriceps weakness, loss of the knee jerk and ankle reflex. Medial thigh sensory loss is seminal. Symphysis pubis lesions may radiate pain to the medial thigh.

Inferior Gluteal Nerve*General Characteristics*

1. The inferior gluteal nerve arises from the dorsal branches of the ventral rami of L5, S1, and S2 nerves
2. The sacral plexus forms anterior to the piriformis muscle and is the origin of:
 - a. Sciatic nerve
 - b. The superior and inferior gluteal nerves
 - c. Pudendal nerves
 - d. Posterior femoral cutaneous nerve
3. The inferior gluteal nerves exits the pelvis through the greater sciatic foramen:
 - a. It courses inferior to the piriformis muscle
 - b. It divides into muscular branches that innervate the gluteus maximus muscle
 - c. It is superficial to the sciatic nerve and at the lower border of the piriformis muscle it divides into upper and downward diverging branches
 - d. Rarely, it may give origin to a branch of the posterior femoral cutaneous nerve
 - e. The nerve enters the deep surface of the gluteus maximus approximately 5 cm from the tip of the greater trochanter of the femur
4. The inferior gluteal nerve courses with the inferior gluteal artery which is a branch of the anterior trunk of the internal iliac artery
5. Is bounded by:
 - a. The superior edge of the piriformis muscle
 - b. The lower edge of the gluteus medius muscle
 - c. The ischium of the sciatic notch
 - d. The piriformis muscle divides the sciatic notch into a superior and inferior foramen
 - i. L5, S1, and S2 roots exit through the infra-piriformis foramen

Clinical Manifestations

1. Difficulty climbing stairs
2. Decreased extension of the flexed thigh
3. It is active in lateral rotation and abduction of the thigh
4. Stabilizes the femur on the tibia when the knee extensors are relaxed
5. Difficulty running and standing up
6. Atrophy of the buttock
7. Pain in the gluteus muscle that radiates into the posterior thigh
8. Pathogenesis of inferior gluteal nerve injury

Pathogenesis of Nerve Injury

1. Hip replacement:
 - a. Possibly most common with the posterior approach
2. The inferior gluteal nerve is injured by intrapelvic mass lesions that include:
 - a. Lymphoma
 - b. Colorectal cancer
 - c. Iliac artery aneurysms

3. The nerve may be compressed by the sciatic nerve
4. Pelvic fractures
5. Prolonged traction during hip replacement

Laboratory Evaluation

1. EMG:
 - a. Denervation of the gluteus maximus muscle
2. High resolution ultrasound
3. MRI neurography

Differential Diagnosis of Inferior Gluteal Neuropathy

1. Diseases of the hip joint
2. L5 and S1 radiculopathy

Superior Gluteal Nerve*General Characteristics*

1. The superior gluteal nerve arises from dorsal division of L4, L5, and S1
2. It exits the pelvis through the greater sciatic foramen above the piriformis muscle associated with the superior gluteal artery and vein
3. It terminates in the gluteus minimus and tensor fascia lata muscle
4. In the suprapiriformis, it is in juxtaposition with the sciatic and posterior femoral nerve
5. It innervates the gluteus medius, minimus, and tensor fascia lata muscles

Clinical Manifestations

1. Injury to the nerve causes a pelvic tilt to the opposite side during walking or standing on the affected leg (Trendelenburg sign)
2. There is destabilization of the pelvis in the coronal plane; there is weakness of hip abduction
3. Bilateral loss of the muscles causes a waddling gait

Pathogenesis of Nerve Injury

1. Pelvic fracture
2. Damaged during hip replacement
3. Rarely entrapped by the piriformis muscle
4. Misplaced injections

Laboratory Evaluation

1. EMG:
 - a. Fibrillation potentials and decreased amplitudes of the CMAP in the tensor fascia lata muscle and gluteus medius muscle
2. High resolution ultrasound
3. MRI neurography

Unusual Entrapments Neuropathies**Lumbosacral Tunnel Syndrome***General Characteristics*

1. The L5 roots are entrapped across the ala of the sacrum or under the lumbosacral ligament

2. The lumbosacral ligament:
 - a. A fibrous ligament that originates from the fifth lumbar vertebra and inserts on the upper border of the ala of the sacrum
3. The L5 spinal nerve courses under the ligament with the iliolumbar artery and vein

Clinical Manifestations

1. Sensor loss and pain in the L5 dermatomal distribution with minimal or no objective findings

Pathogenesis of Nerve Injury

1. Thickening of the ligament
2. Bony osteophytes
3. Tumor
4. Iliolumbar artery aneurysm

Laboratory Evaluation

1. EMG:
 - a. Evaluation of the L5 root
2. MRI neurography
 - a. Both CT and MRI to evaluate alternate areas of involvement (CT better for bony anomalies)
3. 3-dimensional computed tomographic imaging to diagnose extraforaminal stenosis at the lumbosacral junction:
 - a. The minimum cross-sectional area of the bony tunnel was less than 0.8 cm² in symptomatic patients

Non-Vasculitic Ischemic Nerve Injury

Compartment Syndromes

General Characteristics

1. Increased pressure within a closed muscular space
2. Nerves are injured by compromise of the vasa nervorum which decreases their capillary perfusion
3. Normal compartment pressure is usually 0–8 mm Hg
4. Acute compartment syndromes:
 - a. Anterior compartment of the leg is most common
 - b. The volar forearm compartment is most common in the upper extremity
5. Chronic compartment syndrome:
 - a. Overuse and exercise
 - i. Often the anterior and posterior leg compartments are involved

Acute Compartment Syndrome

Clinical Manifestations

1. May occur hours after the inciting event
2. Pain in the involved compartment
3. Swelling tenderness and edematous skin
4. They may be incipient as they develop; full blown after they are established
5. Dysfunction of the nerves that are located in the compartment (anesthesia and paralysis)
6. The distal circulation is spared

Pathogenesis of Nerve Injury

1. The causes of ACS are either an increase in the volume of a compartment or a decreased ability of the compartment sheath to expand
2. Decreased compartment size:
 - a. Tight dressings
 - b. Bandages
 - c. Casts
 - d. Lying on a limb (during coma)
 - e. Following operations that require unnatural positioning (lithotomy position)
 - f. Circumferential burns (develop an inelastic eschar)
3. Increased volume of the compartment:
 - a. Fractures are the most common cause of ACS (possibly 70% of cases):
 - i. Tibial shaft fractures are the most common > distal radius and ulnar fractures
 1. Tissue swelling and hematoma formation are possible mechanisms of raising intracompartmental pressure
 2. ACS may occur with open fractures; formerly they were thought to decompress naturally
 3. Crush injury:
 - a. Multiple compartments are involved, and large muscle may be crushed (gluteus maximus)
 - b. Systemic manifestations of crush injuries include:
 - i. Rhabdomyolysis with myoglobinuria
 - ii. Increased serum K⁺ with cardiac arrhythmia
 - iii. Renal failure
 - iv. Shock
 - c. Causes of compartment syndrome:
 - i. Exercise
 - ii. Fluid infusion
 - iii. Ruptured ganglion cyst
 - iv. Snake envenomations
 - v. Viral myositis
 - vi. Osteomyelitis
 - vii. Rhabdomyolysis
 - viii. Hematoma

Laboratory Evaluation

1. The pressure of a normal myofascial compartment is usually less than 10 mm Hg:
 - a. Intracompartmental pressure of 30 mm Hg for 6–8 hours causes irreversible muscle damage
 - b. Fasciotomy is usually recommended between 30 mm Hg and 45 mm Hg
2. Non-invasive imaging techniques include:
 - a. Near infrared spectroscopy (NIRS)
 - b. Laser Doppler Flowmetry
3. Biomarkers:
 - a. White cell count, creatine kinase (CK) and myoglobin are not specific

Chronic Compartment Syndrome

General Characteristics

1. The pathology of chronic exertional compartment syndrome:
 - a. Related to a marked increase in tissue pressure within a closed fascial space during exercise
 - b. Muscle volume can increase up to 20% of its resting volume during exercise; most feel that increased compartment pressure causes impaired muscle perfusion
 - c. Recent SPECT scan studies demonstrate no significant difference in relative perfusion of those with chronic compartment syndrome; other theories postulate that pain is caused by stimulation of the sensory fibers of the fascia

Clinical Manifestations

1. Pain in the compartment (usually the leg) at the same time or intensity as caused by exercise
2. The pain increases in intensity as the patient continues to exercise. It is relieved by rest
3. The pain is usually burning, aching, or pressure like. It may be bilateral in the same compartment in a significant number of patients
4. Patients may not be able to achieve the same parameters of the exercise they did before the symptoms were noted
5. Muscle tenderness
6. Paresthesia and muscle weakness of the affected nerve located within the compartment
7. Pain may be evoked with passive stretching of the muscle and firmness of the involved compartment
8. Muscle herniation through defects in the fascia may be palpated in between 40 to 60% of patients (usually over the anterior tibia in lower extremity anterior compartment syndrome)
9. Fascial defects occur at the peroneal exit area from the lateral compartment

Pathogenesis of Nerve Injury

1. Exertion and overuse

Laboratory Evaluation

1. EMG:
 - a. Assesses for peroneal nerve entrapment
 - b. Bone scan to rule out stress fractures
 - c. Measurement of intracompartmental pressure:
 1. A resting pressure of greater than 15 mm Hg and 5 minutes post-exercise pressure greater than 20 mm Hg are diagnostic
- d. MRI:
 - i. An MRI suggestive of chronic compartment syndrome demonstrates increased T2-weighted signal intensity within the involved muscles
 - ii. A decrease of T1-weighted sequences intensity suggests fibrosis and muscle atrophy

Differential Diagnosis of Chronic Exertional Leg Pain

1. Medial tibial stress syndrome:
 - a. Also known as shin splints
 - b. A periostitis of the posteromedial border of the tibia
 - c. Symptoms are pain with activity that is relieved with rest; examination reveals diffuse tenderness of the posteromedial border of the tibia
2. Stress fracture:
 - a. Presents as pain over the tibia and fibula exacerbated by activity and relieved by rest
 - b. Examination reveals point tenderness over the tibia or fibula that is exacerbated by mechanical stimuli
3. Fascial defects:
 - a. Fascial defects by themselves are asymptomatic
 - b. Defects are most frequent over the medial and lateral compartments of the lower leg
 - c. Pain results from muscle herniation through the fascia with concomitant nerve compression
 - d. Pain radiates to the dorsum of the foot
 - e. Muscle bulging may be evident
4. Peroneal nerve entrapment:
 - a. Occurs at the point where the nerve pierces the deep fascia on the lateral leg
 - b. Pain is evoked in the lateral leg by dorsiflexion and eversion of the ankle
 - c. Positive Tinel's sign at the site of penetration of the nerve
5. Popliteal artery entrapment syndrome (PAES):
 - a. The artery is compressed in the compartment following chronic exercise
 - b. Exertional calf pain
 - c. Examination reveals a diminished dorsalis pedis pulse with plantar flexion and dorsiflexion
6. Vascular claudication:
 - a. Pain with exercise (usually burning and in the calf) which is relieved with leg elevation; in some patients with recumbency

Ischemic Monomelic Neuropathy

General Characteristics

1. Distal nerve damage in an extremity due to proximal compromise of the arterial supply:
 - a. Compression of the vessel
 - b. Diversion of blood
2. Occurs in both the upper and lower extremities
3. There is often a distal to proximal gradient of both clinical and EMG deficits
4. At any limb level different peripheral nerves are affected uniformly

Clinical Manifestations

1. Deep burning pain in the hand or foot
2. Coexisting paresthesias (different nerve distributions)
3. The upper extremity has greater distal sensory deficits than the lower extremity

4. Weakness and wasting of intrinsic hand and foot muscles; distal > proximal
5. Symptoms appear acutely and reach maximum intensity within days
6. Impairment of all sensory modalities distal > proximal in the extremities
7. Rarely there are signs of vascular insufficiency in the affected extremity

Pathogenesis of Nerve Injury

1. A–V shunts in the antecubital fossa or the proximal arm for dialysis
2. Lower extremity arterial compromise:
 - a. Superficial femoral artery
 - i. Cardiopulmonary bypass communication
 - ii. Intra-aortic balloon pump
 - iii. Bifemoral thrombosis
 - iv. Aortoiliac embolus
 - v. Ergotamine poisoning; methylsurgicide
3. Neuropathology
 - a. Axonal neuropathy

Laboratory Evaluation

1. Decreased motor and sensory NCV
2. Decreased amplitude or absent SNAPs or CMAP
3. Fibrillation potentials in intrinsic hand or foot muscles
4. No concomitant myopathic changes
5. Immediate closure of the A–V access leads to partial or full recovery

Differential Diagnosis of Ischemic Monomelic Neuropathy

1. Compression (anesthetic positioning)
2. Radiculopathy (L4, L5)
3. Intermittent claudication
4. Plexopathy from axillary block
5. Steal syndrome:
 - a. A–V shunt; reversal of distal arterial flow
 - i. Non-healing wounds; tissue loss
 - ii. Neurologic dysfunction with no ischemic damage

Acute Ischemic Mononeuropathy and Plexopathy

General Characteristics

1. Vasculitis and acute compartment syndrome are the most common causes
2. Large vessel atherosclerotic occlusion:
 - a. The vessel is injured during its repair
 - b. The lower extremity nerves and the lumbosacral plexus may be involved concomitantly

Clinical Manifestations

1. Abrupt weakness and sensory loss after the reconstructive procedures
2. Concomitant signs of vascular insufficiency overshadow neural dysfunction prior to surgery

3. Neurogenic claudication:
 - a. Exercise-induced paresthesias of the buttocks and legs (or pain)
 - b. Weakness of leg muscles with exercises
 - c. Impotence

Neuropathology

1. The usually atherosclerotic vessels are:
 - a. The distal aorta (Leriche's syndrome)
 - b. Internal > external iliac artery
 - c. Common iliac artery
2. Cauda equina and sacral plexus
 - a. Receives its blood supply from the internal iliac artery, the ilioinguinal internal iliac artery, the ilioinguinal artery and the great radicular artery of Adamkiewicz whose origin is T12–L1, L2
3. Femoral nerve and the lumbosacral plexus are most frequently ischemic
4. Surgical causes of ischemia of the lower extremity nerves and the lumbosacral plexus include:
 - a. Abdominal aortic-iliac surgery:
 - i. Aneurysms (abdominal aortic)
 - ii. Infected grafts and graft failure
 - b. Atherosclerotic distal aorta or iliac artery stenosis
 - c. Pelvic radiation
 - d. Aortic balloon pumps
 - e. Intra-arterial injections of the iliac or gluteal arteries
5. Rarely the sciatic and common peroneal nerves are affected concomitantly:
 - a. Ischemia of the common iliac artery
6. Ischemia of the nerves and plexus during procedures occurs from:
 - a. Prolonged hypotension
 - b. Embolus to the vasa nervorum
 - c. Inadequate heparinization
 - d. Cross clamping the aorta or major vessels

Laboratory Evaluation

1. EMG:
 - a. Similar findings as those of ischemia monomelic neuropathy
 - b. Arteriography to evaluate the operated artery
 - c. Laser Doppler flowmetry

Differential Diagnosis of Acute Ischemic Mononeuropathy/Plexopathy

1. Cauda equina lesions
2. Conus medullaris lesions (bowel/bladder are involved; no pain)
3. Ischemic femoral neuropathy:
 - a. Psoas and iliacus anterior compartment syndrome; the quadriceps is almost universally involved
4. Sciatic neuropathy:
 - a. Incomplete cauda equina lesion
 - b. Sacral plexopathy
 - c. Ischemic monomelic neuropathy

Differential Features of the Entities

1. Lumbosacral plexopathy:
 - a. Unilateral
 - b. Bladder involvement occurs
 - c. Motor and sensory loss is in the distribution of more than one nerve
 - d. Buttock pain occurs first with ischemic lumbosacral plexopathy
2. Ischemic femoral neuropathy:
 - a. Quadriceps weakness
 - b. Saphenous nerve involvement (sensory loss or paresthesias of the medial lower leg)
 - c. Femoral nerve sensory loss (quadriceps)
 - d. Depressed or absent knee jerk
3. Iliacus acute compartment syndrome:
 - a. Groin mass
 - b. Severe pain with hip flexion
4. Ischemic sciatic neuropathy:
 - a. Presents in the distribution of the common peroneal and tibial nerves
 - b. Weakness and sensory loss below the knee
 - c. Hamstring, paraspinal and glutei muscles are spared

Frostbite*General Characteristics*

1. Tissue injury from temperature below the freezing point on intact skin
2. Men are affected more than women 10:1
3. It is most prevalent in adult men 30 to 49 years of age
4. There is a high incidence in psychiatric and homeless patients
5. The feet are involved in more than 90% of patients; less often the ears, nose, cheeks and penis

Clinical Manifestations

1. Exposure occurs in:
 - a. Outdoor activities in extremely cold weather
 - b. Psychiatric illness
 - c. Trauma
 - d. Homeless patients
2. Pre-freeze stage:
 - a. Loss of light touch, pain and temperature perception
 - b. Edema
 - c. Poor coordination of hands and feet
3. Freezing stage:
 - a. Direct injury of frostbite occurs
 - b. Superficial frostbite:
 - i. Minimal, if any, tissue loss
 - ii. Supple painful skin
 - iii. Large blisters with fluid after thawing
 - iv. Sensation may be intact
 - c. Deep frostbite:
 - i. Significant tissue loss
 - ii. Anesthetic tissue

- iii. Blue-gray discoloration of the tissue
 - iv. Hemorrhagic blisters occur with thawing
 - v. Edematous and suffused tissue
4. Residual signs and symptoms:
 - a. Burning pain
 - b. Hyperhidrosis
 - c. Autonomic dysregulation of the affected part
 - d. Sensory loss of all modalities
 - e. Cold intolerance
 - f. Hyperpigmented and atrophic skin

Neuropathology

1. Direct injury phase (prior to freezing):
 - a. Skin temperature is less than 10°C
 - b. Microvascular vasoconstriction with endothelial damage
2. Freezing phase:
 - a. Skin temperature is usually below 2°C
 - b. Ice crystals that form in the extracellular fluid causes increased osmotic pressure
 - c. Intracellular shrinkage; disruption of membrane lipid complexes
 - d. Cells die an osmotic death when they lose 1/3 of their volume
3. Indirect phase during thawing:
 - a. Vascular stasis with progressive ischemia
 - b. Tissue destruction occurs during this phase (the first few hours)
 - c. Microvascular destruction: affects venules prior to arterioles
 - d. Release of proinflammatory mediators such as prostaglandin F₂ and thromboxane A₂

Laboratory Evaluation

1. Triple phase bone scan
2. Angiography in patients considered for thrombolysis
3. MRI/MRA:
 - a. Direct visualization of occluded vessels and surrounding tissue; may demonstrate demarcation of ischemic tissue

Hand Arm Vibration Syndrome (HAVS)*General Characteristics*

1. Vibrating tools are causative: pneumatic drills, electric grinders, polishers, and gasoline-powered chain saws
2. Occurs after approximately 1000 hours of exposure

Clinical Manifestations

1. Secondary Raynaud's phenomenon
2. Numbness and decreased sensitivity of the affected extremity; tips of the fingers are affected first
3. The palms are not involved
4. Specific vasospastic attacks last 1 to 160 minutes; they occur more commonly in the morning
5. Continued exposure increases the numbers and duration of attacks

6. Attacks may be aborted by warmth; pain and hyperemia occur during warming
7. Intrinsic hand muscle atrophy
8. Vibration at less than 40 Hz causes wrist and elbow osteoarthritis

Neuropathology

1. Osteoarthritic changes of distal phalangeal bones
2. Caustic small bone lesions
3. Local osteoporosis
4. Impaired vascular regulation

Laboratory Evaluation

1. X-ray defined osteoporosis
2. Osteoarthritis of the elbow and shoulder
3. Laser Doppler imaging of skin blood flow before, during, and after cold water immersion
4. Skeletal x-rays of the hands
5. Infrared thermometry

Differential Diagnosis of Neuropathy

Axonal Neuropathies

1. Acute onset:
 - a. Acute demyelinating axonal neuropathy (AIDP)
 - b. Acute intermittent porphyria
 - c. Variegate porphyria
 - d. Coproporphyria
 - e. Tick paralysis
2. Acute intoxications (axonal destruction):
 - a. Heavy metals
 - i. Lead (Pb)
 - ii. Arsenic
 - iii. Mercury
 - iv. Thallium
 - v. Gold
 - vi. Antimony
 - vii. Zinc
 - viii. Bismuth
 - b. Organic solvents:
 - i. N-hexane
 - ii. N-butyl-ketone
3. Subacute toxic neuropathies:
 - a. Misonidazole
 - b. Metronidazole
 - c. Chloroquine and hydroxychloroquine
 - d. Amiodarone
 - e. Colchicine
 - f. Podophyllin
 - g. Thalidomide
 - h. Disulfiram
 - i. Dapsone
 - j. Leflunomide (possible)
 - k. Nitrofurantoin
 - l. Pyridoxine (vitamin B6)
 - m. Isoniazid
 - n. Ethambutol
 - o. Anti-nucleosides
 - p. Phenytoin
 - q. Lithium
 - r. Acrylamide
 - s. Carbon disulfide
 - t. Ethylene oxide
 - u. Organophosphates
 - v. Hexacarbons
4. Subacute and chronic axonal neuropathies associated with systemic disease:
 - a. Diabetes mellitus (mixed neuropathies that have an axonal component):
 - i. Distal symmetric sensory and sensorimotor neuropathy
 - ii. Autonomic neuropathy
 - iii. Neuropathic cachexia
 - iv. Radiculoplexus neuropathy
 - v. Mononeuropathies
 - b. Hypoglycemia
 - c. Insulinoma
 - d. Acromegaly
 - e. Hypothyroidism
 - f. Liver failure
 - g. Chronic obstructive lung disease
 - h. Celiac disease
 - i. Crohn's disease
 - j. Ulcerative colitis
 - k. Pancreatitis
 - l. Uremia
 - m. Sarcoid
 - n. Congestive heart failure
 - o. Primary biliary cirrhosis
 - p. Amyloidosis:
 - i. TTR-met30
 - ii. Familial forms
 - q. Hyperoxaluria
 - r. Scleroderma
 - s. Sjögren's
 - t. Rheumatoid arthritis
5. Axonal neuropathies associated with chemotherapeutic agents (axonal damage may be just a component, as these neuropathies affect dorsal root ganglion cells and are also demyelinating)
 - a. Vinca alkaloids:
 - i. Vincristine
 - ii. Vinblastine
 - iii. Vindesine
 - iv. Vinorelbine
 - b. Cisplatin
 - c. Taxanes (paclitaxel; docetaxel)
 - d. Suramin
 - e. ARA-C

- f. Etoposide (UP-16); possibly pathology is in the DRG
- g. Bortezomib (possible axonal component)
- 6. Axonal neuropathies associated with malignancies; these diseases often have demyelinating features and direct invasion of malignant cells:
 - a. Lymphoma
 - b. Multiple myeloma
 - c. Osteosclerotic myeloma (POEMS syndrome)
 - d. Castleman's disease
 - e. Waldenström's (overwhelmingly a demyelinating process)
 - f. MGUS (primarily demyelinating)
- 7. Infections associated with axonal neuropathy:
 - a. HIV
 - b. Diphtheritic (segmental demyelination and axonal degeneration)
 - c. Lyme's disease (also associated with perivascular infiltration of plasma cells)
 - d. Human T-lymphocyte Type I infection
 - e. Herpes varicella zoster

Hereditary Neuropathies

CMT1

- 1. CMT1A
 - a. AD; chromosome 17p11.2
 - b. PMP22
- 2. CMT1B
 - a. AD; chromosome 1q21-23
 - b. MPZ
- 3. CMT1C
 - a. AD; chromosome 16p12.3-13.1
 - b. LITAF
- 4. CMT1D
 - a. AD; chromosome 10q21.1-22.1
 - b. ERG2
- 5. CMT1E (with deafness)
 - a. AD; chromosome 17p11.1
 - b. Point mutations in the PMP22 gene
- 6. CMT1F
 - a. AD; chromosome 8p13-21
 - b. Neurofilament light chain
- 7. CMT1X
 - a. X-linked dominant; Xq13
 - b. Connexin-32
- 8. HNPP
 - a. AD; 17p11.2; 1q21-23
 - b. MPZ

CMT2

- 1. CMT2A1
 - a. AD; chromosome 1p36.2
 - b. Microtubule motor kinesin-like protein
- 2. CMT2A2
 - a. Allelic to HMSNVI with optic atrophy

- b. AD; chromosome 1p36.2
- c. MFN2
- 3. CMT2B
 - a. AD; chromosome 3q13-3q22
 - b. RAB7
- 4. CMT2B1
 - a. Allelic to LGMD1B
 - b. AR; chromosome 1q21.2
 - c. Lamin A/C
- 5. CMT2B2
 - a. AD; chromosome 19q13
- 6. CMT2C (with vocal cord and diaphragm involvement)
 - a. AD; chromosome 12q23-24
- 7. CMT2D
 - a. Allelic to distal SMA5
 - b. AD; chromosome 7p14
 - c. Glycine tRNA synthetase
- 8. CMT2E
 - a. Allelic to CMT1F
 - b. AD; chromosome 8p21
 - c. Neurofilament light chain
- 9. CMT2F
 - a. AD; chromosome 7q11-q21
 - b. Heat-shock 27-kDa protein-1
- 10. CMT2G
 - a. May be allelic to CMT4H
 - b. AD; chromosome 12q12q13
 - c. Possibly frabin
- 11. CMT2H
 - a. AD; chromosome 8q21.3
 - b. Possibly GDAP1 (ganglioside-induced differentiation-associated protein-1)
- 12. CMT2K1
 - a. Allelic to CMT1B
 - b. AD; chromosome 1q22
 - c. MPZ (myelin protein zero protein)
- 13. CMT2K
 - a. Allelic to CMT4A
 - b. AD; chromosome 8q13-q21
 - c. GDAP1
- 14. CMT2L
 - a. Allelic to distal hereditary motor neuropathy type 2
 - b. AD; chromosome 12q24
 - c. Heat-shock protein 8
- 15. CMT2N
 - a. Mutations in the alanyl-tRNA synthetase gene
- 16. CMT2O
 - a. Mutation in the DYN C1H1 gene
- 17. CMT2P
 - a. Mutation in the LRSAM1 gene
- 18. CMT2S
 - a. Mutation in the IGHMBP2 gene
- 19. CMT2T
 - a. Mutation in the DNAJB2 gene
- 20. CMT2U
 - a. Mutation in the MARS gene

Dominant Intermediate CMT Disease

1. DI-CMTA
 - a. AD; chromosome 10q24.1-q25.1
2. DI-CMTB
 - a. AD; chromosome 19p12-p13.2
 - b. Dynamin-2
3. DI-CMTC
 - a. AD; chromosome 1p34-p35
 - b. Tyrosyl-RNA synthetase

CMT3 (Dejerine-Sottas Disease, Congenital Hypomyelinating Neuropathy)

1. AD; chromosome 17p11.2
 - a. PMP22
2. AD; chromosome 1q21-23
 - a. PO
3. AR; 10q 21.1-22.1
 - a. ERG2 (early growth response-2 protein)
4. AR; chromosome 19q13
5. Periaxin

CMT4

1. CMT4A
 - a. AR; chromosome 8q13-21.1
 - b. GDAP1
2. CMT4B1
 - a. AR; chromosome 11q23
 - b. MTMR2 (myotubularin-related protein-2)
3. CMT4B2
 - a. AR; chromosome 11p15
 - b. MTMR13 (myotubularin-related protein 13)
4. CMT4C
 - a. Autosomal recessive; chromosome 5q23-33
 - b. SH3TC2 (SH3 domain and tetratricopeptide-repeats-2)
5. CMT4D (HSMN-Lom)
 - a. AR; chromosome 8q24
 - b. NDRG1 (N-myc-downstream-regulated gene)
6. CMT4E (congenital hypomyelinating neuropathy)
 - a. AR
 - b. PMP22, MPZ and ERG-2
7. CMT4F
 - a. AR; 19q 13.1-13.3
 - b. Periaxin
8. CMT4G
 - a. AR; 10q23.2
9. CMT4H
 - a. AR; chromosome 12q12-13
 - b. Frabin

Other Hereditary Neuropathies

1. HNA (Hereditary neuralgic amyotrophy)
 - a. AD; chromosome 17q24
 - b. SEPT9 (septin 9)
2. HMSN-P (hereditary motor and sensory neuropathy-proximal)
 - a. AD; chromosome 3q13-q14

Classification of Hereditary Motor and Sensory Neuropathies

1. HMSN I
 - a. CMT-type 1
2. HMSN II
 - a. CMT-type 2
3. HMSN III
 - a. CMT-type 3
4. HMSN IV
 - a. Refsum's disease
5. HMSN V
 - a. CMT with pyramidal features
6. HMSN VI
 - a. CMT-type 6 with optic atrophy
7. HMSN VII
 - a. With retinitis pigmentosa

*Hereditary Motor and Sensory Neuropathy with Proximal Dominance**General Characteristics*

1. AD; 3q13-q14
2. Clinical heterogeneities exist between Japanese and Korean patients
3. Mutation of the TFG gene (demonstrated in Korean patients and Japanese patients)

Clinical Manifestations

1. In Japanese patients, the disease starts in the 40s and is steadily progressive; it has a faster progression in Korean patients
2. In Japanese patients:
 - a. Involuntary and spontaneous muscle contractions
 - b. Asthenia
 - c. Atrophy with distal sensory involvement; the sensory loss is a late development in the disease progression
 - d. Urinary disturbance
 - e. Dry cough
3. Tremor is seen in Korean patients

Neuropathology

1. Hyperlipidemia is associated in Korean patients
2. Mutation in the TRK-fused gene (TFG) is causative
 - a. TFG/ubiquitin and TDP-43-immunopositive cytoplasmic inclusion in motor neurons (experimental)
 - b. The gene appears to be prominent in the protein secretion pathways
 - c. Endoneurial blood vessel narrowing with swollen vesicular endothelial cells

Laboratory Evaluation

1. EMG:
 - a. SNAPs of the sural nerve are lost earlier in Korean than in Japanese patients
2. Hyperlipidemia in Korean patients
3. MRI:

- a. Lower extremity examination reveals a distinct proximal dominant and sequential pattern that is different from CMT1A

Inherited Axonal Neuropathies

1. HMSN Type II
 - a. CMT 2
2. HMSN Type IV
 - a. Optic atrophy
3. HMSN Type VI
 - a. Optic nerve and spastic paraparesis
4. Hereditary sensory autonomic neuropathy:
 - a. Type I – AD
 - b. Type II – AR
 - c. Type III – Riley-Day
 - d. Type IV
5. Leigh's disease
6. NARP (neuropathy, ataxia, retinitis pigmentosa)
7. Acute intermittent and variegate porphyria
8. Coproporphyrinuria
9. Ataxia telangiectasia
10. Giant axonal neuropathy
11. Spinocerebellar ataxia 3
12. Amyloidosis:
 - a. TTR-met 30
 - b. Familial amyloidosis
13. MNGIE (myelopathy, neurogastrointestinal encephalopathy)
14. Fabry's disease

Hereditary Demyelinating Neuropathies

1. HMSN I, III, IV
2. Krabbe's globoid leukodystrophy
3. Tangier's disease
4. Adrenomyeloneuropathy
5. Metachromatic leukodystrophy
6. Cockayne syndrome

Segmental Demyelinating Neuropathies

1. AIDP
2. CIDP
3. Arsenic
4. Lymphoma
5. HNPN-chromosome 17
6. Hypothyroidism
7. Ulcerative colitis
8. Amiodarone
9. Perhexiline
10. Ara-C
11. Waldenström's macroglobulinemia
12. MGUS (IgM, IgG, IgA)
13. Diphtheria
14. Leprosy
15. Diabetes
16. HIV
17. Lyme's disease

18. SLE
19. Cryoglobulinemia
20. Osteosclerotic myeloma

Asymmetric Single or Multiple Neuropathies

1. Diabetic proximal asymmetric neuropathy
2. Polyarteritis
3. Vasculitis
4. Compression neuropathies
5. Traumatic neuropathy
6. Autoimmune (upper extremity > lower)

Acute Demyelinating Neuropathy

1. AIDP
2. HIV
3. Diphtheria
4. Lyme's disease

Chronic Demyelinating Neuropathy

1. Hypomyelinating neuropathy (CHN)
2. HMSN I and III
3. HMSN IV (Refsum's disease)
4. Metachromatic leukodystrophy
5. HNPP (Deletion chromosome 17)
6. Hypothyroidism
7. Diabetes
8. Uremia (axonal > demyelinating)
9. Perhexiline
10. Sodium cyanide
11. Allergic vasculitis
12. HIV (autoimmune form)
13. Paraproteinemias
14. CIP/CIDP/multifocal
15. Waldenström's macroglobulinemia
16. Osteosclerotic myeloma
17. MGUS
18. SLE
19. Melanoma (immunotherapy)
20. Plasma cell dyscrasia
21. Inflammatory bowel disease
22. MAG epitope
23. SGPG-autoimmune epitopes
24. SICCA complex
25. CID-codon 200
26. Mitochondrial DNA neuropathy 3243

Sensory Neuropathies

Autoimmune Epitopes

1. MAG
2. SGPG (small fiber)
3. Anti-Hu (primarily small fiber)
4. Anti-sulfatide (small fiber)
5. Gd1b (Miller-Fisher variant)
6. GD3
7. Gal (B1–B2) Gal Nac

8. GTD1A
9. GALOP
10. GQ1b

Demyelinating Sensory Neuropathy

1. MAG
2. SGPG
3. CM Fisher variant of GBS (primarily ophthalmoplegia and ataxia)
4. CIDP (sensory variant)

Inherited Sensory Neuropathy

1. HSAN (I–V)
2. Bassen-Kornzweig disease (beta hypolipoproteinemia)
3. Fabry's disease (alpha-galactosidase)
4. SANDO
 - a. Sensory ataxia
 - b. Dysarthria
 - c. Ophthalmoplegia
5. Perrault's syndrome (ovarian dysgenesis/VIIIth nerve dysfunction)
6. Neuropathy with spinocerebellar degenerations:
 - a. SCA5
 - b. Friedreich's ataxia (large fiber)

Toxic Metabolic Sensory Neuropathy

1. Vitamin B6 excess (pyridoxine); burning neuropathy
2. Methylmercury
3. Docetaxel/paclitaxel (large and intermediate fibers)
4. Vitamin E deficiency (alpha-tocopherol transporter I deficit)
5. Vitamin B12 deficiency (primarily large fiber modalities; dorsal column degeneration)
6. INH (decreased vitamin B6)
7. Ciguatera poisoning (paradoxical channelopathy; primarily burning pain)
8. Adriamycin (dorsal ganglionopathy)

Infectious Causes of Sensory Neuropathy

1. HIV (distal symmetric painful sensory neuropathy)
2. Tabes dorsalis (posterior column deficits)
3. Herpes zoster (dermatomal)
4. Herpes simplex (regional)
5. HTLV-1 (primarily small fiber)
6. Leprosy (small and large fiber deficits depending on the autoimmune status of the patient)
7. CMV

Sensory Neuropathy Associated with Systemic Disease

1. Diabetes (burning feet syndrome)
2. Uremia (small fiber)
3. Paraneoplastic (dorsal root ganglia with sensory ataxia; "burning" from small fiber component)
4. Sjögren's (large fiber; posterior column deficits; small fiber component)

5. Hypothyroidism (CTS, tarsal tunnel syndrome; mucopolysaccharide involvement of the Vth nerve; generalized neuropathy with all sensory modality involvement)
6. Sensory perineuritis (autoimmune; primarily around the ankles)
7. Ischemic neuropathy (painful; all modalities are involved)
8. Malabsorption syndromes (primarily B12; large fiber)

Ataxic Sensory Polyneuropathy (Large Fiber)

1. Immune-mediated:
 - a. Carcinomatous sensory neuropathy
 - b. Sensory ganglionitis neuropathy
 - c. Sjögren's syndrome
 - d. Miller-Fisher variant of GBS
 - e. MAG
 - f. Sensory CIDP
 - g. Immunoglobulin associated paraproteinemias
 - h. Idiopathic sensory neuropathy
 - i. Paraneoplastic

Inherited Small Fiber Sensory Neuropathy

1. Fabry's disease
2. Tangier's disease
3. Familial amyloid polyneuropathy (FAP)
4. Hereditary sensory neuropathies II and IV (small component)
5. HSAN I–V
6. Hereditary thermosensitive neuropathy (AD)

Sensory Neuropathy Associated with Systemic Illness

1. Amyloid (secondary)
2. Diabetes
3. Primary biliary cirrhosis
4. Sjögren's syndrome
5. Rheumatoid arthritis

Sensory Neuropathy Associated with Drugs and Toxins

1. Ciguatera toxin
2. Metronidazole
3. Misonidazole
4. Kepone
5. Vacor rodenticide
6. Vincristine (erythromelalgia)
7. Chronic ergotamine

Associated with Trauma

1. Chronic regional pain syndrome I and II
2. Triple cold syndrome
3. Angry back firing C nociceptor syndrome (ABC syndrome; transmodality sensitization)

Chronic Painful Neuropathies

1. Diabetes mellitus
2. Alcohol
3. Pantothenic acid deficiency

4. Pyridoxine B6 (excess or deficiency)
5. CRPS I/II (causalgia)
6. Amyloidosis (primary or secondary)
7. Paraneoplastic (sensory neuropathy ganglionopathy)
8. TTR-met 30 (amyloidosis)
9. Anti sulfatide epitopes
10. Uremia
11. Arsenic
12. Fabry's disease
13. Hereditary (Na 1.7 erythromelalgia)
14. ABC syndrome
15. Triple cold syndrome
16. Hypertriglyceridemia
17. Niacin deficiency
18. Thiamine deficiency

Motor Neuropathies

1. Acute intermittent porphyria
2. Variegated porphyria
3. Coproporphyrinuria
4. Lead
5. Vinca alkaloids
6. Diphtheria
7. Diabetes (amyotrophy and radiculoplexus)
8. Acute inflammatory demyelinating polyneuropathy (AIDP)
9. Rabies
10. Thallium
11. Phenytoin
12. HIV
13. Insulinoma/hypoglycemia
14. Osteoclastic multiple myeloma
15. GM1 ganglioside antibody
16. MMNCB (multifocal motor neuropathy with conduction block)
17. Dapsone
18. MAG

Acute Ascending Motor Paralysis with Minimal Sensory Dysfunction

1. AIDP:
 - a. Hepatitis B virus
 - b. EBV (Epstein-Barr virus)
 - c. Mumps
 - d. HIV
 - e. Lymphoma (Hodgkin's or non-Hodgkin's)
 - f. Post vaccination (influenza, typhoid, hepatitis, rabies)
 - g. Following surgery
 - h. *Campylobacter jejuni*
2. Tick paralysis (usually accompanied by severe ataxia)
3. Lyme's disease
4. Porphyria (AIP/variegate)
5. Thallium
6. Ethylene Oxide
7. Triorthocresyl phosphate
8. Diphtheria

Neuropathies with Prominent Autonomic Features

1. Diabetes (gastroparesis; sexual dysfunction)
2. Amyloidosis:
 - a. Transthyretin-related FAP (familial amyloid polyneuropathy)
 - b. Apolipoprotein A-1 related FAP
 - c. Gelsolin-related FAP
3. Paraneoplastic syndrome
4. SICCA complex
5. Acquired generalized amyloidosis
6. Porphyria (AIP, variegate)
7. B12 deficiency
8. Uremia
9. HSAN (I–V)
10. Fabry's disease
11. Pandysautonomia (paraneoplastic/acute infections)
12. EBV (Epstein-Barr virus)
13. Holmes-Adie syndrome
14. Harlequin syndrome
15. Vacor rodenticide intoxication
16. Chronic relapsing autonomic neuropathy
17. Familial sensory autonomic neuropathy (Navajo Indian ancestry)

Hypertrophic Neuropathies

1. HMSN I, III, IV
2. CIDP
3. Longstanding diabetes (minimal)
4. Hypothyroidism
5. Mucopolysaccharidosis (Scheie variant)
6. Amyloidosis
7. Multifocal hypertrophic neuropathy
8. Leprosy
9. Acromegaly

Infectious Causes of Peripheral Neuropathy

1. HIV
2. Syphilis
3. Leprosy
4. Lyme's disease
5. CMV
6. EBV
7. Brucellosis (L5 root involvement)
8. *Campylobacter jejuni*
9. GBS (specific and most often unidentified virus)
10. Mumps
11. Tick paralysis
12. Whipple's disease
13. Mycoplasma
14. Sepsis syndrome
15. Infective endocarditis
16. Herpes simplex
17. Herpes zoster

Intermittent Neuropathies

1. CIDP

2. Vasculitides
3. Myelin-associated glycoprotein (MG) antibody neuropathy
4. SGPG antibody
5. Gal (B1–3) Gal Nac antibody
6. Asido GMI antibody
7. Anti-sulfatide
8. Gd1B antibody
9. GQ1B antibody
10. Acute relapsing axonal GBS
11. Acute intermittent porphyria
12. Variegate porphyria
13. Coproporphyrinuria
14. Refsum's disease (HMSN-IV)
15. Tangier's disease
16. Hereditary heat sensitive neuropathy
17. Fabry's disease
18. Hereditary sensitivity to pressure palsy (HNPP)
19. Chronic relapsing autonomic neuropathy
20. Hereditary neuralgic amyotrophy
4. Thoracic outlet syndrome
5. Rib-band syndrome (C8–T1)
6. Cleido-clavicular syndrome
7. Cubital tunnel (ulnar nerve)
8. Arcade of Frohse (posterior interosseous and radial sensory nerve)
9. Struthers' ligament (medial nerve)
10. Guyon's canal (ulnar)
11. Entrapment of the medial antebrachial cutaneous nerve
12. Dorsal scapular nerve
13. Suprascapular nerve (suprascapular notch)
14. Musculocutaneous nerve
15. Intercostobrachial nerve (from the medial cord of the brachial plexus)
16. Radial nerve (radial groove of the humerus)
17. Anterior/posterior interosseous nerves
18. Recurrent nerve of Kuntz (T1–T4 sympathetic nerve)
19. Lumbosacral syndrome (pelvic entrapment of L5)
20. Ilioinguinal nerve
21. Genitofemoral nerve
22. Sciatic nerve (sciatic notch; piriformis)
23. Piriformis syndrome
24. Posterior popliteal fossa syndrome
25. Peroneal (common; superficial and deep entrapments)
26. Intercostal nerves
27. Rectus abdominis syndrome
28. Sural nerve (usually when it penetrates the deep fascia of the lower leg)
29. Obturator nerve (canal compression)
30. Femoral nerve (under the inguinal ligament)
31. Lateral femoral cutaneous nerve (under the inguinal or through the ligament)
32. Anterior femoral cutaneous nerve
33. Intermediate femoral cutaneous nerve
34. Recurrent nerve of Gonyea (branch of the tibial nerve)
35. Recurrent nerve of Spurling (innervates the dura of L5; radiates to the anterior thigh)
36. Medial plantar nerve (tarsal tunnel)
37. Calcaneal branch of the plantar nerve (posterior tibial nerve)
38. Entrapment of the plantar nerve within septae in the sole of the foot
39. Gluteal nerve
40. Iliohypogastric nerve
41. Posterior tibial nerve
42. Anterior tarsal tunnel syndrome
43. Digital nerves
44. Metatarsal tunnels (entrap the digital nerves)
45. Lumbrical canal entrapment of the metacarpophalangeal digital nerves

Neuropathy from Traumatic/Physical Agents

1. Overuse syndromes (tunnel entrapments, particularly of the upper extremity)
2. Brachial plexus fixation with secondary peripheral nerve tunnel syndromes
3. Compartment syndromes
4. Perioperative neuropathies (compression during malplacement under anesthesia)
5. Prolonged lithotomy position
6. Diaphragmatic neuropathy:
 - a. Trauma
 - b. Thoracic outlet surgery
 - c. Neck surgery
 - d. Spinal cord injury (stabilization procedures)
7. Direct trauma to peripheral nerves:
 - a. Motor vehicle accidents
 - b. Falls
 - c. Contact sports
8. X-RT (ischemia of the vasa vasorum)
9. Bone marrow transplantation (perineural and intraneural hemorrhage)
10. Heat
11. Cold (frostbite)
12. Snake bite envenomation (hemolytic toxins; compartment syndromes)
13. Entrapment syndromes
14. Double and triple crush syndromes (C5–C6 spondylosis, osteophytes with concomitant carpal tunnel syndrome)

Entrapment Syndrome

1. Long neck sloping shoulder syndrome
2. Roos congenital bands (12 bands; entrap various components of the brachial plexus)
3. Cervical rib syndrome

Mononeuropathy Multiplex

1. Vasculitis
2. Vasculopathy
3. Rheumatoid arthritis

4. Connective tissue diseases
5. Systemic necrotizing vasculitides
6. Polyarteritis nodosa
7. Allergic granulomatous angiitis (Churg-Strauss)
8. Hypersensitivity angiitis
9. Wegener's granulomatosis
10. "Overlap" connective disease syndromes
11. Non-systemic vasculitis (isolated vasculitic neuropathy)
12. Mixed cryoglobulinemia
13. Diabetes
14. Amphetamine abuse
15. Sarcoidosis
16. Leprosy
17. Cytomegalovirus (in HIV patients with AIDS)
18. Neurofibromatosis

Multiple Mononeuropathies

1. Immune-mediated neuropathies
2. Entrapments
3. Pressure palsies (including HNPN)
4. Electrical injury
5. Immunization
6. Herpes zoster
7. Carcinomatous infiltration
8. Lymphoma
9. Diphtheritic wound infection (local toxin production)
10. Diabetes
11. All collagen vascular diseases
12. Monomelic sensory neuropathy

Bilateral Carpal/Tarsal Tunnel Syndrome

1. Occupational overuse syndromes
2. Rheumatoid arthritis
3. Double crush syndrome (CTS and brachial plexus traction injury)
4. Scleroderma
5. Mucopolysaccharidosis
6. Acromegaly
7. Ganglion cysts
8. Diabetes mellitus

Neuropathies Involving the Diaphragm

1. Thiamine deficiency
2. Pyridoxine deficiency
3. Trauma (cervical fractures)
4. Following or during brachial plexus decompression (often injured with either first rib removal or medial scalenectomy surgery)
5. Chiropractic manipulation
6. Critical illness neuropathy
7. CMT2C
8. CMT1 (4C)
9. AIDP
10. CIDP
11. AIP

12. Paraneoplastic neuropathy
13. Viral (acute)
14. Hereditary (brachial plexopathies)
15. Neuralgia amyotrophic (hereditary and acute)

Further Reading

Further Reading on Peripheral Neuropathy

General Overview of Hereditary Neuropathies

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CMT-AR/PLEKHG5

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CMT IX

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CMT1C

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Autosomal Recessive Charcot-Marie-Tooth Disease

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CMT4B

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HINT1 (CMT42)

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Chapter 8

The Neuromuscular Junction

Overview

The neuromuscular junction is anatomically divided into:

1. The presynaptic region
2. The synaptic cleft
3. The postsynaptic area

Diseases of the neuromuscular junction are due to abnormalities in each of these compartments. Presynaptic defects occur from reduced release of normal amounts of acetylcholine (ACh) from:

1. Impaired terminal calcium entry
2. Defective synthesis or packaging of ACh into synaptic vesicles
3. Diminished ACh release into the synaptic cleft

Synaptic neuromuscular transmission (NMT) defects occur primarily with congenital myasthenic syndromes in which there are mutations in the gene for acetylcholinesterase, which decreases its amount or its kinetics. Continuous depolarization leads to structural changes in the functional folds of the ACh receptors (AChR) as well as its desensitization. Postsynaptic neuromuscular transmission defects occur from loss of AChR due to antibodies, complement fixation, and cross-linking. In congenital myasthenic syndromes, there are mutations in the genes that encode AChR subunits that change the kinetics of the receptor (post and slow channel myasthenia). In either mechanism, there is a reduced excitatory postsynaptic (EPSP) amplitude that fails to produce depolarization of the innervated somatic muscle fibers.

Synaptic vesicles are clustered in membrane dense areas called active zones. ACh vesicle release is dependent on calcium entry into the presynaptic terminal. The presynaptic L and P/Q calcium channels are pivotal to the process and are located in the active zones where vesicle fusion occurs in the presynaptic membrane. Calcium entry through L and P/Q channels initiates vesicle fusion and exocytotic release of vesicles containing ACh (quanta) into the synaptic cleft. It takes approximately 75 to 100 microseconds from the arrival of the terminal action potential to vesicle release. An average nerve terminal contains between 200 to 400 thousand vesicles: approximately 20% of which are in the active zone that are positioned for immediate release. Each vesicle contains approximately 5 to 10 thousand ACh molecules. The reserve pool of vesicles is estimated to contain 300,000 vesicles that can be rapidly transported to active zones. After vesicle fusion and with the presynaptic membrane and exocytosis acetylcholine is degraded by acetylcholinesterase in the synaptic cleft and also diffuses away. Reuptake mechanisms recycle choline into the presynaptic terminal (acetylcholine transferase) for resynthesis and repackaging. Under normal

physiologic conditions, the rate of resynthesis and ACh release are equal.

The synaptic processes that maintain neuromuscular transmission are extremely complex and include:

1. ACh synthesis and resynthesis
2. Clustering of synaptic vesicles at the active zone
3. Docking of synaptic vesicles at the active zone
4. Fusion pore opening and exocytotic release of ACh into the synaptic cleft initiated by calcium entry into the presynaptic terminal
5. Endocytosis, refilling, and packaging of vesicles in the presynaptic site with further distribution to either the active or reserve vesicle pool

Three major proteins associated with this extremely complicated process are:

1. Synaptobrevin (vesicle-associated membrane protein)
2. Syntaxin
3. SNAP-25

These soluble N-Ethylmaleimide-sensitive factor (NSF) attachment proteins (SNARE) are pivotal for vesicle binding and fusion and creation of the fusion pore. The SNARE complex is also dependent on other proteins that include Munc18-1 and the synaptophysins that interact with synaptobrevin which is pivotal for vesicle fusion and exocytotic release. Synaptotagmin is a calcium sensor in the presynaptic terminal.

The primary synaptic cleft, between the nerve terminal and muscle membrane, has multiple secondary clefts that are composed of postfunctional folds that extend into the postsynaptic area. These secondary folds greatly increase the postfunctional membrane area that increases the density of ACh receptor channels. The synaptic cleft is 50 nm in width between the presynaptic terminal membrane and the convexity of the synaptic folds. The primary and secondary synaptic clefts communicate. The basement membrane of the lateral synaptic space communicates with the extracellular space, and there is also communication between the muscle transverse tubular system and the secondary synaptic clefts. The synaptic cleft contains acetylcholinesterase (AChE) which is attached to the basement membrane by its collagen tail (ColQ) and hydrolyses acetylcholine into acetate and choline. The density of AChRs is 5 to 10 X greater than the molecular density of AChE such that under normal physiologic conditions 50 to 75% of released presynaptic quanta interact with AChRs. AChE exists in two primary isoforms. The cis-form terminates ACh ligand interaction with its receptor. The R isomer lacks an anchoring tail and is soluble. It limits access of ACh to its receptor and may be a regulator of ACh and AChR interaction.

Postfunctional folds develop with age and are perpendicular to the orientation of the synaptic cleft and the afferent presynaptic terminal. Fast twitch muscles have more extreme functional folds than slow twitch muscles. The convexities of the functional folds contain the great proportion of ACh receptors (10,000 particles/mm²).

ACh receptors are anchored to the sarcolemma and are clustered by the protein rapsyn (in conjunction with other proteins) that is located in the immediate subsarcolemmal area. Rapsyn is bound to the transmembrane protein B dystroglycan that is linked to the intracellular cytoskeleton by the protein utrophin. This AChR-utrophin-glycol-protein complex is linked to the extracellular matrix by the protein agrin (also important in AChR aggregation). MuSK (muscle-specific kinase) is also important for AChR and colocalizes with agrin in the sarcolemmal membrane.

AChRs are transmembrane complexes that consist of four different glycoprotein subunits (A, B, G and E). The adult AChR consists of 5 subunits, two alpha (A), one beta (B), one gamma (G), and one epsilon (E). Fetal receptors contain gamma rather than E-subunits on some oculomotor and bulbar muscles. In denervation and some congenital myasthenic syndromes, a gamma subunit may replace the E-subunit.

A nerve action potential causes a muscle non-propagating endplate potential of >50 mV which exceeds the muscle action potential threshold (by approximately fourfold). Voltage-gated sodium channels, primarily located in the depths of the synaptic folds, facilitate the excitatory endplate potential that is generated by ACh receptor openings. Temperature affects neuromuscular transmission. The duration and amplitude of the nerve action potential at the presynaptic terminal increases with cooling. This may be affected by prolongation of calcium channel open states that augments ACh release. The hydrolytic kinetics of the acetylcholinesterase decreases at temperatures below 34°C , which increases the probability of ligand ACh binding with its receptors. Lower temperatures also decrease the resting membranes' potential (bring it closer to the threshold) of the resting muscle membrane. Jitter may improve with reducing muscle fiber temperature.

The excitatory postsynaptic potential (EPSP) is a graded response different from the all-or-none response action potential it initiates. It is decreased by repetitive stimulation at very high frequencies due to depletion of the ACh vesicles in the active zone. After the fourth or fifth stimulus, the EPSP increases due to augmentation of vesicles from the reserve pool. Repetitive stimulation at high frequencies may augment the EPSP due to post-tetonic facilitation from enhanced ACh release which is due to increased calcium within the presynaptic terminals. This response declines in approximately 1 minute due to depletion of ACh vesicles (post-tetonic exhaustion). The loss of the EPSP safety margin is the basis of many neuromuscular function disorders.

Neuromuscular Junction Disorders

General Characteristics

1. Peripheral Neuropathy with Anhidrosis
 - a. Pure autonomic failure
 - b. Diabetes

- c. Amyloidosis
- d. Fabry's disease
- e. Acute autonomic neuropathy (autoimmune/viral)
- f. AIDS
- g. HSAN (I–V)
- h. Tangier's disease
- i. Sjögren's disease
- j. Ross syndrome
- k. Holmes-Adie syndrome
2. Dermatological Causes of Anhidrosis
 - a. Local
 - i. Thermal
 - ii. X-RT
 - iii. Scarring
 - iv. Inflammation
 - b. Anhidrotic ectodermal dysplasia
 - c. Psoriasis
 - d. Exfoliative dermatitis
 - e. Lichen sclerosus atrophicus
 - f. Ichthyosis
 - g. Miliaria
 - h. Incontinentia pigmenti
 - i. Dermatomal distribution fillings

Neuropathy of Connective Tissue Disease

1. SLE
2. Rheumatoid arthritis
3. Mixed connective tissue disease
4. SICCA complex
5. Relapsing polychondritis

Neuropathy with Systemic Necrotizing Vasculitis (Small- and Medium-Sized Arteries)

1. Polyarteritis nodosa (PAN)
2. Allergic anguitin granulomatosis (Churg-Strauss)
3. Wegener's granulomatosis
4. Vasculitis of connective tissue disease
5. Polyangitis over cap syndrome
6. Isolated peripheral nerve vasculitis (PAN)

Neuropathy with Hypersensitivity Vasculitis (Small Vessel, Capillaries, Arterioles, and Venules)

1. Henoch-Schönlein purpura
2. Vasculitis with infectious disease
3. In association with drug reactions
4. Connective tissue disease
5. Neoplasm

Neuropathy with Vasculitis and Malignancy

1. More common in myelo- and lymphoproliferative disease
2. Rare in association with solid tumors
3. Prominent in hairy cell leukemia
4. Chédiak-Higashi disease

5. Unusual Vasculitis of Peripheral Nerves in Association with:
 - a. Cryoglobulinemia
 - b. Sjögren's disease
 - c. Relapsing polychondritis
 - d. Reiter's disease
 - e. Hypereosinophilic syndrome

Differential Diagnosis of CIDP

1. Osteoclastic myeloma
2. Plasma cell dyscrasia
3. HIV
4. SLE
5. Malignant melanoma
6. Monoclonal gammopathy
7. Hepatitis B
8. Inflammatory bowel disease

Differential Diagnosis of Dorsal Root Ganglionopathy

1. Herpes zoster
2. Syphilis (dorsal root entry zone)
3. Paraneoplastic syndromes (sensory variants)
4. GD1b (epitopes)
5. Sjögren's disease
6. Anti-sulfatide epitopes
7. SICCA complex
8. Autoimmune disease

Axonal Restless Leg Syndrome

1. Diabetes
2. Chronic obstructive lung disease
3. Primary amyloid
4. Anemia
5. Cancer
6. Iron deficiency anemia

Neuropathy Primarily of the Upper Extremity

1. Gen I
2. Lead
3. Amyloid
4. Porphyria
5. Multiple myeloma
6. Hypoglycemia (Insulinoma)
7. Hypothyroidism

Neuropathy Associated with Lymphoma/Leukemia/Blood Dyscrasias

1. Polycythemia vera
2. Chronic lymphocytic leukemia
3. Direct lymphomatous infiltration of nerves
4. Bone marrow transplant (interperineural hemorrhage)
5. Acute leukemia (bleeding into nerves)

6. Chédiak–Higashi disease
7. Hypereosinophilic syndrome (idiopathic; tryptophan impurity induced)
8. Paraprotein associated
9. Waldenström's macroglobulinemia

Myasthenia Gravis (MG)

Overview

The most common neuromuscular junction disorder encountered in clinical practice is acquired myasthenia gravis. It is physiologically characterized by decreased endplate potentials that fail to generate an action potential. Its primary cause is the reduction and blockade of acetylcholine receptors (AChR) at the postjunctional membrane from antibodies directed primarily at the alpha subunit. Recently other antigenic targets have been identified. The neuromuscular junction disorders are the clinical representation of deficits in:

1. Quantal release of acetylcholine
2. Postsynaptic membrane architecture alteration (destruction)
3. AChR conduction parameter (kinetic) dysfunction
4. Density of ACh receptors at the neuromuscular junction
5. Acetylcholinesterase activity
6. Calcium-induced releasing factors at the motor nerve terminal. The difference between the membrane potential and the threshold for initiating an action potential in these disorders is the safety factor for neuromuscular transmission

Different physiological mechanisms for failure of neuromuscular transmission are operative in each disorder of neuromuscular function. Specific muscular functions that are affected, the associated diseases and components of the CNS/PNS that are involved differentiate the entities. In general, patients with neuromuscular diseases have no sensory loss (unless peripheral nerves are affected concomitantly) and have intermittent symptoms particularly with exercise. Diaphragmatic and thoracic paralysis lead to hypercarbia that manifests as lethargy, asterixis, dilated retinal and cerebral veins and rarely papilledema (young patients). All forms of NMJ disease lead to muscle weakness. The pupils and reflexes are variably involved, as is the autonomic nervous system.

General Characteristics

1. The incidence of MG is 1–9 per million persons; prevalence is between 25–142/million persons
2. The incidence is greater in women than men
3. The age of onset is bimodal for both sexes:
4. In women the peak incidence is:
 - a. 20–24 years
 - b. 70–75 years
5. The peak incidence in men is:

- a. 30–34 years
 - b. 70–74 years
6. The gender ratio in early disease is women 7:3; in late disease it is 1:1

Clinical Manifestations

1. Most often the onset is subacute
2. Ptosis of one eyelid is the most common early sign
3. Symptoms and signs vary over time
4. Proximal weakness particularly of the lower extremities is greater than distal weakness and is a common pattern
5. In approximately 10% of patients the weakness may be restricted to distal limb muscles; foot or finger drop may be the initial manifestation
6. Head drop may be a presenting feature
7. Ventilatory failure may also occur initially in a small group of patients
8. There is fatigue with exercise of specific muscle groups (chewing, swallowing, and holding the head up)
9. Clinical involvement may be purely ocular in 15% of patients
10. Aggravating features for weakness include:
 - a. Exercise
 - b. Heat
 - c. Menses
 - d. Infection
 - e. Pregnancy
 - f. Stress
 - g. Hypokalemia
 - h. Thyroid dysfunction
11. 40 to 50% of patients present with ptosis or diplopia; mild ocular deviation often causes blurred vision (non-foveation)
12. 20 to 30% of patients have combined ocular complaints and muscle weakness
13. Bulbar complaints at initial presentation occur in approximately 20% of patients

Clinical Examination

1. Ptosis (usually is asymmetric); lifting the ptotic lid may exacerbate droop of the other lid
2. Normal pupil (with a magnifying glass there may be slight slowness of contraction to light)
3. Cranial nerves III, IV or VIth nerve weakness; the IIIrd nerve is the most commonly affected
4. A pseudo intranuclear ophthalmoplegia may be demonstrated
5. Cogan's twitch sign (overactivation of coinnervated yoked muscles; overstimulation or stimulation of the levator palpebrae after fatigue of the inferior oblique and superior rectus muscles)
6. Lower facial muscle weakness (transverse smile); prominent jaw weakness; patients may hold them closed with their hand

7. Neck flexor and extensor muscle weakness to a similar degree (flexor are weak with myopathy and extensor are weak with motor neuron disease)
8. Triple furrowed tongue (differential weakness of intrinsic tongue muscle contraction)
9. Peek-a-boo sign (slight opening of the eyelids occurs after forced eyelid closure due to weakness of the orbicularis oculi)
10. Sluggish gag reflex, difficulty swallowing liquids and nasal speech
11. Weakness increases with repetitive use
12. Reflexes are normal to increased (spread of acetylcholine sensitivity of the sarcolemmal membrane to mechanical stimuli)
13. Respiratory weakness may appear as an isolated sign
14. Patients may suffer isolated distal limb weakness and neck extensor weakness
15. Difficulty in weaning from a respirator following a surgical procedure
16. Rarely isolated bulbar weakness
17. No sensory loss
18. No autonomic dysregulation

Osserman Scale for Disease Severity

1. Group 1
 - a. Ocular
 - b. 15–20%
 - c. Extraocular muscle involvement
2. Group 2A
 - a. Mild generalized disease
 - b. 30%
 - c. Oculo bulbar and limb muscle
 - d. Minimal ventilator embarrassment
 - e. Respond well to anticholinesterase medication
3. Group 2B
 - a. Moderately severe generalized disease
 - b. 20%
 - c. Severe brainstem signs that include:
 - i. Ptosis
 - ii. Diplopia
 - iii. Dysarthria
 - iv. Dysphagia
 - v. Fatigue with exercise
4. Group 3
 - a. Severe generalized weakness with rapid progression over 6–8 months
 - b. Ventilatory difficulties
5. Group 4
 - a. Initially have mild disease that plateaus over approximately 2 years
 - b. Progresses to severe disease

Clinical Manifestations of Patients with MuSK Antibodies

1. Higher female to male ratio
2. Disease onset in the third or fourth decade

3. Ocular bulbar weakness with dysarthria
4. In long-standing disease patients may develop face and tongue atrophy
5. Drooped head, shoulder and respiratory muscle weakness
6. Myasthenic crises may be more frequent than in patients with AChR disease

Clinical Manifestations of Patients with Antibodies to KV 1.4 Voltage-Gated Potassium Channels

1. Bulbar involvement
2. Thymoma
3. Myocarditis
4. Long QT interval

Clinical Manifestations of Juvenile Myasthenia Gravis

1. Approximately 10% of acquired disease
2. Onset is prior to age 18
 - a. Most prior to puberty
 - b. Mean age is between 7–14 years
3. Majority of patients present with ocular signs and symptoms
4. Similar signs and symptoms to adult MG

Clinical Manifestations of Neonatal MG

1. Transient neonatal MG occurs in approximately 10% of infants born to affected mothers
2. Onset is usually within the first 3 days of life
3. Failure to suck and feed properly
4. Facial muscle weakness
5. Duration of the illness is approximately 3 weeks

Associated Medical Illnesses

1. Rheumatoid arthritis
2. Systemic lupus erythematosus
3. Sjögren's syndrome
4. Red blood cell aplasia
5. Ulcerative colitis
6. Sarcoid
7. Addison's disease
8. Hyper- and hypothyroidism
9. Diabetes mellitus
10. Platelet abnormalities (ITP)
11. B12 deficiency

Associated Neuromuscular Diseases

1. Thymomas increase the number of other associated concomitant autoimmune mediated neurological diseases
2. Acute and chronic inflammatory demyelinating polyneuropathy
3. Severe autoimmune neuropathy (may be associated with encephalopathy; concomitant with MG and thymoma)
4. Rare combination of MG and Lambert-Eaton syndrome
5. Approximately 5% of patients with MG suffer an associated inflammatory myopathy (often with thymoma and myocarditis)

6. Myasthenia and thymoma may be associated with:
 - a. Acquired neuromyotonia
 - b. Rippling muscle disease
 - c. Stiff person syndrome
 - d. Granulomatous myositis
 - e. Cerebellitis
 - f. Autonomic neuropathy

Neuropathology

1. The thymus gland is pivotal in the pathogenesis of MG with AChR autoantibodies
2. Almost all MG patients have thymic alterations; approximately 50% have thymic hyperplasia
3. 10–15% have a thymic tumor
4. Hyperplastic thymus glands contain:
 - a. T-cells
 - b. B-cells
 - c. Plasma cells
 - d. Muscle-like myoid cells that express AChR
5. The components for an immune response to AChR
6. Thymocytes in culture spontaneously secrete anti-AChR antibodies
7. Suggested that there is an intrathymic source for the initiation of the anti-AChR immune response with the productions of AChR antibodies in MG patients with thymic hyperplasia

Thymoma

1. A neoplasm of thymic epithelial cells
2. Express self-antigens that include:
 - a. AChR
 - b. Titin
 - c. Ryanodine receptor-like epitopes
3. There is no autoantibody production within thymomas; sensitized autoreactive lymphocytes proliferate and exit the tumor to activate B-cells that produce autoantibodies
4. The thymus gland is a primary site for immune regulation; in MG there may be a defect in immune suppression of autoreactive lymphocytes
5. ACh-specific CD4+ T-cells are present in the serum of MG patients concomitantly with antibodies and are also expressed in the thymus, which suggests that the thymus is the site of T-cell sensitization
6. There may be deficiency of the autoimmune regulator gene and a selective loss of regulatory T-cells in the disease process

Muscle Biopsy

1. Type 1 fiber predominance; mild fiber type grouping
2. Type 2 fiber atrophy
3. Focal interstitial inflammatory infiltrates (lymphorrhagias) may be seen at endplates
4. Electron microscopy:
 - a. Postsynaptic membrane:

- i. IgG and complement precipitation on the membrane
- b. Increased synaptic space
- c. Reduced postsynaptic membrane complexity with diminished post-junctional folds
- d. Decreased AChR; those that remain may be cross-linked with IgG antibodies
- e. Presynaptic terminals are normal
- f. MuSK antibody disease:
 - i. Has normal density and distribution of AChR
 - ii. No structural changes of the NMJ
 - iii. No complement deposition

Laboratory Evaluation

1. EMG:
 - a. Normal motor and sensory conduction velocities
 - b. Fibrillation potentials and positive sharp waves are rare but have been noted in paraspinal, bulbar and proximal muscles
 - c. Short duration and low amplitude MUAP with early recruitment can occur (due to neuromuscular blockade within a specific motor unit)
 - d. Unstable MUAP variability
 - e. Decremental response to slow repetitive stimulation
 - i. A Jolly response is positive in 85% of patients with generalized MG
 - ii. At least a 10% decrement between the first and fourth compound muscle action potential (CMAP) at 2–3 Hz
 - iii. 30–40% will have a negative repetitive stimulation test in pure ocular MG
 - iv. In the face of a decremental response:
 1. Maximal contraction of the tested muscle for 30–60 seconds abolishes the discriminant for 120 seconds after exercise (post-tetanic potentiation)
 2. The decrement is increased (post-tetanic exhaustion) for 120–240 seconds following further vigorous exercise
 - v. Single-fiber electromyography
 1. Jitter (latency variability between single muscle fiber potentials innervated by the same axon) is increased in MG
 2. Blocking (absence of the second muscle fiber potential) may be noted
 3. Single-fiber EMG is abnormal in 95–100% of MG patients
2. Serological evaluation
 - a. AChR antibodies are detected in the great majority of patients
 - b. There are 3 types of antibodies that include:
 - i. AChR binding antibodies
 - ii. AChR modulation antibodies
 - iii. AChR blocking antibodies
 - c. An elevation of one or more of these antibodies occurs in 80–90% of patients with MG:

- i. In patients with ocular myasthenia the sensitivity is 70–80%
- ii. In generalized MG it is usually >90% sensitive
- iii. There is no phenotype difference between seronegative or positive patients
- d. Most patients demonstrate both binding and modulation antibodies
- e. Approximately 75% of patients with a thymoma have modulating antibodies
- f. AChR blocking antibodies occur in 30% of patients with restricted ocular myasthenia and in 50% of patients with generalized disease
- g. AChR binding antibodies are found in:
 - i. Autoimmune liver disease
 - ii. LEMS (approximately 13%)
 - iii. Cancer (in the absence of neuromuscular disorder)
- h. The serum level of antibodies does not correlate with the severity of disease

MuSK Antibodies

1. Muscle-specific kinase (MuSK) antibodies are found in 40% of MG patients who do not have AChR antibodies
 - a. It is a NMF (neuromuscular function) protein that is specifically expressed at the postsynaptic membrane:
 - i. Colocalized with the AChR
 - b. Has a pivotal role in the maintenance of the NMF by mediating clustering of the AChRs; inhibition of MuSK synthesis causes AChR dispersion and endplate disruption
 - c. MuSK and low-density lipoprotein receptor-related protein 4 (LRP4 is a receptor for neural agrin – a nerve-derived extracellular protein)
 - i. MuSK antibodies bind to the N-terminal half of the extracellular domain of MuSK that inhibits agrin-induced AChR clustering
 - ii. Anti-MuSK antibodies in human MG are of the IgG4 subclass and do not activate complement
 - d. Approximately 7 to 8% with MG are double seronegative and have neither anti-AChR nor anti-MuSK antigens:
 - i. Approximately 60% of these patients have “low affinity” AChR antibodies as opposed to the “high affinity” antibodies of detached autoantibodies to AChR and MuSK
 - ii. These antibodies activate complement

Striated Muscle Antibodies

1. These are antibodies directed against components of skeletal muscles and include:
 - a. Titin
 - b. Ryanodine
 - c. Myosin
 - d. L-actin
2. These antibodies are detected in:
 - a. 30% of MG patients without thymoma

- b. 24% of patients with thymoma and without MG
- c. 70 to 80% of patients that have a thymoma with MG
- d. They may be detected in patients without MG or thymoma
- 3. Antibodies against KV.1 subunit of the voltage-gated potassium channels:
 - a. Do not occur in patients with thymoma-induced inflammatory myopathy

Pulmonary Function Tests

- 1. Are positive or abnormal in 85 to 90% of patients with generalized MG
- 2. Pulmonary function tests:
 - a. Abnormal spirometry
 - b. Decreased mean ventilatory volume:
 - i. Fatigue
 - ii. Restrictive pattern
 - c. CT scan of the chest:
 - i. Evaluation for thymoma
 - d. Blood evaluation to rule out associated autoimmune disease

Differential Diagnosis of Ocular Myasthenia Gravis

- 1. Brainstem lesions that affect the IIIrd cranial nerve (in this instance the pupil is often involved)
 - a. Pseudo intermuscular ophthalmoplegia from MG (convergence is often affected)
 - b. Central Horner's syndrome (pupil is meiotic)
 - c. Painless and alternating ptosis over several days favors MG
 - d. Graves (thyroid) ophthalmopathy:
 - i. All ocular muscles enlarge
 - ii. Forced ductions demonstrate decreased motility
 - iii. Pathologic retraction of the globe
- 2. Kearns-Sayre syndrome:
 - a. Associated heart block
 - b. Usually ophthalmoplegia involves several extraocular muscles
- 3. Progressive external ophthalmoplegia (PEO):
 - a. Symmetric ptosis
 - b. Associated cardiomyopathy, peripheral neuropathy and proximal muscle weakness
 - c. Slow saccades are associated with PEO; MG demonstrates rapid saccades within the limits of EOM weakness
- 4. Aneurysm:
 - a. Retro-orbital pain
 - b. Pupillary involvement; it is often oval along with decreased response to light
- 5. Diabetic IIIrd nerve palsy:
 - a. Sudden onset of dysfunction
 - b. No pupillary involvement (most often)
- 6. Autoimmune thyroid disease:
 - a. Commonly exists with MG
 - b. Periorbital pain

Differential Diagnosis of Generalized MG Paralysis from Central Disorders

- 1. Brainstem lesions (have associated long tract signs)
- 2. Basilar meningitis (fever, stiff neck)
- 3. Demyelinating disease (sensory loss; cerebellar signs; optic nerve involvement)

Differential Diagnosis from Other Neuromuscular Disorders

- 1. ALS (bulbar presentation):
 - a. Extraocular muscle (EOM): extremely rare – involvement with ALS
 - b. Fibrillation in affected muscles
- 2. Diphtheria
 - a. Pupils are involved
- 3. Polymyositis:
 - a. Swallowing may be involved
 - b. Painful muscles with proximal weakness
- 4. Inclusion body myositis:
 - a. Swallowing may be involved
 - b. Contractions and atrophy of forearm flexor muscles
- 5. Granulomatous myopathy (sarcoid):
 - a. VIIth nerve involvement
 - b. More symmetric muscle involvement than with MG
- 6. Lambert-Eaton syndrome:
 - a. Autonomic involvement (dry mouth)
 - b. "Load in the pants" gait
 - c. Minimal ptosis (less cranial nerve involvement)
 - d. Exercise-induced increase in strength
- 7. CM Fisher syndrome:
 - a. May have severe ophthalmoplegia
 - b. Loss of reflexes (does not occur in MG)
- 8. Botulism:
 - a. Symmetrical pupillary involvement
 - b. Pharyngeal dysfunction
 - c. Autonomic alterations

Congenital Myasthenic Syndromes

Overview

The congenital myasthenic syndromes are a heterogeneous group of disorders in which specific mechanisms involved in neuromuscular transmission fail.

These include:

- 1. The syntheses and packaging of acetylcholine (ACh) quanta into synaptic vesicles
 - 2. The Ca^{2+} -dependent release of ACh from the afferent nerve terminal
 - 3. The effectiveness of the released quanta in depolarizing the postsynaptic membrane
- The ability of the released ACh quanta to depolarize the postsynaptic membrane in turn depends upon:
- 1. Endplate geometry
 - 2. The density and effectiveness of acetylcholinesterase (AChE) in the synaptic cleft
 - 3. The kinetic parameters of the acetylcholine receptor (AChR)

Presynaptic Congenital Myasthenic Syndromes

1. A defect in the transfer of an acetyl group from acetyl – CoA to choline in cholinergic neurons

Clinical Manifestations

1. Patients may present with hypotonia, bulbar weakness and apneustic episodes at birth
2. A subgroup of patients is normal at birth but suffer apneic attacks during infancy and childhood. Rare respiratory insufficiency may last a long time following an apneic attack. The attacks may be precipitated by infection or emotional upset
3. Apneic attacks may require ventilatory support and have been associated with cerebral hypoxemia and cerebral atrophy. A few are paralyzed since birth
4. The patients that improve with age have variable ptosis, ophthalmoplegia, weakness with exercise and recurrent cyanotic episodes. The signs and symptoms are aggravated by cold

Neuropathology

1. Pathologic mutations may alter expressions of the enzyme, diminish its catalytic efficiency or structural stability
2. Repetitive firing is associated with a decreased rate of ACh resynthesis, which depletes ACh content of synaptic vesicles
3. Electron microscopy:
 - a. Synaptic vesicles are smaller
 - b. Postsynaptic structures are normal

Laboratory Evaluation

1. Physiology:
 - a. Amplitude of the miniature EP potential (MEPP) decreases with repetitive stimulation

*Paucity of Synaptic Vesicles and Reduced Quantal Release**General Characteristics*

1. The number of acetylcholine quanta released by nerve impulses is decreased

Clinical Manifestations

1. Ptosis
2. Ophthalmoparesis
3. Facial weakness
4. Fatigable muscle weakness

Neuropathology

1. Decreased store of quanta
2. Decreased density of synaptic vesicles in the release zone of the presynaptic terminal

Laboratory Evaluation

1. EMG
 - a. Amplitude of the MEPP decreases with repetitive stimulations

Congenital Lambert-Eaton-Like Syndrome*General Characteristics*

1. The number of quanta released by the afferent impulse is decreased

Clinical Manifestations

1. Hypotonia and decreased reflexes
2. No ocular or facial signs
3. No response to 3,4-DAP:
 - a. Enhances quantal release in the acquired forms of Lambert-Eaton syndrome

Neuropathology

1. Decreased probability of quantal release
2. Normal endplate ultrastructure

Laboratory Evaluation

1. Repetitive nerve stimulation demonstrates marked facilitation of the compound action potential at physiological stimulation rates

Synaptic Basal-Lamina-Associated CMS*General Characteristics*

1. The components of the endplate form of the AChE enzyme is encoded by two genes:
 - a. AChE
 - b. Encodes the catalytic subunit
2. COLQ
 - a. Encodes the collagen structural subunit
 - b. COLQ protein anchors the complex in the synaptic basal lamina
3. ACh time in the synaptic cleft is increased

Clinical Manifestations

1. Most patients present in infancy and are severely disabled; the clinical course, however, is variable depending on the specificity of the mutation
 - a. The patients with a severe course have mutations in the N-terminal or rod domain of COLQ
 - b. Abolishes the expression of AChE in the synaptic cleft
2. Patients with missense mutations that don't affect the triple helical assembly of COLQ or do not inhibit the insertion of COLQ into the synaptic basal lamina present later in children and have a less severe clinical course
3. Mild slowness of the pupillary light reflex
4. Adult patients:
 - a. Reduced muscle bulk
 - b. Axial weakness
 - c. Hyperlordosis and kyphoscoliosis

Neuropathology

1. The cation overload at the endplate causes degeneration of the functional folds and loss of AChRs
2. Altered endplate geometry

3. Reduction in the size of the nerve terminals that fail to cover the endplate
4. Atrophy of presynaptic terminals
5. Decreased number of secondary ending postsynaptic clefts
6. Presence of fetal AChR that contain the G-subunit rather than the E-subunit
7. Muscle biopsy:
 - a. Normal tissue
 - b. Type 1 fiber predominance
8. Mutations of the COLQ gene on chromosome 3p24.2 have been well described

Laboratory Evaluation

1. Electrophysiology
 - a. The decrease of acetylcholinesterase within the synaptic cleft increases the half-life of acetylcholine
 - i. The EPP is prolonged; if it exceeds the refractory period of the muscle fiber there may be multiple depolarizations (discharges) from a single nerve action potential
 - ii. AChR desensitization

CMS Associated with B2-Lamina Deficiency

General Characteristics

1. B2 laminin is encoded by LAMB2 gene that maps to chromosome 6 of 22, 33
2. The protein is the basal lamina component of many tissues and is highly expressed in the kidney, eye, and NMJ
3. Synaptic B2-laminin aligns the axon terminal with the postsynaptic region
4. Pivotal for trophic interactions

Clinical Manifestations

1. The patient suffered Pierson syndrome with ocular and kidney dysfunction
2. Patients had heteroallelic missense and frameshift mutations in the LAMB2 gene
3. One patient suffered ocular, respiratory and limb-girdle weakness

Neuropathology

1. Electron microscopy:
 - a. Abnormally small endplates that are often encased by Schwann cells
2. Decreased quantal release
3. A widened synaptic space with simplified functional folds
4. Electrophysiological evaluation:
 - a. Reduced MEPP amplitude

Postsynaptic CMS – Primary AChR Deficiency

General Characteristics

1. The endplate deficiency is caused by AR homozygous or heterozygous mutations of the E-subunit of the AChR
2. There are other mutations in the E-subunit promoter region, the signal peptide region or in areas important for

subunit assembly (usually in an N-glycosylation site, in CYs128, the canonical CYN loop and in the long cytoplasmic loop of the subunit)

3. Homozygous subunit mutations occur in Mediterranean and Near Eastern ethnicities

Clinical Manifestations

1. Bulbar and severe extraocular muscle weakness
2. Weakness of both proximal and distal muscles
3. Incomplete response to AChE inhibitors; same response to 3,4-DAP and recently to albuterol

Neuropathology

1. An increased number of small endplate regions with an increased area of the muscle fiber
2. Attenuated and patchy distribution of the AChR's on the functional folds
3. The endplates in some areas demonstrate less complex functional folds although in general their structural integrity is intact
4. Type 1 fiber predominance
5. Fetal AChRs with the G-subunit rather than the E-subunit

Laboratory Evaluation

1. Reduced synaptic response to acetylcholine

Slow Channel Syndromes

General Characteristics

1. Most patients have gain of function
2. The mutation either enhances receptor affinity for ACh or increases its gating efficiency due to an accelerated rate of channel opening or may have a slow rate of channel closing

Clinical Manifestations

1. There is a variable phenotype that usually has a progressive course
2. Weakness in adult patients involves the cervical, wrist and finger extensor muscles
3. Mild ophthalmoparesis
4. Infant may be ventilator dependent

Neuropathology

1. Muscle biopsy:
 - a. Type 1 fiber predominance with type grouping of atrophic type I or II fibers
 - b. Fiber size variation
 - c. Tubular aggregates
 - d. Fiber splitting and endomysial fibrosis
 - e. Vascularization near the NMJ
2. Electron microscopy:
 - a. Endplate functional fold degeneration
 - b. Apoptotic nuclei
 - c. Degenerating organelles
 - d. An abnormal distribution of endplates over a large region of the muscle fiber

Laboratory Evaluation

1. Electrophysiology:
 - a. EPPs are prolonged; if the EPP (endplate potential) exceeds the absolute refracting period of the muscle fiber there may be repetitive CMAP; the repetitive response is accentuated with edrophonium – the opposite of AChE deficiency
2. At physiological rate of stimulation:
 - a. A depolarizing block may occur
3. Mutant channels may open in the absence of ACh which causes a leak into the postsynaptic area
4. The safety margin of neuromuscular transmission is decreased by:
 - a. Progressive depolarization block
 - b. Endplate myopathy (see neuropathology)
 - c. Desensitization of a proportion of mutant receptors
5. The syndromes (slow channel) are exacerbated by cholinergic agonists and improved by open-channel blocks of the AChR that include:
 - a. Quinine or quinidine
 - b. Fluoxetine

Fast Channel Syndrome*General Characteristics*

1. Recessively inherited
2. They have a decreased affinity for ACh, reduced gating efficiency, destabilization of channel kinetics or a combination of these mechanisms
3. Each mechanistic dysfunction causes an abnormally brief channel opening

Clinical Manifestations

1. Often have severe weakness
2. Muscle weakness involves limb, trunk, bulbar, respiratory, facial and extraocular muscles
3. Severe respiratory crisis in infancy and childhood
4. Patients respond to 3,4-DAP and anticholinesterase medications

Neuropathology

1. There are no neuropathological abnormalities

Laboratory Evaluation

1. Electrophysiology
 - a. There is an abnormally rapid decay of the EP potential and current

Prenatal Syndromes Caused by Mutation in AChR Subunits and Other Endplate Specific Proteins*General Characteristics*

1. AChR with the fetal gamma V subunit are demonstrated in myotubes in the ninth week of development; they cluster at early NMJ at the sixteenth week
2. The gamma-subunit is replaced by the E-subunit at the 31st week

Clinical Manifestations

1. Pathogenic mutations of the gamma-subunit cause:
 - a. Hypomotility in utero (16–31 weeks)
 - b. At birth, there are multiple joint contractions
 - c. Decreased muscle bulk
 - d. Multiple pterygia (webbing of the neck, axilla, fingers, elbows and popliteal fossa)
 - e. Camptodactyly (fixed flexion contraction of the fingers)
 - f. Facial dysmorphism (mild ptosis, small mouth with downturned corners)
 - g. Rocker-bottom feet (flat arches)
2. Myasthenic symptoms are absent after birth (there is normal expression of the E-subunit)
3. Lethal fetal akinesia occurs from biallelic null mutations in the AChR that affect:
 - a. Alpha, beta, and gamma (G) subunits
 - b. Rapsyn
 - c. Dok-7

Defects of Rapsyn That Cause CMS*General Characteristics*

1. Rapsyn along with agrin, LRP4, MuSK and Dok-7 clusters AChR in the postsynaptic membrane
2. Links it to the cytoskeleton through dystoglycans
3. Mutations have been demonstrated in the entire open reading frame and promoter regions
4. Mutations cause:
 - a. Decreased rapsyn colocalization with AChR
 - b. Decreased agrin-induced AChR clusters
 - c. Decreased rapsyn self-association
 - d. Decreased rapsyn expression
 - e. Indo-European ethnicity patients often have common N88K mutation

Clinical Manifestations

1. In most patients symptoms and signs are present at birth; rarely they present in the second or third decade
2. Arthrogryposis and other congenital anomalies occur in approximately 1/3 of patients
3. Increased weakness and respiratory crises occur with febrile illnesses and may be associated with anoxic encephalopathy
4. Open reading frame mutations may cause a phenotype that resembles autoimmune MG except that ophthalmoparesis is rare
5. Ptosis, facial and bulbar weakness is common and is associated with neck muscle weakness
6. Proximal muscle weakness is greater than distal
7. Severe weakness of foot dorsiflexor muscle is characteristic of the late onset patients
8. Patients may respond to 3,4 DAP AChE inhibitors

Neuropathology

1. Small cholinesterase reactive EP (endplate regions) are dispersed over an extended area of the muscle fiber

2. The synaptic contacts have altered geometry from the compact pretzel-shaped synaptic contacts at normal endplates

Laboratory Evaluation

1. May require single-fiber EMG to demonstrate defects in neuromuscular transmission

Defects in Plectin That Cause CMS

General Characteristics

1. Plectin is encoded by the PLEC gene that maps to chromosome 8q 24.3
2. It is an ubiquitously expressed intermediate neurofilament linking protein
3. It is a versatile link of cytoskeletal components to target organelles
4. It is found primarily at the site of mechanical stress that includes:
 - a. Postsynaptic membrane lining junctional folds
 - b. Sarcolemma
 - c. Z-disks in skeletal muscles
 - d. Hemidesmosomes in skin
 - e. Intercalated discs of cardiac muscle
5. Due to tissue and organelle-specific transcript isoforms it is a versatile linker of cytoskeletal components to specific organelles in different tissues

Clinical Manifestations

1. Plectin deficiencies in muscle cause progressive muscular dystrophy
2. Deficiency of plectin in skin causes epidermolysis bullosa simplex (EBS)
3. Epidermolysis bullosa simplex (EBS) – MD with a myasthenic syndrome has been documented
4. Clinical signs and symptoms in two patients:
 - a. Patient 1:
 - i. Had EBS as an infant; myasthenic symptoms and signs emerged at nine years of age
 - ii. She suffered dysphagia dyspnea on slight exertion with generalized weakness
 - b. Patient 2:
 - i. Infantile onset with poor suck which gradually improved
 - ii. At age 15:
 1. Reduced muscle bulk
 2. Bilateral ptosis
 3. Weakness of extraocular muscles
 4. Facial weakness
 5. Diffuse cervical and limb muscle weakness
 6. Ankle jerks were intact, but otherwise, he was areflexic
 7. Wheelchair-bound by age 18 and respirator dependent by age 26

Neuropathology

1. Study of 2 patients:

- a. Dislocated and degenerating muscle fiber organelles
- b. Plasma membrane defects with Ca^{2+} overload of the muscle fiber
- c. Degeneration of junctional folds (lack of skeletal support)

Laboratory Evaluation

1. Electrophysiology:
 - a. Normal conduction studies
 - b. Repetitive stimulation at 2 Hz demonstrated a decremental response (corrected by endophonium chlorite)
 - c. Reduction of the mean miniature endplate potential to 50% of normal
 - d. Quantal content of the EPP is low normal

Non-Channel Myasthenia

General Characteristics

1. Mutation in the SCN4A gene that encodes the Nav1.4 channel was found causative in a well-studied patient

Clinical Manifestations

1. Abrupt attacks of respiratory and bulbar paralysis since birth which lasted 3 to 30 minutes
2. Similar to attacks characteristic of CHAT deficiency

Laboratory Evaluation

1. Supra threshold EPP failed to generate a muscle action potential
2. The mutation caused:
 - a. Enhancement of fast inactivation to close the resting membrane potential
 - b. Use-dependent inactivation at high-frequency stimulation
 - c. A large fraction of the Nav1.4 channels is inexcitable

Defects in Endplate Development and Maintenance

Defect in Agrin That Causes a CMS

General Characteristics

- a. Agrin is encoded by AGRN gene that maps to 1p36.33
 - i. It is a multi-domain proteoglycan
 - ii. Secreted into the synaptic basal lamina by the afferent nerve terminal
 - iii. Agrin phosphorylates and activates MuSK in association with its LRP4 receptor

Clinical Manifestations

1. Eyelid ptosis with normal ocular ductions
2. Mild weakness of facial and hip-girdle muscles

Neuropathology

1. Endplates demonstrate misshaped synaptic gutters; filled by nerve endings and formation of new endplate areas
2. Normal postsynaptic regions
3. AChR and agrin expression at the endplate are normal

Laboratory Evaluation

1. Electrophysiology
 - a. Decrease of the amplitude of miniature endplate potentials (autoimmune agrin deficiency)

Defects in MuSK in CMS*General Characteristics*

1. MuSK (muscle-specific receptor tyrosine kinase) is controlled by agrin that is mediated by LRP4 (concomitant with Dok-7)
 - a. Is pivotal in the maturation and maintenance of the endplate and directs rapsyn to cluster AChR into the post-synaptic membrane
2. Both mutations and autoimmune processes are responsible for MuSK defects

Clinical Manifestations

1. Dependent on specific mutations which include:
 - a. Phenotype consistent with AChR deficiency
 - b. Severe congenital myasthenic syndrome with dropped head, prenatal onset, and severe bulbar symptomatology
 - c. A subset with a relatively mild course

Neuropathology

1. Specific ultrastructural features that are dependent upon mutation and include:
 - a. Decreased AChR aggregation
 - b. Endplates consist of multiple small areas linked by nerve sprouts
 - c. AChR expression of less than 45% of normal
 - d. Simplified postsynaptic areas with few secondary synaptic clefts

Laboratory Evaluation

1. Electrophysiology (dependent on the mutation)
 - a. Reduction of MEPP and MEPC amplitudes (approximately 30% of normal)
 - b. Decreased EPP quantal content

Dok-7 CMS*General Characteristics*

1. Dok-7 is a muscle intrinsic activator of MuSK
2. Expressed in postsynaptic areas of skeletal muscle and the heart

Clinical Manifestations

1. Typically patients have a limb-girdle distribution of weakness
2. Some patients have mild ptosis and facial weakness
3. Severe bulbar symptoms are rare; laryngeal stridor may occur in infants
4. One mutation causes hypomotility in utero and infancy

5. The course varies from mild static weakness of the limb-girdle muscles to severe generalized progressive weakness with muscle atrophy
6. All patients have fatigability with exercise
7. May have episodes of exacerbation that last for days to weeks

Neuropathology

1. Muscle biopsy:
 - a. Type 1 fiber predominance and Type 2 fiber atrophy
 - b. Decreased oxidative enzyme activity
 - c. Synaptic contacts are small relative to fiber size
 - d. Endplates may lack the usual pretzel shape
2. Ultrastructure:
 - a. Destruction and regeneration of endplates
 - b. Loss of junctional folds; absence of nerve terminals; degeneration of subsynaptic organelles

Laboratory Evaluation

1. Electrophysiology (14 patients)
 - a. The mean MEPP and MEPC amplitudes were reduced to 2/3 of normal
 - b. Some patients demonstrated decreased quantal content of EPP

Centronuclear Myopathy with a Myasthenic Syndrome*General Characteristics*

1. Centronuclear myopathies:
 - a. Clinically and genetically heterogeneous
 - b. The anatomical alteration is abnormal centralization of the muscle fiber nucleus
 - c. Involved genes include:
 - i. Myotubularin (MTM1)
 - ii. Dynamin 2 (DNM2)
 - iii. Amphiphysin 2 (BIN1)
 - iv. Ryandine receptor (RYR1)

Clinical Manifestations

1. Associated myasthenic features in some patients with centronuclear myopathy include:
 - a. Ptosis
 - b. Ophthalmoparesis
 - c. Muscle fatigue
 - d. Weakness

Neuropathology

1. Muscle biopsy consistent with centronuclear myopathy
2. EM studies in one patient demonstrated simplified postsynaptic structure with decreased ADCH deficiency

Laboratory Evaluation

1. EMG: (one patient)
 - a. 35% decremental response partially corrected with pyridostigmine
2. Electrophysiology: (one patient)
 - a. Decreased MEPP amplitude (60% of normal); decreased quantal release to 40% of normal

CMS Associated with Alteration of the Hexosamine Biosynthetic Pathway

General Characteristics

1. Mutation of the GFPT1 gene (glutamine-fructose-6 phosphate transaminase 1) gene is causative of this CMS; it maps to chromosome 2p13
2. It controls the entry of glucose into the hexosamine pathway
3. Mutations decrease the availability of precursors for the N- and O-linked glycosylation of proteins

Clinical Manifestations

1. Multiple kinships demonstrated a limb-girdle CMS syndrome that was associated with tubular aggregates in which this mutation of GFPT1 was demonstrated
2. Presents in the first decade of life
3. Some patients had distal and proximal weakness
4. Ptosis and respiratory weakness are rare

Neuropathology

1. Muscle biopsy:
 - a. Immunoblot arrays demonstrated decreased expression of O- N- acetyl glucosamine residues on muscle proteins
 - b. One patient demonstrated a decreased number of AChR endplates

Laboratory Evaluation

1. Approximately 25% of patients showed elevated CK levels
2. Neurotransmission defects have not been demonstrated in detail

Recent discovery of genes that code for extraconjunctional molecules have demonstrated that abnormalities in the post-translational modification of proteins cause neurotransmission defects that expand both the clinical and physiological spectrum of congenital myasthenic syndromes.

Recently described mutations in genes that cause CMS include:

1. N-glycosylation pathway
2. Several proteases
3. Lipoprotein-like receptor
4. Splicing mutations of non-functional exon of CHRNA1

Familial Limb-Girdle Myasthenia

General Characteristics

1. Primarily an AR disease; two new mutations have recently been described that cause this phenotype
2. Genomic deletion affecting exons 2–3 of MuSK
3. DPAGT1:
 - a. Encodes dolichyl-phosphate (UDP-N-acetylglucosamine) N-acetyl glucosamine phosphotransferase 1
 - b. The enzyme is involved in the asparagine-linked glycosylation pathway
 - c. Impaired glycosylation of the muscle acetylcholine receptor in pathogenesis
 - d. GFPT1 mutation may have a similar phenotype

Clinical Manifestations

1. Onset is in childhood
2. Patients may have myasthenic features associated with tubular aggregates
3. Fatigable muscle weakness
4. Proximal muscles are involved
5. No ocular or facial muscle involvement
6. Marked fluctuations in muscle weakness
7. Muscle cramps (also noted with Dok-7 CMS)
8. There may be hand weakness in some patients
9. Loss of reflexes in some patients
10. Mutations in DPAGT1 may also cause glycosylation defect type 1J (CDG-type 1J)
 - a. Defects in formation or processing of glycoproteins or glycolipids that may cause disorder characterized by:
 - i. Intractable seizures
 - ii. Congenital cataracts
 - iii. Mental retardation
 - iv. Developmental delay
 - v. Microcephaly
 - vi. Fetal hypoplasia (death in infancy or early childhood)

Neuropathology

1. Impairment of subunit glycosylation may decrease assembly and transport of AChRs to the postsynaptic membrane
2. Muscle biopsy:
 - a. Decreased number of muscle fibers replaced with fat
 - b. Some fibers with central nuclei
 - c. No tubular aggregates

Laboratory Evaluation

1. EMG:
 - a. Decremental response in some muscles (intrinsic hand muscles)
 - b. Myopathic change in proximal muscles

Lambert-Eaton Myasthenic Syndrome (LEMS)

General Characteristics

1. LEMS is possibly the second most common neuromuscular disorder
2. It is an autoimmune disorder with antibodies primarily directed against voltage-gated calcium channels
3. In approximately two-thirds of patients:
 - a. It is paraneoplastic
 - b. Underlying malignancies include:
 - i. Small cell carcinoma of the lung
 - ii. Lymphoproliferative disease
 - iii. Breast, pancreatic and ovarian cancer
4. LEMS may precede diagnosis of the tumor
5. Greater than 80% of patients are older than forty years of age
6. There is no difference clinically between seronegative or positive patients

7. Approximately one-third of patients with LEMS have no underlying malignancy and occur most commonly in young females with other autoimmune diseases that include:
 - a. Rheumatoid arthritis
 - b. SLE
 - c. Inflammatory bowel disease
 - d. Primary biliary cirrhosis

Clinical Manifestations

1. Weakness and easy fatigability with muscular exercise
2. The majority of patients present with proximal and lower extremity weakness although 80% develop upper extremity proximal weakness during the course of the disease
3. Approximately 1/3 of patients have muscle aches and stiffness during or following exercise
4. Hot weather or any form of heat exacerbates weakness in approximately 20% of patients
5. Ocular muscle weakness other than ptosis is less common than in myasthenia gravis. Bulbar symptoms are also less common, but both may be presenting symptoms
6. Neck flexor, extensor, and facial weakness may also be seen in patients with cranial nerve involvement
7. Cholinergic dysautonomia manifests as:
 - a. Xerostomia and xerophthalmia
 - b. Blurred vision
 - c. Constipation
 - d. Decreased sweating
 - e. Impotence
8. Ventilatory embarrassment is rare although it is documented
9. There are complaints of numbness and paresthesias in the extremities
10. Muscle potentiation occurs:
 - a. In hip- and shoulder-girdle muscles
 - b. Dissipates after several minutes
 - c. Exercise may improve ptosis (opposite of MG); observed by sustained voluntary lid elevation
 - d. Muscle atrophy occurs in advanced stages
 - e. Sluggish pupillary light reflex, decreased sweating and salivation
 - f. Reflexes may be diminished but improve with sustained contraction of the affected muscles
 - g. LEMs associated with anti-Hu antibodies is associated with:
 - i. Small cell cancer of the lung
 - ii. Sensory neuropathy
 - iii. Cerebellar ataxia
 - iv. Limbic encephalitis
 - h. A small percentage of patients have an MG/LEMS overlap syndrome

Neuropathology

1. The acquired autoimmune disorder is due to:

- a. Antibodies against P/Q type voltage-gated calcium channels primarily, with some directed towards N-type voltage-gated calcium channels and synaptotagmin
- b. The antibody attack occurs on and in presynaptic motor terminals
- c. The mechanism suggested is “molecular mimicry” due to cross-reaction of embryonic type calcium channels or their component proteins on tumor cells with neuronal calcium channels
- d. Cross-linking of antibodies with neighboring calcium channels induces their internalization and degradation; complement does not appear to be involved
- e. The major physiological mechanics for the syndrome is decreased quantal release of ACh although the vesicles are normal histologically
- f. Muscle biopsy:
 - i. Type 2 fiber atrophy is occasionally demonstrated
- g. Electron microscopy:
 - i. Nerve terminals are normal in size and numbers of synaptic vesicles
 - ii. The postsynaptic membrane has an increase in the size of the postsynaptic fold
 - iii. Freeze-fracture analysis demonstrates a decrease of intramembranous proteinaceous particles that are thought to be P/Q voltage channels

Laboratory Evaluation

1. EMG:
 - a. CMAP amplitude is increased (the electrodiagnostic characteristic that distinguishes presynaptic from postsynaptic processes)
 - b. Preserved SNAPs
 - c. In the majority of patients with LEMS brief exercise causes an incremental response of 100%; patients with endstage disease may not demonstrate an incremental response
 - d. Low rates of repetitive stimulations (2–3 Hz) may yield a decremental response similar to MG; a brief maximal period of exercise (10 seconds) may block the decremental response, and this post-exercise facilitation may last for 20–30 seconds
 - e. Post-exercise exhaustion may last for up to 20 minutes
 - f. Insertional activity is normal and usually there is no positive sharp waves or fibrillation in potentials
 - g. Abnormalities of MuAP morphology may occur
 - h. Single-fiber EMG reveals:
 - i. Increased jitter values
 - ii. Blocking is more prevalent and severe than in MG
 - iii. Increased stimulation rates (2–15 Hz) decreases blocking
 - i. Decreasing temperature increases:
 - i. CMAP amplitude at rest
 - ii. Decreases decremental response at low rates of stimulation
 - iii. Prolongs the duration of postactivation facilitation

- j. Autonomic evaluation in LEMs is altered and demonstrates deficits in:
 - i. Sudomotor function
 - ii. Cardiovagagal reflexes
 - iii. Salivation (decreased)
 - iv. Adrenergic function

Botulism

General Characteristics

1. The neurotoxin is derived from the bacterium (*Clostridium botulinum*)
 - a. It is an anaerobic and requires alkaline conditions for growth
 - b. The spores are heat resistant; temperatures of 120°C are required for sterilization
 - c. High-altitude cooking is a risk factor (because water boils at lower temperatures and does not inactivate spores; there may also be inadequate sterilization of canned goods)
 - d. There are eight antigenic types of botulinum toxins: A, B, C1, C2, D, E, F, G; they are zinc-dependent endopeptidases
 - e. Human disease is caused primarily by types A, B, E; a fatal dose is between .05–1 mg
 - f. There are approximately 250 cases of botulism/year in the USA
 - i. Type A: Western USA
 - ii. Type B: Eastern USA and Europe
 - iii. Type E: from fish; more prevalent in Japan (approximately 20% of USA patients)
 - iv. Ingested toxin from food (USA)
 - a. Vegetables ~60%
 - b. Fruit ~12%
 - c. Fish ~15%
 - v. Infantile form of the toxin is produced by organisms in the GI tract
 - vi. Wound infection as a source of primary botulism is rare but that from I.V. drug abuse is increasing

Clinical Manifestations

1. Adult disease:
 - a. The clinical presentation is similar irrespective of the sources of the toxin
 - b. Foodborne and infantile varieties are the most common forms of the illness
 - c. Neurologic signs and symptoms:
 - i. Dysphagia, xerostomia, diplopia and dysarthria begin acutely and progress over 12–36 hours
 - ii. Anxiety may be severe
 - iii. The course is dependent on the amount of toxin exposure
 - iv. In foodborne illness:
 - a. Nausea, vomiting, and diarrhea may occur prior to or concomitantly with neurologic symptoms

- v. Abdominal cramps, constipation, dizziness, fatigue occur with other signs and symptoms
- vi. Dyspnea may occur prior to extremity weakness
- vii. Usually, there are no sensory complaints; a few patients complain of paresthesia of the face or extremities
- viii. Cranial nerve involvement causes:
 - a. Ptosis
 - b. Decreased gag reflex
 - c. Dysphagia
 - d. Dysarthria
 - e. Facial weakness
 - f. Tongue weakness
 - g. Nystagmus (Rare)
- ix. Diminution to absent muscle stretch reflexes
- x. Respiratory muscles are affected with between 31–81% of patients requiring mechanical ventilation
- xi. Forced vital capacity is reduced in most patients
- xii. Autonomic alterations include:
 - a. Decreased vagal cardiac responses
 - b. Hypothermia
 - c. Urinary retention
 - d. Ileus
 - e. Hypotension without tachycardia
 - f. Decreased pupillary light reflex
 - g. Decreased vasomotor response to postural stress

Clinical Manifestations of Wound Botulism

1. A traumatic event may not be elicitable in the patient (particularly in patients with drug abuse)
2. Gastrointestinal complaints are less severe than in patients who have food-borne illness
3. Incubation period is usually 4–14 days as compared to 6 hours in toxin or spore disease

Clinical Manifestations of Infantile Botulism

1. Variable phenotype from mild symptoms to sudden death:
 - a. Constipation is common and may be the sole manifestation in mild disease
 - b. Listlessness and diminished spontaneous movements are noted
 - c. Diminished suck
 - d. In severe forms, the infant may be hypotonic and “floppy”
 - e. Excessive drooling and a weak cry; ptosis and loss of facial movement
 - f. Fatigue of the pupillary light reflex
 - g. Deep tendon reflexes may be diminished to absent
 - h. Approximately 50% of infants require mechanically assisted ventilation
 - i. Botulism toxin A may produce a more severe course than toxin B (similar to adults)

Adverse Events Associated with Therapeutic and Cosmetic Use of Botulinum Toxin

1. Serious adverse events include:
 - a. Dysphagia
 - b. Respiratory compromise
 - c. Generalized muscle weakness
 - d. Marked ptosis
 - e. Pseudoaneurysm of the frontal branch of the temporal artery
 - f. Necrotizing fasciitis

Neuropathology

1. The majority of strains produce one type of BTX which is released after the infected cell undergoes lysis
2. All of the BTXs are composed of a heavy chain and a light chain linked end to end; a proteolytic enzyme within the bacterium or the involved host is required to cleave the bond between the chains to activate the molecule
3. After ingestion, the toxin is absorbed and hematogenously transported
4. The toxin is active at:
 - a. Cholinergic presynaptic terminals
 - b. NMJs
 - c. Autonomic ganglia
 - d. Post-ganglionic parasympathetic and sympathetic nerves
 - e. Adrenal glands
5. The toxin is internalized by receptor-mediated endocytosis
6. Toxic intracellular activity is mediated by zinc-dependent specific proteases
7. BTX B, D, F and G
 - a. Cleave vesicle-associated membrane protein (VAMP/synaptobrevin)
8. BTX A, D, and E
 - a. Hydrolyze SNAP-25 (synaptosomal-associated protein)
9. BTX C
 - a. Cleaves syntaxin (only animals are affected)
10. BTX D and F
 - a. Cleaves cellubrevin
11. Types A, B and E cause food poisoning
12. Denervation atrophy has been demonstrated in muscle biopsy

Laboratory Evaluation

1. EMG:
 - a. CMAP amplitude reduction (documented in 85% of patients)
 - b. Most often NCV, F-wave or H-reflex latencies are normal
 - c. CMAP amplitude decrease at baseline, incremental response to brief exercise or "fast" repetitive stimulation and decremental response to "slow" repetitive stimulation may not be seen in early illness

- d. The incremental response is usually <100% and more prevalent in proximal muscles
- e. Facilitation is common
- f. Abnormalities may be seen in specific muscles, in particular those that are weak
- g. Early in the course of the illness there is usually normal insertional and spontaneous activity; several affected patients may demonstrate positive sharp waves and fibrillation potentials
- h. MuAPs may demonstrate a low amplitude, short duration morphology with early recruitment
- i. Single-fiber EMG:
 - i. Increased filter values
 - ii. Blocking
 - iii. May be seen in 40–50% of patients early in the course of illness
2. CSF evaluation:
 - a. An increased protein in some patients
3. Culture of serum gastric contents, stool and wound aspirate; food for toxin and organisms
4. BTX assay (indirect bioassay utilizing mice) is positive
5. Toxin test evaluation:
 - a. A positive yield in only 1/3 of patients
 - b. Higher in blood and stool than gastric contents
6. Positive culture occurs in 50–70% of patients (anaerobic culture)

Differential Diagnosis of Botulism vs GQIb GBS

1. GBS (CM Fisher variant) GQIb has absent reflexes
2. Pharyngeal cervical brachial variant of GBS; GT1a (antibody)
3. Lambert-Eaton syndrome (increased reflexes and strength with exercise)
4. MG (normal pupillary responses; weakness with exercise)
5. Tick paralysis (ataxia with weakness)
6. Toxic shellfish (pain at the site of envenomation)
7. Diphtheritic neuropathy (sore throat); eschar or membrane

Summary of Specific Botulism

Infant Botulism

General Characteristics

1. Spores are ingested and germinate in the infant GI tract
2. Honey consumption is a risk factor; Type B > A organisms

Clinical Manifestations

1. Affects infants less than six months old
2. Weakness of bulbar and limb muscles; hypotonia with loss of head control; decrease of spontaneous movements
3. Parasympathetic signs and symptoms

Wound Botulism

General Characteristics

1. Primarily in IV drug abuse patients (abscesses)
2. Sinusitis in cocaine users

Clinical Manifestations

1. Approximate incubation period of 4–14 days
2. Most often a clear wound
3. Bulbar signs and descending paralysis

Hidden Botulism**General Characteristics**

1. No obvious source of toxin
2. Abnormality of the GI tract may be a risk factor which includes:
 - a. Achlorhydria
 - b. Surgery
 - c. Crohn's disease
 - d. Recent antibiotic treatment

Clinical Manifestations

1. Similar to the chronic form
2. *C. botulinum* has been cultured from the stool of an adult patient

Iatrogenic Botulism**General Characteristics**

1. Toxin injected for movement disorder or cosmetic indications

Clinical Manifestations

1. Signs and symptoms in the somatic, motor, sympathetic and parasympathetic systems
2. May develop distant and generalized weakness

Tetanus**General Characteristics**

1. Approximately one million cases occur annually worldwide
2. Twenty-five percent (approximately) from occupational injury
3. *Clostridium tetani*:
 - a. Obligate anaerobe
 - b. Requires extrachromosomal DNA (plasmid for production of tetanospasmin)
 - c. Inhibits release of ACh from the presynaptic terminals
 - d. Retrogradely transported to enter the CNS
 - e. Blocks release of glycine and GABA-b from presynaptic terminals
 - f. Toxin transported to both the sensory neurons of the dorsal root ganglia and archenteric neurons

Clinical Manifestation

1. Generalized tetanus:
 - a. Rigid masseters ("lock-jaw") at presentation
 - b. Generalized spasms with opisthotonus; no loss of consciousness
 - c. Painful muscles with increased reflexes
2. Localized tetanus

- a. May progress to generalized disease
3. Cephalic form:
 - a. Involves the lower cranial nerves
 - b. Facial weakness, dysphagia, and rarely ophthalmoplegia
 - c. Source is chronic middle ear infection
 4. Neonatal variety
 - a. 50% of tetanus infection with an approximate 90% mortality
 - b. Infection of the umbilical stump
 - c. Weakness and inability to suck during the second week of life
 5. Mechanisms of death are:
 - a. Respiratory
 - b. Autonomic dysregulation

Laboratory Evaluation

1. EMG:
 - a. Continuous and excessive motor unit activity
 - b. Normal nerve conduction studies
 - c. Absent silent period from affected muscles

Tick Paralysis**General Characteristics**

1. There are three major families of ticks:
 - a. Ixodidae (hard body ticks)
 - b. Argasidae (soft body ticks)
 - c. Nuttalliellidae
2. The saliva of Ixodidae and Argasidae cause human disease
3. In North America, the wood tick, *Dermacentor andersoni* most often causes the disease; the second most common tick that causes illness is the dog tick *Dermacentor variabilis*; very rarely *Amblyomma americanum* and *Amblyomma maculatum* have been implicated; in Australia, *Ixodes holocyclus* (Australian marsupial tick) causes very severe disease
4. The site of the tick attachment is often the scalp, neck and perineum
5. In North America the illness is seen most frequently in states west of the Rocky Mountains
6. The peak occurrence of disease is during the spring and summer; gravid female ticks feed longer (days) and are thought to be the most common vector; their attachment is most often painless

Clinical Manifestations

1. Children are affected three times more frequently than adults
2. Patients present with an ascending weakness that evolves over hours to days which may cause flaccid paralysis
3. Cranial nerve involvement includes;
 - a. Internal and external ophthalmoplegia
 - b. Facial weakness
 - c. Dysarthria

- d. Respiratory and muscle weakness
- e. Dysphagia
- 4. Sensory symptoms include:
 - a. Paresthesias
 - b. Burning and itching
 - c. Pain
 - d. Numbness
- 5. Sensory complaints may be out of proportion to the objective findings
- 6. Some patients develop sensory ataxia
- 7. There are decreased or absent muscle stretch reflexes
- 8. The onset may be more abrupt and the course more rapid than GBS
- 9. Symptom onset usually occurs after 4–7 days of tick feeding; resolution of symptoms usually occurs within 24 hours of the tick's removal

Neuropathology

- 1. The Australian tick *Ixodes holocyclus* injects a toxin that:
 - a. Decreases ACh release at presynaptic terminals
 - b. North American cases of tick paralysis may be caused by the released toxins block of sodium channels at the nodes of Ranvier and distal motor nerve terminals

Laboratory Evaluation

- 1. EMG:
 - a. Mild reduction of motor conduction velocities
 - b. Mild decrease of SNAP in paretic extremities
 - c. Sensory nerve conduction parameters may increase with resolution of the illness suggesting that there is a mild sensory neuropathy
 - d. In most patients, repetitive nerve stimulation shows no decremental or incremental responses
 - e. There are no positive sharp waves or fibrillation potentials
- 2. CSF protein is normal

Drugs/Toxins That Alter Neuromuscular Transmission

Toxins

General Characteristics

- 1. The best descriptions have been from ingestion of Fungi or Puffer fish; it is found in species of the order Tetraodontidae
- 2. May be found in certain mollusks, the horseshoe crab, California newt and the blue ringed octopus

Clinical Manifestations

- 1. The severity and delay of symptoms onset depends on the quantity of the toxin ingested
- 2. Paresthesias may be the first symptom reported and initially involves the lips, tongue and mouth
- 3. Gastrointestinal symptoms include nausea and vomiting

- 4. An ascending flaccid paralysis can occur with large ingestions
- 5. Other manifestations may include:
 - a. Dilated pupils
 - b. Seizures
 - c. Sweating
 - d. Pleuritic chest pain

Neuropathology

- 1. Blocks sodium channels

Laboratory Evaluation

- 1. High performance liquid chromatography with tandem mass spectrometry identifies the toxin in urine and blood samples

Saxitoxin

General Characteristics

- 1. Saxitoxin and its derivatives are collectively referred to as paralytic shellfish toxins
- 2. They are unique neurotoxins as they are found in both marine and fresh water environments; prokaryotic cyanobacteria are responsible for the toxin in fresh water while eukaryotic dinoflagellates produce the toxin in marine water
- 3. The organisms have a world-wide distribution

Clinical Manifestations

- 1. Ascending paralysis with respiratory failure

Neuropathology

- 1. Inhibition of voltage gated sodium channels

Laboratory Evaluation

- 1. Molecular sensor binding methodologies are used for detection

Ciguatoxin

General Characteristics

- 1. Caused by the ingestion of fish that have been bioaccumulated ciguatoxins of the photosynthetic dinoflagellate gambierdiscus toxins
- 2. Ciguatoxins accumulate in all fish tissues; they are heat stable polyether toxins

Clinical Manifestations

- 1. The presenting signs are primarily neurotoxic in greater than 80% of patients; these include:
 - a. Paresthesias and dysesthesias
 - b. Paradoxical cross modality sensitization (a cold object may feel hot)
 - c. Metallic taste
 - d. Arthralgias and myalgias
 - e. Dental pain
- 2. Rarely ataxia and weakness
- 3. Autonomic dysfunction with hypotension bradycardia
- 4. Mild cases have primarily GI symptomology

Neuropathology

1. They are potent lipophilic sodium channels activators which bind to the voltage sensitive (site 5) of the sodium channel on cell membranes of all excitable tissue

Laboratory Evaluation

1. Mouse bioassay; detected with high performance liquid chromatography
2. Other toxins that cause nerve sodium channel overactivation include:
 - a. Sea anemone (*Anemonia sulcata*)
 - b. The Brazilian scorpion (*Tityus serulatus*)
 - c. The spider (*Phoneutria nigriventer*) that causes:
 - i. Spastic paralysis
 - ii. Muscle pain
 - iii. Abdominal cramps
 - iv. Seizure
 - v. Cardiovascular dysfunction
 - vi. Nerve terminal sodium channel activation

Black and Green Mamba Envenomation*General Characteristics*

1. African snakes; there are four species of mamba that inhabit equatorial and southern Africa
2. Black mamba (*Dendroaspes polylepis*)

Clinical Manifestations

1. Paralysis, cranial nerve dysfunction and respiratory failure
2. Cramps and fasciculations

Neuropathology

1. Blockade of nerve terminal potassium channels that cause prolongation of the action potential with an increased ACh release
2. Envenomation causes an increase of EPP amplitude and repetitive EPP
3. Similar clinical and physiological effects can be seen with envenomation from the scorpion (*Pandinus imperator*)
4. The Australian Tiger snake
 - i. Toxin (notexin) blocks potassium channels and decreases the release of ACh

Calcium Channel Inhibitor*General Characteristics*

1. Myasthenia gravis patients may be affected by drugs that inhibit the calcium channel. These include:
 - a. Verapamil
 - b. Diltiazem
 - c. Aminoglycosides
 - d. Neomycin and polymyxin B
 - e. Clindamycin
 - f. Oxytetracycline

Clinical Manifestations

1. Exacerbation of myasthenia muscle weakness

Neuropathology

1. Verapamil (block L type Ca^{++} channels)
2. Diltiazem
 - a. Non-dihydropyridine (non-DHP) calcium channel blocker
3. Aminoglycosides
 - a. Block presynaptic voltage calcium channels
 - b. Presynaptic Ca^{++} sensor receptor enhanced activation with decreased terminal excitability rather than direct inhibition of voltage activated calcium channels
4. Clindamycin
 - a. Less severe depression of voltage dependent calcium entry into nerve terminals

Magnesium Salts*General Characteristics*

1. Primarily administered for pre-eclampsia and eclampsia; may be significant in myasthenia gravis patients
2. A possible central mechanism of action may occur at low concentrations

Clinical Manifestations

1. Serum levels $> 5 \text{ mg/L}$ may abolish deep tendon reflexes
2. Levels > 9 to 10 mg/L are associated with generalized weakness and loss of reflexes

Neuropathology

1. Competitive inhibition of calcium entry into the nerve terminal

Laboratory Evaluation

1. EMG:
 - a. Similar to conditions with presynaptic defects of neuromuscular transmission
 - b. Low amplitude CMAP
 - c. Facilitation with exercise "fast" repetitive stimulation

Conotoxins*General Characteristics*

1. Conopeptides are a diverse group of recently evolved venom peptides
2. Each species of cone snail produces greater than 1000 conopeptides that target a wide spectrum of membrane proteins with high potency or specificity
3. Two toxins secreted by the marine snail (*Conus geographus*) affect neuromuscular transmission

Clinical Manifestations

1. The snail has a dart-like proboscis that injects the toxin
2. Severe local pain
3. Within 30 minutes, there is a generalized weakness
4. Respiratory failure occurs within 1 to 2 hours
5. Approximately 60% of envenomations are fatal

Neuropathology

1. Omega-conotoxin: binds to presynaptic voltage-dependent calcium channels, which prevents calcium entry into the nerve terminals and consequent decrease of ACh release

Drugs That Affect Neuromuscular Transmission**Corticosteroids**

1. Directly affect the nerve terminal membrane by inducing depolarization which causes:
 - a. Depletion of ACh
 - b. Alteration of MEPPs
 - c. Decreases intratubular potassium homeostasis

Azathioprine, Theophylline, and Papaverine

1. Inhibit phosphodiesterase and thereby increases intracellular cyclic AMP (as phosphodiesterase hydrolyze)
2. Increased intracellular cyclic AMP potentiates ACh release
3. Imidazole decreases ACh release by increasing phosphodiesterase and thereby lowering intra-nerve terminal cyclic AMP

Snake Envenomation*General Characteristics*

1. Major species:
 - a. Viperidae (pit vipers)
 - b. Crotalinae (rattlesnakes and pit vipers)
 - c. Elapidae (coral snakes, mambas, kraits, and cobras)
 - d. Hydrophiidae (sea snakes)
 - e. Neuromuscular blockade occurs with:
 - i. Elapidae
 - ii. Hydrophiidae
 - iii. Crotalinae (South American rattlesnakes)

Clinical Manifestations

1. Pit viper or cobra:
 - a. Local pain
 - b. No pain with other elapidae and hydrophiidae
2. Swelling and necrosis within one hour of bite from viperidae and crotalinae
 - a. No swelling from mamba, krait or coral snake bite
3. Preparalytic stage (viperidae and crotalinae):
 - a. Headache
 - b. Loss of consciousness
 - c. Paresthesia
 - d. Hematuria and hemoptysis
 - e. These manifestations are rarely seen with cobra or mamba envenomation
4. Neuromuscular toxicity:

- a. Usual time from envenomation to paralysis
 - i. 1/2 hour to 19 hours
 - ii. Mamba envenomation as short as 10 minutes
 - iii. Location of the bite and direct venous access are determining features, as is the variant of injected toxin
- b. Sequence of clinical signs:
 - i. Ptosis and ophthalmoptosis
 - ii. Facial and bulbar weakness
 - iii. Extremity, diaphragm and intercostal weakness
 1. May progress over a 2 to 3 day period
 - iv. No sensory abnormalities except at the site of envenomation
 - v. Cardiovascular collapse, seizure, and coma are terminal events
5. Hemotoxic effects (Viperidae/Crotalinae)
 - a. Cerebral hemorrhage
 - b. Subarachnoid hemorrhage (SAH)
 - c. Intracerebral hemorrhage (ICH)
 - i. The leading cause of viperidae death
 - d. Crotalinae (rattlesnakes)
 - i. Persistent fasciculations long after clinical recovery of the affected muscles

Neuropathology

1. Presynaptic toxins:
 - a. Hemorrhage; a phospholipase constituent from the multi-banded krait (*Bungarus multicinctus*)
 - b. Brazilian rattlesnake (*Crotalis durissus*)
 - i. Initially, increases and then decreases the amount of ACh released from the nerve terminal
 - c. Taipan:
 - i. Initial augmented release of ACh
 - ii. Late depletion of the neurotransmitter
 - iii. Presynaptic toxins are often more potent than postsynaptic toxins
2. Postsynaptic toxins:
 - a. Alpha-neurotoxins
 - b. Cause a non-depolarizing neuromuscular block
 - c. Most toxins are mixtures of pre- and postsynaptic compounds
 - d. Sea snakes inject less toxin; it is more potent than other snake toxins
3. Alpha-neurotoxins
 - a. Bind the nicotine ACh receptor of muscles
 - b. More potent than curare
 - c. Slower onset of action and longer duration than presynaptic toxins

Beta-Neurotoxins

1. Contain phospholipase
2. All suppress release of presynaptic ACh
3. Taipan (Australia) has an additional myotoxin (causes rapid muscle necrosis)

Arthropod Envenomation – Black and Brown Widow Spiders

General Characteristics

1. The most common envenomations in the USA are from the black widow spider (*Latrodectus mactans*, *L. hesperus*, and *L. variolus*) and the brown widow (*Latrodectus geometricus*)
2. The toxin alpha-latrotoxin is the most extensively studied

Clinical Manifestations

1. Female black widow spiders have an hour-glass pattern that is red or orange on their black abdomen; they are 2 to 2 1/2 times more poisonous than males
2. Approximately 15% of their bites are non-envenomating
3. Onset of clinical signs occurs during the first 8 hours post-envenomation and include:
 - a. Pain at the site of the bite
 - b. Pain in the extremity that migrates to other muscle groups
 - c. Muscle cramps and severe abdominal rigidity
 - d. Priapism (described in children)
 - e. Hypertension may supervene within 2–4 hours
 - f. Mild cardiac arrhythmia may occur; fulminant myocarditis has been reported
 - g. Opisthotonus may occur in severe envenomation
 - h. Autonomic instability
 - i. Recovery may be prolonged

Neuropathology

1. Electron microscopy:
 - a. Swollen nerve terminals without synaptic vesicles
2. Acetylcholine, noradrenalin, dopamine, glutamate and enkephalin systems are affected
3. Alpha-latrotoxin causes an initial surge of spontaneous MEPP frequency which then decreases and disappears over the next 30 minutes (depolarizing block)

Funnel-Web Spider

General Characteristics

1. The Australian funnel-web spiders are the most lethal spiders worldwide
2. The Sydney funnel-web spider (*Atrax robustus*) caused approximately 14 deaths per year until the introduction of antivenom in 1980
3. Hexatoxin, a 42-residue peptide, is the major toxin in this spider venom causing neuromuscular transmission defects

Clinical Manifestations

1. Male spiders' toxins have greater potency than that from females
2. Nausea, vomiting, and dizziness are the initial symptoms
3. Fasciculation and paralysis of striated muscle and the diaphragm supervene
4. Death occurs by asphyxia and concomitant cardiac arrest

Neuropathology

1. Hexatoxin delays the inactivation of voltage-gated sodium channels
 - a. Massive ACh release
 - b. Both somatic and autonomic nerve endings are affected
 - c. Repetitive firing and prolongation of action potentials

Scorpion Envenomation

General Characteristics

1. Scorpion envenomation is a potential threat to 2 billion people worldwide
2. Annual envenomations are estimated at one million; the lethality rate is 27%
3. Most stings are reported from North Africa, South India, Latin America and the Middle East:
 - a. *Hottentotta tumulus* (India)
 - b. *Leiurus quinquestriatus* and *Androctonus crassicauda* of North Africa and the Middle East
 - c. *Tityus serrulatus* (Brazil)
 - d. *Centruroides suffusus* of Mexico
4. The severity of scorpion envenomation varies with species, size, and age and is much more severe in children

Clinical Manifestations

1. Primary signs and symptoms reflect overstimulation of the sympathetic and parasympathetic nervous system, and include:
 - a. Local pain and paresthesia
 - b. Agitation, dizziness, and disorientation
 - c. Vomiting and abdominal pain
 - d. Salivation and diaphoresis
 - e. Muscle rigidity and fasciculation
 - f. Pupillary abnormalities
 - g. Priapism
 - h. Tremor and ataxia
2. Systemic symptoms:
 - a. Bradycardia and tachycardia
 - b. Hypertension > hypotension
 - c. Cardiac failure
 - d. Shock
3. *Tityus obscurus* (Brazilian Amazon, northern Brazil)
 - a. Clinical manifestations:
 - i. Acute onset of signs within a minute of envenomation
 - ii. Ataxia
 - iii. Nausea and vomiting
 - iv. Myoclonus
 - v. Fasciculations
 - vi. Paresthesias, burning and radiating from bite site

Neuropathology

1. Some toxins increase ACh release
2. Most affect sodium and potassium channel function

Laboratory Evaluation

1. Hyperglycemia
2. Pleocytosis
3. Elevation of cardiac and pancreatic enzymes
4. Ischemic EKG changes
5. Cardiac dysfunction on ECHO cardiography

Drugs That Interfere with Neuromuscular Transmission**Botulinum Toxin***General Characteristics*

1. Primarily used in specific neuromuscular disorders (dystonia, spasticity, spasms)
2. Cosmetic
3. Migraine

Clinical Manifestations

1. Decreases pain (migraine)
2. Paralysis of specific musculature (dystonia, spasticity, cosmetics)

Neuropathology

1. Botulinum toxins A, B and E cleave SNARE proteins which prevent the fusing of vesicles with the inner surfaces of the plasma membrane at release sites, which blocks the release of neurotransmitter (ACh)

Aminopyridine*General Characteristics*

1. 4-aminopyridine is one of three isomeric amines of pyridine

Clinical Manifestations

1. Primarily utilized to improve gait in demyelinating disease
2. Major adverse effect is seizure
3. Experimentally has been shown to reverse saxitoxin and tetrodotoxin

Neuropathology

1. 4-AP is a voltage-gated potassium channel blocker:
 - a. Delays egress of potassium from the nerve terminal, which prolongs action potential duration, which allows a greater concentration of calcium to enter the nerve terminal
 - b. Increases quantal ACh release

Guanethidine*General Characteristics*

1. A nitrogenous analog of carbonic acid

Clinical Manifestations

1. Has been used as an adjuvant in the treatment of botulism (guanidine hydrochloride)

Neuropathology

1. Inhibits calcium egress from the postsynaptic terminal
2. Increases vesicle fusion and thereby quantal ACh release

Hemicholinium-3*General Characteristics*

1. Has no clinical use

Clinical Manifestations

1. Inhibition is noted only with increased firing rates of a neuron

Neuropathology

1. Blocks the reuptake of choline by the high-affinity choline transporter (ChT) in the presynaptic terminal
2. Reduces ACh resynthesis

Anticholinesterases*General Characteristics*

1. Anticholinesterases bind with the enzyme and decrease the hydrolysis of ACh in the synaptic cleft

Clinical Manifestations

1. Increases muscle strength in MG
2. Affects ACh synapse of the autonomic nervous system to induce gastrointestinal effects as well as hypotension (some autonomic conditions)
3. At high doses produces severe dizziness and convulsions

Neuropathology

1. Augments ACh-ACh receptor interactions
2. Increase EPP and thus the depolarization of the postsynaptic membrane

Organophosphates*General Characteristics*

1. Organophosphates:
 - a. Highly effective acetylcholinesterase inhibitors that are primarily used as multipurpose insecticides
 - b. They are also used as chemical weapons, and use the active core of G-series and V-series chemical warfare agents that include:
 - i. Tabun
 - ii. Sarin
 - iii. Soman
 - iv. Cyclosarin
 - v. VX

Clinical Manifestations

1. Intoxication is usually from accidental or dermal exposure. The latter is prominent in agricultural workers (insecticide sprayings)
2. Initial signs and symptoms:

- a. Miosis
- b. Bronchoconstriction and increased secretions
- c. Diaphoresis
- d. If ingested:
 - i. Abdominal cramping
 - ii. Nausea, vomiting, and defecation
 - iii. Increased salivation
 - iv. Urinary incontinence
 - v. Bradycardia and hypotension
- 3. Neuromuscular signs and symptoms:
 - a. Muscle paralysis that may include respiratory failure
 - b. Fasciculations
 - c. Patients with chronic organophosphate exposure (agricultural workers) may develop a length-dependent axonal motor sensory neuropathy that may not completely resolve

Neuropathology

- 1. Increased EPP and prolonged depolarization of postsynaptic membranes of ACh neurons
- 2. The enzyme may be reactivated with an oxime antidote (2-PAM C.1), which is administered with atropine

Neuromuscular Blocking Drugs

General Characteristics

- 1. Neuromuscular blocking agents are primarily used for intubation and during surgical procedures for muscle relaxation
- 2. All agents interact with the acetylcholine receptor, by effecting competitive antagonism against acetylcholine or by continuous activations of the receptor
- 3. Several nerve agents have additional physiological actions

Clinical Manifestations

- 1. Compounds related to curare, used in anesthesia for neuromuscular blockade that maintains muscle relaxation, are:
 - a. Pancuronium
 - b. Vecuronium
 - c. Atracurium and gallamine
- 2. Acetylcholine blocking agents are the major depolarizing muscle relaxants in clinical use
- 3. Critical illness paralysis:
 - a. Occurs after the prolonged administration of the short acting blocking drug vecuronium or atracurium, often in conjunction with corticosteroids (severe asthma attacks)
 - b. The clinical features of critical illness paralysis include effects on peripheral nerves, muscles, and the neuromuscular junction in various combinations
 - c. It masks latent myasthenia gravis (poor recovery from anesthesia)
 - d. Succinylcholine causes early muscular overactivity (fasciculations) with later flaccid paralysis

Neuropathology

- 1. Curare-like compounds bind to ACh receptors (which enlist neuromuscular transmission) by competitive blockades
- 2. Succinylcholine and decamethonium have high affinity and persistently bind to the ACh receptor, maintaining depolarization of the postsynaptic membrane
- 3. Vecuronium may suppress activity of the A(3)B(2) subunit of the AChR in the presynaptic membrane and enhance quantal release:
 - a. Vecuronium also blocks L-type calcium channels, which may decrease calcium influx into the presynaptic terminals
 - b. Vecuronium may decrease neuromuscular transmission in both a pre- and postsynaptic manner

Drugs That Act Primarily Postsynaptically

- 1. Polymyxin B, polymyxin E, netilmicin and colistin
 - a. Act primarily postsynaptically
- 2. Tetracycline, oxytetracycline, and rolitetracycline
 - a. Act primarily postsynaptically but less severely than the polymyxins or colistin
- 3. Lincomycin and clindamycin
 - a. Act primarily postsynaptically in lower concentrations, but at higher dosages can decrease ACh release
- 4. Aminoglycosides
 - a. May act pre- and postsynaptically
 - b. Can precipitate abrupt onset of weakness (particularly in myasthenia gravis)
 - c. Blockage of presynaptic voltage-activated calcium channels; has a relatively low affinity for voltage-activated calcium channels
 - d. An alternative mechanism recently described is aminoglycoside activation of a presynaptic Ca^{2+} sensing receptor that modulates synaptic transmission
 - e. Aminoglycoside-induced weakness may be primarily due to increased activation of a channel that decreases terminal excitability
 - f. Presynaptic mechanisms of decreased neurotransmission with aminoglycosides are operative at lower concentrations
 - g. Activation of the CaSR channel inhibits the NSCC current, which shortens action potential duration that reduces the time for Ca^{2+} entry, which in turn decreases the probability of neurotransmitter release
 - h. Aminoglycosides may inhibit voltage-gated calcium channels at high concentrations
- 5. Procainamide:
 - a. May exacerbate weakness in patients with NMJ disease
 - b. Both pre- and postsynaptic mechanisms that are not completely established
- 6. Penicillamine and alpha-interferon:
 - a. General characteristics:

- i. Both of these drugs can initiate an autoimmune disease that has the clinical, serological and electrophysiological characteristics of myasthenia gravis
- b. Clinical manifestations:
 - i. The onset of the illness is within days to months of drug use; some rare cases have developed years after exposure
 - ii. The syndrome usually resolves within 2–6 months after cessation of drug use
- c. Laboratory evaluation
 - i. Serologic and electromyographic features are similar to MG
7. Myasthenic syndromes have been precipitated by:
 - a. Beta-interferon
 - b. Riluzole
 - c. Chloroquine
 - d. Trimethadione
 - e. Ritonavir
 - f. Statins
8. Analgesics:
 - a. Morphine and its derivatives do not depress neuromuscular transmission.
 - i. Depress respiration (clinically)
 - ii. Are potentiated by anticholinesterases
9. General anesthetics:
 - a. Potentiate neuromuscular blocking agents in MG patients
 - b. Ethrane and nitrous oxide do not cause neuromuscular blockade
10. Local anesthetics:
 - a. Lidocaine, procaine, and mexiletine potentiate neuromuscular blockade when administered intravenously
 - b. Mechanism may include:
 - i. Reduction of ACh release
 - ii. Possible decreased sensitivity of the postsynaptic ACh receptor
11. DL-carnitine:
 - a. NMJ block may occur during dialysis
 - b. Presynaptic block similar to that produced by hemicholinium
 - c. Postsynaptic block possibly due to the accumulation of acylcarnitine esters
12. Psychotropic drugs:
 - a. Chlorpromazine and promazine
 - b. Postsynaptic block
 - c. Prolongs the effects of succinylcholine
13. Lithium:
 - a. Possible decrease of the quantal release of ACh
 - b. Decreases the synthesis of ACh
 - c. Possible induction of an increased rate of receptor degradation
2. The painless weakness can be focal or diffuse:
 - a. Motor neuron disease
 - b. Myopathy
 - c. Motor neuropathies
 - d. Rarely, diabetic radiculoplexus neuropathy or brachial plexopathy are primarily motor
3. Disorders of oculomotor and brainstem receptors:
 - a. Miller-Fisher syndrome (no reflex loss in acquired MG)
 - b. Fazio-Londe and other motor neuron diseases of childhood
 - c. In adult patients:
 - i. Bulbar ALS (rare ocular involvement)
 - ii. Kennedy's disease (fasciculation of the face rather than ocular involvement)
 - iii. In general, ptosis and ophthalmoparesis exclude acquired or hereditary myopathy:
 1. Hereditary myopathies that involve the oculomotor system and bulbar functioning include:
 - a. Oculopharyngeal muscular dystrophy (symmetric ptosis and progressive course; genetic)
 - b. Mitochondrial myopathies (short stature, hearing loss, diabetes mellitus, cardiac involvement; PEO in adults may start with asymmetric ptosis and EOM weakness)
 - c. Myotonic muscular dystrophy (abnormal facies, cataracts, some patients with cognitive impairment)
 - d. Adult onset of some congenital myopathies (dysmorphic features, non-fluctuating course)
 - e. Rarely:
 - i. Subacute autoimmune paraneoplastic syndrome (anti-Ri antibody disease; some with opsoclonus myoclonus)
 - ii. Carcinomatosis of the meninges (usually cognitive impairments, rarely only one cranial nerve involved; progressive course)
 - iii. Rare infection processes may involve the oculomotor and brainstem early in their course. This includes:
 1. Listeria monocytogenes (dorsal pontine lesion in pregnant patients)
 2. Mucormycosis (immuno-suppressed patients, diabetic ketoacidosis; ophthalmoparesis; severely ill patients)
 - f. Herpes zoster (ophthalmicus) the overwhelming number of patients have characteristic rash; third nerve involvement; may have a concomitant headache
 - g. Rhombencephalitis (presentation of several viruses)
 - h. Chronic tuberculous meningitis (usually the VIth and VIIIth nerves are involved; associated headache and cognitive impairment)

Differential Diagnosis of Neuromuscular Transmission Diseases

1. Overwhelmingly motor signs and symptoms

- i. Syphilis (most often Argyll-Robertson pupillary abnormalities; rare EOM involvement; often VIIIth nerve is affected)
- j. Lyme's disease (VIIIth nerve involvement)

Differential Diagnosis of Congenital Myasthenic Syndromes

1. The "floppy infant" which includes myopathy, anterior horn cell disease, and arthrogryposis multiplex
2. Most floppy infants have corticospinal disorders and dysmorphisms
 - a. Floppy infants with neuromuscular disorders that are primary include:
 - i. Spinal muscular atrophy
 - ii. Congenital hypomyelinating neuropathy
 - iii. Neonatal myasthenia
 - iv. Congenital myotonic dystrophy
 - v. Congenital Duchenne and Becker muscular dystrophy
 - vi. Congenital myopathies:
 1. Lipid
 2. Mitochondrial
 3. Glycogen

Differential Diagnosis of Congenital Ptosis

1. Muscle diseases:
 - a. Congenital myotonic dystrophy
 - b. Central nuclear myopathy
 - c. Nemaline myopathy
2. NMJ disorders:
 - a. LEMS (Lambert-Eaton myasthenic syndrome)
 - i. Less cranial nerve involvement than MG increased strength with exercise, autonomic involvement (dry mouth); "load in the pants" gait and some sensory symptoms
 - ii. Diseases that could be confused with LEMS include:
 1. Subacute myopathy (no increase of strength with exercise, no autonomic symptomatology)
 2. Pure motor forms of CIDP (no autonomic symptomatology, rare cranial EOM involvement, no increase of strength with exercise)

Differential Diagnosis of Fulminant Myasthenia (Severe General Weakness and Cranial Nerve Involvement)

1. Botulism (involvement of pupils, bulbar and the autonomic nervous system, and loss of reflexes)
2. Tick paralysis (ataxia and sensory loss; motor weakness)
3. Guillain-Barré (particularly Miller-Fisher variants; loss of reflexes is prominent)
4. Brainstem stroke (cognitive impairment; sensory loss, may have flaccid asymmetric weakness; rarely isolated IIIrd or VIth nerve palsy)

Differential Diagnosis of Neuromuscular Transmission at the Neuromuscular Junction

1. Presynaptic:
 - a. Lambert-Eaton myasthenic syndrome
 - b. Botulism (acquired and iatrogenic)
 - c. Botulism A, C and E cleave SNAP-25; type B, D, F and G cleave synaptobrevin; all cleave SNARE proteins required for the synaptic fusion complex
 - d. Congenital myasthenic syndrome:
 - i. Choline acetyltransferase deficiency
 - ii. Paucity of synaptic vesicles and reduced quantal release
 - iii. Congenital Lambert-Eaton syndrome
2. Drugs:
 - a. Hypermagnesemia (blockade starts at approximately 75 mg/L)
 - b. Antibiotics:
 - i. Aminoglycosides:
 1. Decrease the nerve terminal entry of calcium with consequent reduction of quantal acetylcholine release
 - ii. Primary aminoglycosides
 1. Amikacin
 2. Tobramycin
 3. Kanamycin
 4. Paromycin (paromomycin)
 5. Gentamicin
 6. Streptomycin
 7. Neomycin
 8. Other antibiotics (lesser effects on voltage-dependent calcium entry):
 - a. Clindamycin
 - b. Oxytetracycline
 - iii. Calcium channel blockers:
 1. Verapamil (L-type Ca^{2+} channels)
 2. Diltiazem
 - iv. Corticosteroid (affects the nerve terminal membrane; depolarization causing depletion of ACh)
 - v. Amidopyridines:
 1. Primarily 4-AP (utilized in demyelinating disease)
 2. Voltage-gated potassium blocking drugs
 3. Delay the egress of potassium from the nerve terminal, which prolongs the duration of the action potential, increasing calcium in the presynaptic terminal and thus increasing ACh quantal release

Differential Diagnosis of Toxins

1. Black and green mamba snakes:
 - a. Dendrotoxin
 - b. Blockade of nerve terminal potassium channels that prolongs the action potential allowing more calcium entry and increased ACh release

2. Scorpion (*Pandinus imperator*):
 - a. Blockade of nerve terminal potassium channels
3. Australian tiger snake:
 - a. Notexin
 - b. Blockade potassium channels that decrease the release of ACh
4. *Conus* marine snail (*C. geographus*):
 - a. Omega-conotoxin
 - b. Binds presynaptic calcium channels, preventing calcium entry and ACh release
5. Multi-banded krait:
 - a. Beta-bungarotoxin
 - b. Alpha-phospholipase
 - c. Presynaptic specific site-directed phospholipase A2-induced permeabilization of the plasma membrane
 - d. Impairs ACh release
6. Brazilian rattlesnake (*Crotalus durissus*)
 - a. Crotoxin
 - b. Initially, increases and then reduces the quantal release of ACh at presynaptic terminals
7. Black widow spider (*Latrodectus mactans*) and the brown widow spider (*Latrodectus geometricus*)
 - a. Produced alpha-latrotoxin
 - b. Affects motor nerve endings and endocrine cells
 - c. The toxin forms pores in the lipid membranes, inducing calcium entry
 - i. A dramatic early surge of spontaneous MEPP frequency which dissipates over 30 minutes
 - ii. Neuromuscular blockade occurs due to depletion of synaptic vesicle contents

Differential Diagnosis of Synaptic Structural Disorders

1. Synaptic basal-lamina-associated congenital myasthenic syndrome
 - a. Endplate acetylcholinesterase deficiency
 - i. Mutations in the gene encoding the anchoring and the catalytic component of AChE in the synaptic basal lamina complex
 - ii. Acetylcholine is prolonged in the synaptic cleft with prolonged duration of MEPP and EPP and degeneration of the junctional folds and loss of ACh receptors
 - b. B2-laminin deficiency:
 - i. Mutation in LAMB2 gene
 - ii. Widened synaptic space
 - iii. Decreased quantal release
 - iv. Simplified MEPP
2. Drugs that act in the synaptic cleft:
 - a. Acetylcholinesterase inhibitors
 - i. Edrophonium
 - ii. Pyridostigmine
 - iii. Neostigmine
 - b. Organophosphates
 - i. Increased EPP and prolonged depolarization of postsynaptic membranes

Differential Diagnosis of Postsynaptic Disorders

1. Myasthenia gravis
 - a. Neonatal
2. Primary AChR deficiency:
 - a. Mutations in AChR genes concentrated in the E-subunit
 - b. Fewer receptors and less folding of the junctional folds
3. Slow-channel syndrome:
 - a. Gain of function mutations
 - b. Enhances receptor affinity or increases its gating efficiency
 - c. Prolonged endplate currents
4. Fast-channel syndromes:
 - a. Recessively inherited
 - b. Decreased affinity for AChR and reduced gating kinetics
 - c. Abnormal short channel opening time
5. Prenatal myasthenic syndrome:
 - a. Mutation of the subunit (gamma)
6. Rapsyn mutations:
 - a. Mutations in the open reading frame and promoter region of Rapsyn
 - b. Less concentrations of AChR in the postsynaptic membrane
7. Plectin mutations:
 - a. Heteroallelic, nonsense, frame-shift and splice-site mutations
 - b. Low amplitude of MEPPs
 - c. Lack of cytoskeletal support from defects of the intermediate filament-linking protein
8. Non-channel myasthenia:
 - a. Mutation in SCN4A that encodes Na_v1.4
 - b. Enhanced fast inactivation of the sodium channels
 - c. Na_v1.4 are inexcitable in the resting state
9. MuSK (muscle-specific receptor tyrosine kinase):
 - a. In conjunction with agrin, Lrp4, and Dok-7, is involved in the maturation and maintenance of the endplate and in concentration of AChR in the postsynaptic membrane
 - b. Specific mutations in frame-shift and missense that are heteroallelic result in specific electrophysiological and structural deficits
 - c. MEPP amplitude may be reduced: a decreased EPP quantal content was detected in one kinship
10. Dok-7 mutations:
 - a. A muscle-intrinsic activator of MuSK
 - b. Multiple mutations in Dok-7
 - c. MEPP and MEPC amplitudes are reduced; some patients have decreased quantal content of ACh vesicles
 - d. There are both pre- and postsynaptic structural defects of the neuromuscular junction

Myasthenic Syndromes Associated with Centronuclear Myopathy

1. Centronuclear Myopathy (CNM) is a heterogeneous congenital myopathy whose defined genes are:
 - a. Myotubularin (MTM)
 - b. Dynamin 2 (DNM2)
 - c. Amphiphysin (BIN1)
 - d. Ryanodine receptor (RYR)
2. A decremental EMG response has been documented in CNM with myasthenic features

CMS in Defect of the Hexosamine Pathway

1. Mutation in the GEPT1 gene that encodes glutamine-fructose-6-phosphate transaminase 1
2. The enzyme controls glucose entry into the hexosamine pathway and ultimately N-O-linked glycosylation of protein
3. Limb-girdle weakness
4. Electrodiagnostic features have not been determined

Differential Diagnosis of Drugs and Toxins That Block the NMJ

1. D-tubocurarine
2. Vecuronium
3. Non-depolarizing agents
4. Depolarizing agents
 - a. Succinylcholine

Envenomations

1. Elapid species (cobras and kraits)
2. Conus marine snails

Drugs That May Cause Myasthenia Gravis

1. D-penicillamine
2. Alpha-interferon
3. Rarely reported (case reports):
 - a. Trimethadione
 - b. Riluzole
 - c. Ritonavir
 - d. Chloroquine
 - e. Statins
 - f. Beta-interferons

Drugs That Exacerbate Myasthenia Gravis

General Characteristics

1. Patients may develop cranial nerve dysfunction, generalized weakness and respiratory failure abruptly
2. Failing to awaken with full strength after anesthesia (often precipitated by the stress of surgery, neuromuscular blocking agents, and antibiotics administered during the procedure)
3. Myasthenic signs and symptoms are unmasked with specific drug administration due to concomitant electrolyte disorders or an increased concentration of the drug due to drug interaction, failure of metabolism or excretion (liver or renal dysfunction)

Calcium Channel Blockers That Exacerbate Myasthenia Gravis

1. May affect neurotransmission both pre- and postsynaptically by blockade of L-type calcium channels
 - a. Verapamil:
 - i. Blockade of L-type postsynaptic channels
 - ii. Decreases potassium efflux at the motor endplate
 - iii. Decreases intracellular ionized calcium levels
 - b. Nimodipine and nifedipine
 - i. Have caused dysphagia, ptosis and weakness after 18 months to 12 years of use
 - ii. Decremental response on EMG
 - iii. Nifedipine has been shown to exacerbate myasthenia
 - iv. Both oral verapamil and amlodipine taken for three months in normal subjects may cause abnormal single-fiber EMG
2. Antiarrhythmic agents
 - a. Procaine amide:
 - i. May both induce and exacerbate MG
 - ii. Decreases the release of ACh quanta
 - iii. Raises the threshold of action potential generation of the postsynaptic membrane
 - iv. Procaine amide and propafenone block sodium channels
 - v. The duration of use to NMJ dysfunction varies from hours to 8 months
 - b. Quinidine:
 - i. Blocks fast sodium channels
 - ii. Its concentration may be increased if it is used with dextromethorphan in the treatment of "pseudo bulbar palsy"; dextromethorphan blocks its metabolism
 - c. Lidocaine:
 - i. Blocks sodium channels
3. Antimicrobial agents:
 - a. Aminoglycosides
 - i. Streptomycin
 - a. Prevents release of presynaptic ACh quanta
 - b. Streptomycin acts primarily by blocking the receptor
 - i. Some blocking effects at the postsynaptic receptor
 - ii. Neomycin
 - a. Reduces the quantal release of acetylcholine by competitive antagonism with calcium for a common presynaptic site required for transmitter release
 - b. May block acetylcholine channels in their open configuration
 - iii. Clindamycin affects neuromuscular transmission less severely; it interacts with the open state of the AChR
 - iv. Lincomycin also has less severe neuromuscular blocking effects
 - v. Gentamicin, tobramycin and amikacin
 - a. Decrease presynaptic release of ACh quanta

- vi. Polymyxin B, polymyxin E (colistin), and netilmicin
 - a. Postsynaptic effects
- b. Macrolides:
 - i. Erythromycin:
 - a. Worsens myasthenia in patients with postsynaptic defects
 - b. Decreases presynaptic release of ACh quanta
 - c. Telithromycin and azithromycin may also exacerbate myasthenia by a similar mechanism
- c. Fluoroquinolones, including:
 - i. Ciprofloxacin
 - a. Blocks voltage-gated potassium channels that affect presynaptic calcium channels affecting ACh release mechanisms
 - ii. Gemifloxacin
 - iii. Levofloxacin
 - iv. Norfloxacin
 - v. Ofloxacin
 - vi. Profloxacin (ciprofloxacin)
 - vii. All may cause neuromuscular transmission defects, but the mechanisms have not been completely established

Other Drugs That May Worsen Myasthenia

1. Other antibiotics that may worsen myasthenia:
 - a. Ampicillin and other penicillins
 - b. Bacitracin
 - c. Tetracycline, oxytetracycline, chlortetracycline:
 - i. Postsynaptic blockade
 - ii. Less severe clinical effects than other antibiotics
 - d. Imipenem/cilastatin
2. Quinolone derivatives:
 - a. Quinine, quinidine, and chloroquine
 - b. Decreased acetylcholine quantal release due to blockade of voltage-dependent sodium channels (located deep in the secondary synaptic cleft)
 - c. Postsynaptic potentiation of depolarization
 - d. Antibodies have been detected in some patients to ACh receptors
3. Beta blockers:
 - a. Propanolol
 - b. Practolol
 - c. Oxprenolol
 - d. Atenolol
 - e. Sotalol
 - f. Nadolol
 - g. Ophthalmic timolol:
 - i. May interfere with presynaptic ACh quantal release or work at the level of the muscle membrane
4. Corticosteroids:
 - a. Affect the nerve terminal membranes that causes continual depolarization
 - b. Depletes presynaptic ACh vesicles (decreased MEPP amplitude)

- c. Alters intracellular potassium concentration
- 5. H₂ receptor antagonists
 - a. Cimetidine, ranitidine, and roxatidine:
 - i. Pre- and postsynaptic interactions
 - ii. Inhibition of acetylcholinesterase
- 6. Depolarizing neuromuscular blocking agents:
 - a. Succinylcholine and decamethonium
 - b. Prolonged binding to the AChR with persistent depolarization of the postsynaptic membrane
- 7. Non-depolarizing blocking agents:
 - a. Vecuronium
 - b. Atracurium
 - c. Mivacurium
 - d. Doxacurium
 - e. Cisatracurium
 - f. Pancuronium
 - g. Rocuronium
- 8. Chloroquine:
 - a. Decreased ACh quantal release
 - b. Competitive post-junctional blockade
 - c. Decreased excitability of the sarcolemmal membrane
- 9. Magnesium:
 - a. >5 meq/L; severe deficit at 10 meq/L
 - b. Decreased release of ACh-containing vesicle
- 10. Drugs with potential NMJ blocking properties in myasthenia patients
 - a. Anesthetics:
 - i. Diazepam (chloride channel)
 - ii. Ketamine (primarily NMDA receptor)
 - iii. Propanediol ether
 - iv. Proparacaine
 - b. Anticonvulsants:
 - i. Phenytoin (sodium channel blockers)
 - ii. Carbamazepine (sodium channels)
 - iii. Ethosuximide (calcium channels)
 - iv. Gabapentin (alpha2delta subunit of calcium channel)
- 11. Drugs of abuse with possible NMJ blocking effects
 - a. Cocaine
- 12. Miscellaneous drugs:
 - a. DL-carnitine
 - b. Tropicamide
 - c. Iodinated radiographic contrast
 - d. Trihexyphenidyl
 - e. Echothiopate
 - f. Phenothiazine
 - g. Lithium

Further Reading

Further Reading on Neuromuscular Junction

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Chapter 9

Muscle Diseases

Overview of Muscular Dystrophies

The estimated prevalence rate of the most common muscular dystrophies are 1 in 5,000 live births for Duchenne dystrophy, 1 in 7,000 for facioscapulohumeral muscular dystrophy and 1 in 20,000 live births for myotonic muscular dystrophy. The muscular dystrophies are caused by mutations in over 30 genes that cause myofiber degeneration and atrophy. Similar or identical mutations in a single gene can produce different phenotypes. A more accurate classification of these illnesses is by both their muscular deficits and their phenotype dystroglycanopathies, laminopathies or ion channelopathies. The dystrophies demonstrate mechanisms of genetic disease: 1. Duchenne muscular dystrophy is a single gene loss of function disorder; 2. Facioscapulohumeral muscular dystrophy is due to epigenetic dysfunction; 3. myotonic dystrophy is a toxic gain of function illness from a tandem gene repeat.

The different muscular dystrophies are the results of mutations in genes that encode proteins pivotal to the:

1. Sarcolemma
2. Myonuclei
3. Basement membrane
4. The muscle extracellular matrix
5. The sarcomere
6. Non-structural enzymatic proteins

The major proteins affected in the dystrophies and their mechanism of action will be briefly discussed.

Dystrophin-Glycoprotein Complex and Related Proteins

Dystrophin

Dystrophin is the abnormal gene product in Duchenne and Becker muscular dystrophy. It is located on the cytoplasmic face of skeletal and cardiac muscular membrane. It is a large rod-shaped molecule composed of four domains. It is a 427 KDa submembrane cytoskeletal protein that is incorporated into a large macromolecular complex of proteins known as the dystrophin associated protein complex (DAPC). The DAPC is composed of dystroglycans, sarcoglycans, sarcospan, dystrobrevins and syntrophins. The dystrophin glycoprotein complex (DGC) is localized to a lattice-like structure in the muscle fiber that transmits force radially from the Z-disc to neighboring muscle fibers. Dystrophin has four domains, two globular domains and its N- and C-termini that are connected by a large rod domain. The rod domain consists of 24 spectrin-like repeats that includes four interspersed hinge regions. The C-Terminal domain binds the cytoplasmic tail of beta-dystroglycan. Dystrophin interacts with actin filaments

at two sites: 1. ABD1 at its N-terminus, a tandem calponin homology domain and 2. ABD2 site within the spectrin-like repeats 11–17 which interact with actin filaments by electrostatic attraction. These two binding sites anchor the sarcolemma to the muscle actin cytoskeleton that stabilizes the membrane against the mechanical forces of contraction. The dystrophin cysteine rich domain and the first half of the carboxy terminal domain link dystrophin to beta-dystroglycan and other glycoproteins that span the sarcolemma. Recent studies have demonstrated that phosphorylation within the cysteine rich region of dystrophin augments its interaction with beta-dystroglycan.

Dystrophin Associated Protein/Glycoproteins

The dystrophin glycoprotein complex consists of oligomeric proteins tightly bound to dystrophin. Mutations of the genes that code for the proteins of this complex cause many of the muscular dystrophies.

Other proteins that compose the dystrophin associated protein complex (DAPC) are: 1. dystroglycan; 2. sarcoglycans; 3. sarcospan; 4. dystrobrevins and syntrophin. The DAPC is a scaffold for various signaling and channel proteins as well as anchoring a variety of signaling molecules near their sites of action. The DAPC may be a component in the transduction of extracellular mediated signals to the muscle cytoskeleton. Recent work has demonstrated that beta-dystroglycan is involved in MAPK and Rac1 (small GTP-ase) signaling although it has been suggested to serve as a cell surface receptor for extracellular matrix proteins.

The syntrophins are a family of cytoplasmic membrane associated adaptor proteins that are characterized by a unique domain organization that is composed of a C-terminal syntrophin unique domain (SU) and an N-terminal Pleckstrin homology (PH) domain that is split by a PDZ domain. There are several isoforms B1, B2, and U2 that are encoded by different genes. A-Syntrophin is the primary isoform expressed in striated and cardiac muscle in the sarcolemma. MNI B1-syntrophin also localizes similarly while B2- and U2-syntrophin localize to the NMF. A-syntrophin interacts with dystrobrevin at the Ur3 domain. Syntrophin coordinates the assembly of 1. nitric oxide synthase, 2. stress activated protein kinase; 3. Grb2 and 4. calmodulin to the DAPC. Nitric oxide synthase generates NO from L-arginine that regulates focal blood flow in contracting skeletal muscle by antagonizing sympathetic induced vasoconstriction. Decreased vasodilation from decreased expression of nNOS is a feature of many muscular dystrophies. Transient receptor potential channels (TRPCs) also associate with syntrophin and are anchored to the DAPC. Emerging evidence suggests that they are a signaling complex for cations and regulate calcium homeostasis in skeletal muscle that is pivotal for muscle contraction, metabolism, and gene expression. The DAPC can bind as many as four syntrophins through binding domains or both dystrophin and dystrobrevin that allows the

scaffolding of multiple signaling proteins to be in close proximity. The multiple interactions of the Pleckstrin domain and PDZ domains of syntrophin form a signal plexus that enables regulated signal transduction and ion transport. The syntrophins also serve as a link between the extracellular matrix and downstream intracellular targets that include the cell cytoskeleton through their interactions with F-actin.

The mammalian dystrobrevin protein family consists of A- and B-dystrobrevin that are encoded by the genes DTNA and DTNB on chromosome 2p22. They are cytoplasmic proteins that bind to the syntrophin complex and to the C-terminus of dystrophin in striated muscle. In striated muscle dystrobrevin is localized to the cytoplasmic face of the sarcolemma. B-dystrobrevin is also expressed in non-muscle tissue.

Dystrobrevin is comprised of four major domains. Its two EF-hand motifs are thought to bind calcium, a 2Z domain, a helical coiled-coil domain that contains a dystrophin binding site and a tyrosine kinase substrate domain. Dystrobrevin is subject to extensive splicing regulation that generates three major dystrobrevin isoforms: 1. dystrobrevin 1; 2. dystrobrevin 2 and dystrobrevin 3. Dystrobrevin is associated with dystrophin by interaction at its coiled-coil domain and with the sarcoglycan complex through its N-terminal half. Additional dystrobrevin-binding proteins are syncoilin, B-synemin and dysbindin. Syncoilin and B-synemin are intermediate filament proteins. The interfilaments are an important part of the cell cytoskeleton by providing mechanical stability to the cell. Intermediate filaments include the two lines of each myofibril that connects all adjacent myofibrils and links the 2-lines of the peripheral layer of myofibrils to the sarcolemma.

Syncoilin, an intermediate filament protein, is highly expressed in striated muscle and colocalizes with dystrobrevin at the NMJ and the sarcolemma. It organizes and directs desmin filaments to the Z-line and provides further linkage of the DAPC and the cytoskeleton. This linkage may also be important for force transduction during muscle contraction. Syncoilin has been found to be increased in the sarcolemma of immature regenerating fibers. Thus syncoilin and dystrobrevin may play a role in muscle regeneration.

B-Synemin is a large heteropolymeric intermediate filament protein that interacts and colocalizes with dystrobrevin at NMJs and myotendinous junctions (MTJs). B-synemin dystrobrevin interacts with plectin, a linker protein of intermediate filaments to Z-discs, which interacts directly with dystrobrevin.

Dysbindin is a coiled-coil containing protein that is located in the sarcolemma. It binds to dystrobrevin and interacts with myospryn and other muscle-specific proteins localized to the sarcolemma. Myospryn may be a docking platform for structural and signaling molecules.

A recently described catenin/ninutin-related molecule, alpha-catulin has been shown to be another binding partner of dystrobrevin 1. It colocalizes with alpha-dystrobrevin at nerve bundles and blood vessels to regulate $\alpha 1D$ -adrenergic receptor signal transduction.

The sarcoglycan complex is a component of the major dystrophin complex and is a transmembrane protein. The sarcoglycans are transmembrane proteins that mature in the endoplasmic reticulum to reach their normal conformation by the activity of a quality control system. Misfolded proteins are identified and retrotranslocated to the cytosol where they undergo proteasomal degradation by the ER-associated protein degradation (ERAD) pathway. Defects in each sarcoglycan destabilize the entire sarcoglycan complex.

The sarcoglycan complex is composed of four membrane spanning proteins: 1. Sarcoglycan; 2. B-sarcoglycan; 3. U-sarcoglycan; 4. I-sarcoglycan. The sarcoglycan complex interacts with the cystein-rich domain or the first half of the carboxy terminal of dystrophin via the dystroglycan complex. Pathogenic mechanisms that effect sarcoglycans are: 1. the processing of defective sarcoglycan subunits; 2. failure of complete sarcoglycan complex assembly; 3. targeting of a dysfunctional sarcoglycan complex to the sarcolemmal membrane; 4. inadequate N- and O-glycosylation.

Sarcospan is a transmembrane protein that colocalizes with the sarcoglycan complex. The functions of sarcospan include:

1. Increased expression of the dystrophin and glycoprotein complexes
2. Increased expression of the 7B1 integrin
3. Interactions between integrin and sarcospan are pivotal for maintenance of the dystrophin-glycoprotein complex
4. Is a regulation of AKt signaling pathways that are important for muscle regeneration
5. Regulates glycosylation of some dystroglycans, the laminins-binding receptors for dystrophin and utrophin at the neuromuscular junction
6. Mutations of sarcoglycan genes are responsible for limb girdle muscular dystrophies (LGMDs) 2S, 2D, 2E and 2F

Laminin/Merosin

Laminins are large heterotrimeric proteins composed of three different homologous β -beta and γ -gamma chains held together by disulfide binds. There are five different α -alpha chains, three β -beta chains and two γ -gamma chains. The trimeric proteins intersect to form a lattice-like structure that binds other cell membranes and extracellular molecules. Laminin-2, composed of $\alpha 2$, $\beta 1$, and $\gamma 1$ chains is the major isoform of laminin heavy chains in muscle. Muscle also has a component of laminin 4 that is composed of $\alpha 2$, $\beta 2$ and $\gamma 1$ subunits. Greater than 15 laminin trimers have been identified. Merosin refers to laminins that have a common $\alpha 2$ chain. Basement membranes also are composed of type I and IV collagen, heparan sulfate, proteoglycans, fibronectin and laminin. They attach to cell membranes through integrin receptors and other molecules in the plasma membrane that include the dystroglycan complex. Laminin is a component of the basal lamina that surrounds each muscle fibril and is closely adherent to the sarcolemma. Alpha-dystroglycan binds to lamin-2. The sarcoglycan complex may associate with laminin 4. Merosin is a ligand in the Schwann cell

dystroglycan complex and binds alpha-dystroglycan. Mutations of the merosin gene are a cause of congenital muscular dystrophy and may also be associated with dysmyelination in the peripheral and central nervous system. LAMA2-gene mutations cause an autosomal recessive severe early-onset congenital muscular dystrophy as well as a limb-girdle muscular dystrophy (LGMD2).

Integrins

Integrins are transmembrane heterodimeric receptors composed of α and β chains. They are pivotal for cell-cell and ECM (extracellular matrix) interactions. After activation, they initiate signal transduction that induces the chemical composition and mechanical status of the ECM. They work in concert with cadherins, selectins, syndecans and the immunoglobulin super family cell adhesion molecules. They are also important for cell adhesion, proliferation, migration, and cytoskeletal organization. The major integrin expressed in the sarcolemma of skeletal muscle is $\alpha 7 \beta 1$ D. Ligands for integrins include fibronectin, collagen and laminins. $\alpha 7 \beta 1$ D integrin binds to merosin in skeletal muscle which links α -dystroglycan to merosin which augments sarcolemmal structural stability. Muscle fibers attach to lamin in the myofibril basal lamina by the dystrophin glycoprotein complex and the $\alpha 7 \beta 1$ integrin. Defects in these linkage mechanisms cause Duchenne muscular dystrophy, $\alpha 2$ laminin congenital muscular dystrophy, sarcoglycan-related muscular dystrophy and $\alpha 7$ integrin congenital muscular dystrophy.

Sarcolemmal Proteins Dysferlin

Dysferlin is a member of a family of proteins that are composed of multiple Ca^{2+} sensitive domains. They are important for vesicle fusion, trafficking, and membrane repair. There are seven domains in the dysferlin protein with different affinities for calcium and phospholipids that regulate its association with multiple protein complexes. Emerging evidence indicates association of dysferlin with the (t)-tubule membrane, where it is postulated to maintain Ca^{2+} homeostasis, during mechanical stress. Experimental studies in cultured muscle cells that demonstrated translocation from internal structures as well as its binding partners (tubulin, annexins, coneolin 3, BIN1) suggests its role in membrane repair. The most recent model of dysferlin function supports its role as a Ca^{2+} sensitive signaling scaffold protein that is localized to the t-tubule membrane. Its major function is postulated to involve the maintenance of t-tubules structure and function. Mutations of the gene that encodes dysferlin cause LGMD2B and Miyoshi distal myopathy.

Caveolae

Caveolae are specialized lipid rafts that form flask-shaped invaginations in the sarcolemmal membrane. They are 10–100 nm invaginations of approximately 14–16 caveolin-3

monomers that form a scaffolding complex of protein and lipids. Caveolin-1 is the major protein essential for their formation. Emerging evidence indicates that other caveolae-associated proteins, the cavin proteins are required for their formation and organization. The cavin proteins work in concert with caveolins for caveolae biogenesis. The N-terminal domain of the cavin HR1, is required for their homo- and hetero-oligomerization that form distinct subcomplexes on caveolae. Caveolae interact with dysferlin and caveolae-3 may have a function in the formation of (t) tubules and the organization of signaling complexes (dihydropyridine and ryanidine receptors and sodium channels). Caveolae interact with membrane associated signaling molecules that are important for cholesterol incorporation, macromolecular transport and permeability. Caveolin-3 gene mutations cause LGMD1C, rippling muscle disease and some forms of hyper-CK-emia.

Sarcomere Proteins

The cyclic interactions between the contractile proteins myosin and actin driven by the turnover of adenosine triphosphate (ATP) produce muscle contraction. In striated skeletal muscle actin and myosin in conjunction with accessory proteins are organized into sets of interdigitating thin and thick filaments which are connected in series with each other to form 1 μm wide myofibrils that run the entire length of the muscle cell. A thick filament is a polymer of myosin that is composed of approximately 300 myosin molecules. Muscle contraction occurs when globular myosin motor domains (“heads”) which extend from the thick filaments to interact with actin-binding sites to form “cross-bridges.” This anatomical arrangement produces effective summation of length changes by sarcomeres that are arranged in series. A structural working stroke in the myosin head pulls the thin actin filament towards the center of the sarcomere by 11 nm. Molecular motors are classified depending on whether they require several steps or only one step along their track prior to their detachment. The myosin II motor of muscle (the head on the thick filament) requires only one step along an actin filament before detaching (non-processive movement). The production of force and displacement by this actin-myosins mechanism is the result of cyclic interactions of billions of myosin motor domains with actin filaments. The force generating interaction cycles between actin and myosin is provided by the turnover of ATP. The “cross-bridge” globular head has two flexible hinges one at the head and the other at the arm filament interface. The myosin filament is coiled around a central axis that allows the cross-bridges 360° of longitudinal and circumferential extension. The globular heavy chain myosin head contains actin-binding sites and functions as an ATPase. The three major myosin heavy chain (MyHC) isoforms are expressed in different fiber types:

1. Type I expresses MYH7 in type I fibers
2. Type IIa expresses MYH2 in 2A fibers
3. Type IIx expresses MYH1 in 2B fibers

Mutations in the genes that encode the various MyHC isoforms cause both myopathies and cardiomyopathies.

Three subcomponents composed of actin, tropomyosin and troponin comprise the thin filament. G-actin has a globular structure that consists of two lobes separated by a cleft which is the "ATPase fold". This fold is the enzymatic center of catalysis which binds ATP and Mg^{2+} and hydrolyses it to ADP and phosphate. G-actin is only functional with ATP or ADP in its cleft. F-actin has a filamentous structure that is a single-stranded levorotatory helix. F-actin has a structural polarity in that all of its subunits are oriented to the same end. The helical F-actin filament of striated muscle contains a tropomyosin molecule, a 40 nanometer long protein that wraps around the F-actin helix. At rest, the tropomyosin covers the actin active sites that blocks actin-myosin contraction coupling. Troponins are the third subcomponent of the actin thin filament. Troponin I binds to actin, troponin T binds to tropomyosin and troponin C has high affinity for calcium. The troponin complex links tropomyosin to actin to form the complete thin filament. One end of an actin filament is anchored to the Z-disc that extends from myofibril to myofibril across the diameter of the muscle fiber while its other end is interspersed between myosin filaments. The Z-discs defines the lateral borders of sarcomeres whose core consists of actin filaments from adjacent sarcomeres that are cross-linked by α -actinin in myosin. They (Z-discs) are composed of hundreds of proteins and are an extremely complex macromolecular structure. The disc size varies in different types of muscle. F-actin filaments, the large protein titin, the nebulin/nebulette complex directly attach to Z-discs. In addition to its function in the mechanical stability of the sarcomere it has a role in signaling and mechanosensation. The Z-disc also communicates with the t-tubular system, the sarcoplasmic reticulum and E3 ubiquitin ligases.

Other major proteins of the Z-disc include:

1. Nebulin, a giant 500–900 KDa filamentous protein that courses alongside actin filaments and is attached to α -actinin at the Z-disc. The giant muscle proteins (titin, nebulin and obsurin) have major roles in muscle elasticity, stretch response and sarcomeric organization. Nebulin consists of multiple tandem structural domains arranged in a modular pattern that span 500 KDa. Each thin filament has two nebulin molecules. Nebulin is also found in cardiac muscle. Mutations in the nebulin gene (NEB) causes nemaline myopathy
2. Desmin is an intermediate filament protein (along with vimentin and lamin A/C) and is essential for the structure of the extra-sarcomeric cytoskeleton in muscle cells. It has a three-dimensional filamentous frame work. It has a central alpha helical rod and globular domain in its amino-terminal and carboxyl terminal ends. Desmin interacts with several proteins and may be the sensor of deformation in cellular structures. There is evidence that it is linked to mechano sensation and is associated with the intracellular cytoskeletal network. It also links the Z-disc to the sarcolemma myonuclei and neighboring myofibrils

3. Alpha-B crystalline and HSPB7 alpha crystalline. Alpha crystalline (alpha A) is restricted to the lens. Alpha-B crystalline interacts with desmin, vimentin and actin and is localized to the Z-disc. It is a member of the small heat shock protein family. They have some molecular chaperone functions but they do not renature proteins. They hold proteins in soluble aggregates. They have autokinase activity and AB-crystalline functions with desmin to assemble and stabilize the Z-disc. Syncoilin and plectin may also augment the link of desmin filaments to the Z-disc
4. ZASP (Z-band alternatively spliced PDZ motif containing protein) functions to bind α -actinin and crosslink thin filaments of adjacent sarcomeres. Mutations in ZASP cause one form of myofibrillar myopathy
5. Titin. Titin is encoded by the TTN gene, is a giant protein greater than 1 μ m in length and connects the Z line to the M line in the sarcomere. It has been suggested to serve as a "molecular ruler" that determines the spacing of sarcomeres. It has Ig and fibronectin domains. The protein contributes to force transmission at the Z line as well as resting tension in the I-band. It contributes to sarcomere stabilization, the prevention of overstretching and the return to normal length after muscle contraction. Its semi-rigid rod-like A-band region has been suggested to act as a scaffold in the formation of thick filaments during muscle development. Titin is the third most abundant protein in muscle. It has a length of 27,00–33,000 amino acids (due to splice variant isoforms which makes it the largest protein). Its gene contains 363 exons
6. Titin interaction with other sarcomeric proteins include:
 - a. Telethonin and alpha-actinin at the Z-line region
 - b. Calpain-3 and obscurin at the I-band region
 - c. Myosin-binding protein C, calmodulin I, CAPN3 and MURF1 at the M line region

Titin Mutations Cause:

1. Myopathy with early respiratory failure
2. Early-onset myopathy with fatal cardiomyopathy
3. Core myopathy with heart disease
4. Centronuclear myopathy
5. Limb-girdle muscular dystrophy type 2J
6. Familial dilated cardiomyopathy 9
7. Hypertrophic cardiomyopathy and tibial muscular dystrophy
8. Scleroderma has autoantibodies to titin
9. Telethonin: Telethonin is a 167 amino acid protein that is striated muscle-specific with a B-sheet structure. It binds to the Z1–Z2 domains of the titin protein and attaches the N-terminals of two adjacent titin molecules at the Z-disc and along thick filaments. Telethonin interacts with multiple other proteins, is linked with myotitin that interacts with α -actinin and actin. Nonsense mutations in the telethonin gene cause limb-girdle muscular dystrophy type 2G (LGMD2G), while heterozygous missense mutations cause dilated and hypertrophic forms of cardiomyopathy

10. **Myofilin:** Myofilin is a 5 KDa cytoskeletal protein localized to the sarcomeric Z-disc and augments the stability of thin filaments during muscle contraction. Its functions include: 1. the binding of F-actin, 2. cross-linking actin filaments and 3. preventing latrunculin A induced filament disassembly
11. **Filamin-C:** Filamin-C is encoded by the FLNC gene and is primarily expressed in cardiac and striated skeletal muscles. It functions at Z-discs and subsarcolemmal areas. It has an N-terminal filamentous actin-binding domain and a long C-terminal self association domain that contains immunoglobulin-like domains as well as a membrane glycoprotein-binding domain. Filamin is a component of a focal adhesion protein. Filamin-C interacts with specific proteins in different parts of the sarcomere:
 - a. It interacts with γ -sarcoglycan and IL sarcoglycan at the sarcolemma
 - b. Myotilin and FATZ/calsarcin/myozenin at Z lines
 - c. LL5beta is a phosphatidylinositol (3,4,5)-trisphosphate sensor that binds the cytoskeletal adaptor, gamma-filamin
 - d. Filamin-C interacts with INPPL1, KCND2 and MAP2K4

Filamin-C:

1. Binds actin
2. Is involved in Z-disc formation
3. Binds γ -gamma and L sarcoglycan at the sarcolemma
4. Is involved in signaling pathways from the sarcolemma to the myofibril

Summary of Z-Disc Proteins

1. Core Z-disc proteins:
 - a. α -actinin
 - b. Stabilization of the sarcomere during contraction (mechanical function)
2. Partial Z-disc proteins:
 - a. Titin, nebulin and actin
 - b. Functions:
 - i. Stabilization of the sarcomere during contraction
 - ii. Signal transduction
 - iii. Relaxation
 - iv. Contractibility
 - v. Passive elasticity
3. Peripheral Z-disc proteins:
 - a. Telethonin, calcineurin, calcarcin and MLP (muscle LIM protein)
 - b. Function:
 - i. Signaling
 - ii. Survival
4. Mutations in Z-disc genes give rise to Z-discopathies that include:
 - a. Cardiomyopathies:
 - i. DCM (dilate cardiomyopathy)
 - ii. HCM (hypertrophic cardiomyopathy)
 - iii. ARVC (autosomal recessive ventricular compaction)
 - b. Myopathies:

- i. Titinopathy
- ii. Zasopathy
- iii. Myotitinopathies
- iv. Myofibrillar myopathy
- v. LGMD
- vi. XMPMA (X-linked myopathy with postural muscle atrophy)

Sarcoplasm

Sarcoplasm is the intracellular fluid that surrounds myofibrils. It contains mitochondria and a variety of organelles that includes the sarcoplasmic reticulum. The intracellular calcium concentration determines skeletal muscle force that is regulated by the uptake and release of calcium from the sarcoplasmic reticulum. The sarcoplasmic reticulum is an intrinsic series of channels that terminate in cisternae at either end of the sarcomere. The ryanodine receptor (RyR) is the calcium release channel in the sarcoplasmic reticulum. The free calcium in the sarcoplasmic reticulum regulates its own excitability by activating Ca^{2+} release channels in its membrane that involves Ca^{2+} sensing mechanisms on both the luminal and cytoplasmic sides of the ryanodine receptor. Inositol 1, 4, 5-trisphosphate receptors (IP3R) are also Ca^{2+} release channels on the endo/sarcoplasmic reticulum. T-tubules are closely associated with terminal SR cisternae. Two terminal cisternae associated with one T-tubule form a triad that conducts the action potential into both the cisternae and the interior of the muscle fiber. Calcium release from intracellular stores plays an essential role in excitation-contraction coupling. Ryanodine (RyR) and inositol 1, 4, 5-trisphosphate receptors (IP3Rs) are the major release channels of the endo/sarcoplasmic reticulum. The sarco (endo) plasmic reticulum Ca^{2+} ATPase (SERCA) are the uptake channels. Calsequestrin is the major calcium buffer in the sarcoplasmic reticulum. Calsequestrin both inhibits and activates muscle RyR1 depending on its binding status that may be direct or through anchoring proteins. Its phosphorylation status influences its Ca^{2+} -binding capacity, the regulation of the RyR1 receptor and its interaction with the anchoring protein junction 5. The calcium reuptake channel also located in the sarcoplasmic reticulum is the calcium ATPase (SERCA1) receptor. Mutations in the genes that encode these channels cause hypokalemic periodic paralysis, central core disease, and malignant hyperthermia. Mutations in the gene encoding the SERCA1 receptor causes Brody disease in which there is impaired relaxation of muscle.

Nuclear Proteins

The nuclear envelope is made of two lipid bilayers. The outer nuclear membrane is contiguous with the endoplasmic reticulum and the inner nuclear membrane. The inner nuclear membrane contains a variety of integral membrane proteins that include LAP2, Emerin and MAN1. Emerin is a LEM domain nuclear protein. The LEM domain mediates binding to

BAF (chromatin-associated protein barrier to autointegration factor), which is essential for higher order chromatin structure, nuclear assembly and gene regulation. The binding of LEM proteins to chromatin bound BAF recruits chromatin to the nuclear envelope. In addition to LEM proteins there are between 80–100 integral inner nuclear membrane proteins. Emerin is a serine rich nuclear membrane protein and belongs to the nuclear lamin-associated protein family. It is located on the inner nuclear membrane of skeletal, cardiac and smooth muscle.

The nuclear lamina consists of lamins and nuclear lamin-associated membrane proteins. The lamins are type V intermediate filaments that are either type A (lamin B1, B2). Type V intermediate filaments have arm extended rod domains, a nuclear localization signal at their C-terminus and typical tertiary structures. The nuclear lamina is a multimeric matrix composed of lamins A, B and C that are associated with the nucleoplasmic surface of the inner nuclear membrane.

The nuclear lamin associated membrane proteins are either integral or peripheral membrane proteins, the most important are:

1. Lamin associated polypeptide 1 and 2 (LAP, LAPa)
2. Emerin
3. Lamin B-receptor (LBR)
4. Otefin and MAN1

The assembly of the nuclear lamina is accomplished by the interactions of two lamin polypeptides. Their α -helical regions are intertwined to form a coiled-coil structure that is followed by a head to tail linkage of these dimers. The elongated linear polymer has side-to-side polymers that give it a 2D structure that forms the nuclear envelope. The functions of the nuclear envelope include:

1. Mechanical stability of the nucleus
2. Chromatin organization
3. Cell cycle regulation
4. DNA replication
5. Cell differentiation and apoptosis
6. Binds nuclear pore complexes

Emerin attaches to the inner nuclear membrane by its carboxyl terminal tail. Lamins bind to emerin, other LAPs, and specific lamin receptors on the inner nuclear membrane. This protein complex is essential for the structural integrity and organization of the nuclear membrane as well as signal transduction between the nucleus and the sarcoplasm. Mutations in the gene that codes for emerin causes Emery-Dreifuss muscular dystrophy. Lamins A and C are caused by alternate splicing while mutations in the LMNA gene is responsible for autosomal dominant limb-girdle muscular dystrophy Type 1B.

Valosin containing protein (VCP) is encoded by the valosin-containing protein gene that has been mapped to chromosomal region 9p13.3-12. It is a type II member of the AAA⁺-ATPase family and localizes to nuclei around nucleoli. It serves a variety of functions that include:

1. A ubiquitin segregase that remodels multimeric protein complexes by extracting polyubiquitinated proteins that are subsequently recycled or degraded by the proteasome

2. Mitochondrial quality control
3. Autophagy
4. Vesicle transport and fusion
5. 26S proteasome activity
6. Proteasome assembly
7. It is associated with calthrin, heat shock protein Hsc 70 in a complex
8. Valosin is a component of cellular events that are regulated during mitosis which include:
 - a. Membrane fusion
 - b. Spindle pole body physiology
 - c. Ubiquitin dependent degradation
9. Mutation in the VCP gene cause inclusion body myopathy associated with Paget's disease of bone and frontotemporal dementia. Mutations in the VCP1 gene are also responsible for amyotrophic lateral sclerosis, in 10–15% of patients with hereditary inclusion body myopathy as well 2–3% of isolated familial amyotrophic lateral sclerosis

Poly(ADP-ribose) binding nuclear protein 1 (PABNP1) is encoded by the PABN1 gene that is located in chromosome 14q11.1. Mutations in the gene cause short (GCG) (8–13 expansion that lengthens an N-terminal polyalanine domain). The mutation mechanisms have been postulated to cause slippage and unequal recombination. Under normal circumstances, the encoded protein polymerizes poly (A) tails on the 3' ends of eukaryotic genes and controls the size of the poly (A) tail to approximately 250 nt. The major function of PABNP1 is to polyadenylate mRNA and shuttle it from the nucleus to the cytoplasm. Mutation of the PABNP1 gene causes oculopharyngeal dystrophy. The GCG expansion is stable in subsequent generations and is translated into a polyalanine tract. The pathologic hallmark of the disease is intranuclear inclusions that contain the aberrant protein that may interfere with normal RNA function.

Enzymatic Proteins in Muscle

Calpain-3 is a heterodimer that consists of a large and small subunit. It is a major intracellular cysteine protease. In addition to its enzymatic activity recent research supports that, its phosphorylation is involved in the pathology of LGMD2A through defects in the structure of myofibrils and their signaling pathways rather than its function as a protease. It is found in both the nucleus and cytoplasm of myofibrils. It may activate other enzymes involved in muscle metabolism.

Tripartite motif-containing protein 32 (TRIM32) is encoded by the TRIM32 gene on chromosome 9. The TRIM motif includes three zinc-binding domains, A Ring, a B-box type 1 and type 2 and a coiled region. It is localized to cytoplasmic bodies and the nucleus. It has two mechanisms of action:

1. Acting through the N-terminal RING finger as an E3 ubiquitin ligase it attaches ubiquitin molecules to lysine residues of target proteins, which marks them for proteasome degradation. It ubiquitinates multiple proteins that include:

- a. C-Myc
 - b. Dysbindin
 - c. Actin
 - d. Abl-interactor 2
2. It activates microRNAs by binding proteins to the c-terminal repeat
 3. Recent evidence signaling that causes muscle atrophy supports evidence that mutation in TRIM-2 gene causes LGMD2H

Fukutin is a glycosyl transferase encoded by the FCMD gene located on chromosome 9q31. Mutation of the gene causes abnormal glycosylation of alpha-dystroglycan that causes congenital muscular dystrophy and LGMD2L. Mutations in fukutin related protein cause congenital muscular dystrophy with normal merosin as well as LGMD2I. Glycosylation defects of alpha-dystroglycan also cause muscle-eye-brain disease and Walker-Warburg syndrome.

The muscle-eye brain (MEB) gene encodes a protein O-mannase b-1, 2-N acetyl glucosaminyl transferase (POMGnT1) which also causes LGMD2M. Walker-Warburg syndrome is caused by mutations in O-mannosyl transferase (POMT1) and the recently described GTDC2 genes. Presently there are 7 gene mutations defined in WWS that explain approximately 50–60% of patients. GTDC2 is predicted to encode a glycosyltransferase. Mutations in the DAG1 gene cause the loss of both α -alpha and β -beta dystroglycan and have been shown to cause WWS. LGMD2K is also seen with POMT1 mutations.

Mutations in the LARGE gene, another member of the N-acetylglucosaminyl transferase gene family, is a golgi protein. Mutations of the gene cause congenital muscular dystrophy 1D that is characterized by severe mental retardation. Abnormal glycosylation of alpha-dystroglycan and possibly defective synthesis of glycoprotein and glycosphingolipid are reported with this mutation LARGE may also function in tumor specific genomic rearrangements.

Mutations in the GNE gene in chromosome 9 which encodes UDP-N-acetylglucosamine 2-epimerase/n acetylmanosamine cause an autosomal recessive inclusion body myopathy from defects of post-translational glycosylation.

Sarcomere Structure

A sarcomere is the segment of a myofibril between two Z-lines. The I-band is the zone of thin filaments that is not superimposed by thick filaments and surrounds the Z-line. Next to the I-band is the A-band (anisotropic under a polarizing microscope). It contains the entire length of a single thick filament. The A-band contains the H-band that is a zone of thick filaments that is not superimposed by thin filaments. The H-zone contains the thin M-line that is formed by cross connecting elements of the cytoskeleton. Actin thin filaments extend into the A-band and are the major component of the I-band. Myosin thick filaments extend throughout the A-band and are cross-linked at their center by the M-band. Titin extends from the Z-line where it is attached to the thick filament

system to the M-band where it interacts with myosin. Nebulin extends along the thin filaments and the entire I-band. The M-band proteins myomesin and C-protein cross link myosin and the M-band component of Titin. The thin filaments are anchored in the Z-disc and the thick filaments (myosin) in the M-band. The alignment and linkage of actin and myosin filaments depends on the accessory proteins α -actinin, myomesin, M-protein, titin, desmin and the myosin-binding proteins (MYBP)-C and H. Alpha actinin is the major protein of the Z-line and cross links and fixes actin filaments in a lattice at the Z-disc. Myomesin and M-protein connect titin and myosin. Myomesin may also be essential in the integration or the assembly of sarcomeres. Titin courses parallel to the filament array and is a continuous filament system in myofibrils.

Desmin is a major intermediate filament protein that is essential for maintaining the structural integrity and alignment of myofibrils. Myosin-binding protein C runs parallel to the M-band and interacts with both the thick and titin filaments for their linkage and alignment in the A-band. Other functions of myosin-binding proteins include:

1. MyBP-C:
 - a. Reduces the critical concentration for myosin polymerization that forms longer filaments that are more uniform in length
 - b. Both MyBP-C and H are involved in the assembly of thick filaments into their precise lengths
 - c. MyBP-C and H may be a regulator of muscle contraction

The Structure of Myosin

Myosin is a hexameric protein composed of two myosin heavy chain (MyHC) subunits and two pairs of non-identical light chain (MyLC) subunits. The lobular domain of myosin binds the MyLC and forms the cross-bridges that contain the binding sites for actin and ATP. The rod domain is an elongated alpha-helical coiled-coil carboxyl-terminal with filament-forming characteristics. Proteolytic enzyme cleavage of MyHC produces two subfragments: 1. heavy meromyosin (HMM) that contains the head region (subfragment 1-S1) and a part of the coiled-coil-forming sequences (subfragment 2-S2) which connects the myosin head to the thick filament. The light meromyosin (LMM) is the C-terminal portion of the rod that is adjacent to the thick filament. The myosin motor domain is complicated and is formed by three domains connected by flexible linkers. An amino-terminal nucleotide-binding domain that is connected to the upper subdomain that in turn is connected to the lower domain. The third domain is the converter region from which extends a long helix that is the binding site for MyLCs. The essential light chains (ELC) are closest to the converter domain and the regulatory light chains (RLC) attach at the second site. The elongated neck region in S1 functions as a lever arm that amplifies small configured changes of the motor domain into greater displacements of actin. The six striated muscle MyHCs:

1. Are encoded by a cluster of genes on chromosome 17
2. The genes are arranged in the following sequence: MyH3, MyH2, MyH1, MyH8, MyH13 and MyH4
3. There are three major MyHC isoforms in adult limb muscles:
 - a. MyHC1 is encoded by MyH7 and is expressed in type I slow fibers and the heart ventricles
 - b. MyHC 11a is encoded by MyH2 is expressed in fast contracting type 2A muscle fibers
 - c. MyHC IIX is encoded by MyH1 and expressed in fast type 2B muscle fibers
 - d. There are special MyHC isoforms expressed in specific muscles (extraocular muscles)
 - e. Specific MyHC isoforms are expressed in developing and regenerating muscles

The Structure of Actin

Actin is the major protein component of sarcomeric thin filaments. F-actin is the backbone of the thin filament that is a two-stranded helical structure.

TM is an actin-binding protein that forms a rod-shaped coiled-coil dimer from its two alpha-helical chains. It is encoded by four TM genes (TPM1, TPM2, TPM3 and TPM4). It is localized along the length of the actin filament. Transmission from Ca^{2+} dependent movement of the Tn complex, TM blocks or opens myosin-binding sites on actin. TM has three homologous isoforms in striated muscle: 1. α -TM (fast); 2. β -TM and 3. VTM (slow). TM is encoded by the TPM1 gene and is present in fast type 2 and cardiac muscle. β -TM is encoded by the TPM2 gene and is predominantly expressed in slow type 1 muscle and to a lesser extent in cardiac and fast muscle fibers. VTM is encoded by the TPM3 gene and is expressed in slow muscle fibers and the heart.

Tn is a complex of three component proteins: 1. troponin C (TnC), 2. troponin I (TnI) and 3. troponin T (TnT). These three proteins are regulators of muscle contraction:

1. TnC is the Ca^{2+} -binding subunit
2. TnI binds to actin and inhibits actomyosin ATPase
3. TnT links the Tn complex to TM

There are isoforms of TnI, TnC and TnT expressed by different genes. Nebulin is a giant filamentous protein that spans the length of the thin filament. It functions as a length-regulating template of the sarcomeric actin filament.

An Overview of Muscle Contraction

During rest, the myosin head is bound to an ATP molecule and is unable to access cross-bridge binding sites of actin. Muscle afferents release acetylcholine that initiates a postsynaptic action potential that propagates along the transverse Tubules to the sarcoplasmic reticulum that activates voltage gated L-type calcium channels of the plasma membrane. L-type calcium channels are in close proximity to the ryanodine receptors on the sarcoplasmic reticulum. The increased

calcium concentration mediated by L-type calcium channels activate ryanodine receptors that release calcium from the sarcoplasmic reticulum known as calcium-induced calcium release. Calcium ions bind with troponin-C molecules that are on tropomyosin that alters its structure and uncovers the cross-bridge binding sites on actin. In a muscle at rest, the myosin head is bound to an ATP molecule in a low energy configuration and is unable to bind with actin because the binding sites are blocked by tropomyosin. Myosin head actin site binding hydrolyzes ATP into adenosine diphosphate and an inorganic phosphate ion. The energy of the reaction changes the shape of the myosin head placing it into a high-energy configuration. As a consequence of binding with actin the myosin head ADP and the inorganic phosphate ion are released. Myosin remains attached to actin until it is bound by another ATP molecule that dissociates actin from its cross-bridge binding site. Hydrolysis of the ATP associated myosin reaches the sarcomere for another cycle of contraction.

The sarcoplasmic reticulum controls the concentration of calcium within muscle cells. Muscle contraction terminates when calcium ions are pumped back into the sarcoplasmic reticulum.

The structure of the sarcomere determines the length-tension curve. Sarcomere force output decreases when the muscle is stretched which decreases the number of cross-bridges that can be formed. During muscle contraction, actin filaments interact with each other. Sarcomere length affects both force and velocity. A longer sarcomere has more cross-bridges and more force but this is counteracted by a reduced range of shortening.

Dystrophinopathies

Duchenne Muscular Dystrophy (DMD)

General Characteristics

1. DMD is an X-linked recessive disorder with an estimated prevalence of 1 in 5,000 live births
2. The disease is a consequence of the loss of functional dystrophin protein that is essential in linking the muscle cytoskeleton to the extracellular matrix, but also has a role in signaling and regulating muscle response to oxidative stress

Clinical Manifestations

1. Most male children appear normal at birth although some demonstrate slightly hypertrophied and firm gastrocnemius muscles
2. Minimal or no delay in reaching the milestones of sitting or standing; a few patients are hypotonic and weak at birth
3. Between the ages of 2–6 it is clear that the child has a waddling gait, difficulty in running and jumping, may walk on his toes, has calf hypertrophy and suffers falls; Gower's sign is noted when the child rises to a standing position

4. Weakness is greater proximally and is more severe in the lower extremities; by 6–12 the upper extremity and axial muscles are affected
5. Most patients are wheelchair bound by age 12
6. The weakness is progressive and is accompanied by kyphoscoliosis and contractures
7. Reflexes diminish and by age 10, approximately 50% of patients have lost the biceps, triceps and quadriceps reflexes. The ankle jerks tend to be less affected
8. Postural changes are exacerbated by ankle and hip contractures
9. Respiratory muscles are affected and in addition to cardiac involvement cause death in the early 20's
10. Smooth muscle may be involved and a subset of patients develops gastroparesis and intestinal pseudo obstruction
11. The average IQ of patients is usually one standard deviation less than normal children

Neuropathology

1. Muscle biopsy:
 - a. Variability in fiber size
 - b. Increased endomysial and perimysial connective tissue
 - c. Some small rounded regenerating fibers
 - d. Central nuclei and fiber splitting
 - e. Scattered “glassy” and necrotic fibers
 - f. Increasing replacement of necrotic muscle tissue with fat and connective tissue
 - g. Cytotoxic T-lymphocytes and macrophages phagocytise necrotic muscle fibers; there is a variable degree of endomysial inflammation
 - h. A few non-necrotic fibers that express major histocompatibility antigen are attacked by cytotoxic T-cells
 - i. Reduced or absent dystrophin on the sarcolemma
 - j. Utrophin (normally restricted to the NMJ) is overexpressed
 - k. Approximately 0–3% of dystrophin may be demonstrated but is truncated

Laboratory Evaluation

1. The serum creatine kinase is elevated to 50–100 times normal at birth, peaks at around three years of age and declines at approximately a rate of 20% per year
 - a. Electrodiagnostic testing:
2. EMG:
 - a. Needle evaluation reveals increased insertional activity, positive sharp waves and fibrillation potentials
 - b. The amplitude of nonpolyphasic MuAP are decreased; an admixture with large amplitude polyphasic potentials. Short and long MuAPs occur in individual muscles
 - c. Early recruitment is noted
3. EKG:
 - a. EKG abnormalities are seen in approximately 90% of patients and include:
 - i. Sinustachycardia

- ii. Tall right precordial R waves
- iii. Deep narrow Q waves in this left precordial leads
4. ECHO:
 - a. Dilatation and hypokinesis of ventricular walls with a decreased ejection fraction
5. Genetic testing:
 - a. Exon skipping which utilizes antisense oligonucleotides to initiate alternating splicing in an attempt to restore the open reading frame of dystrophin mRNA is being tested
 - b. The product of this experimental approach is an altered, but functional dystrophin molecule
 - c. Genetic testing for mutations in the dystrophin gene on the X-chromosome for definitive diagnosis

Becker's Muscular Dystrophy (BMD)

General Characteristics

1. The incidence of Becker's muscular dystrophy is approximately five patients per 100,000 people
2. Approximately 10% of patients occur from spontaneous mutations

Clinical Manifestations

1. BMD has a slower rate of progression than DMD
2. A family history of X-linked recessive inheritance
3. Ambulation is maintained after 15 years of age
4. Limb girdle pattern of muscle weakness
5. Calf pseudohypertrophy
6. A subgroup of patients have predominant involvement of the quadriceps muscles
7. Spectrum of clinical phenotypes include:
 - a. Approximately 50% of patients cannot walk by the 4th decade
 - b. A subgroup of patients only demonstrate:
 - i. Myalgias
 - ii. Myoglobinuria
 - iii. Cardiomyopathy
 - iv. Asymptomatic hyperCKemia
8. Cardiac function is similar but not as severe as in DMD
9. A borderline or slightly impaired IQ has been demonstrated in some patients

Neuropathology

1. In general, the same pathology as that seen with DMD
2. Immunostaining demonstrates dystrophin in muscle membranes although the staining pattern is often reduced and can vary both between and within fibers. There is decreased quantity and size of dystrophin
3. The dystrophin gene is located on chromosome p21
 - a. It is composed of 2.4 megabases of genomic DNA
 - b. Includes 79 exons which code for the 14-kb transcript
 - c. Large deletions that range from several kilobases to over one million base pairs have been demonstrated in 2/3rd of patients
 - d. Approximately 5–10% of DMD mutations are point mutations that cause premature stop codons; duplications occur in 5% of patients

- e. Hot spots for mutations are in the gene center (80%) as those near the amino terminal are 20%
- f. Mutations in the translational reading frame lead to severe loss of dystrophin (DMD); inframe mutations cause translation of a semifunctional dystrophin of abnormal size or quantity that is seen in BMD or outlier patients

Laboratory Evaluation

1. Serum CK are greatly elevated in most patients; those patients only manifesting exertional myalgias may have minimally elevated CK levels
2. EMG:
 - a. Similar characteristics as DMD in weak muscles
3. Skeletal MRI:
 - a. Fatty infiltration of affected muscles

Female Carriers of BMD

General Characteristics

1. The daughters of men with BMD and the mothers of affected children who have a family history of DMD or BMD are obligate carriers of the mutated dystrophin gene on the X-chromosome
2. Other at risk females are the mothers and sisters of isolated patients
3. Males born to carrier females have a 50% chance of inheriting the defective X-chromosome; 50% of daughters will become carriers

Clinical Manifestations

1. Most women carriers are asymptomatic; a few develop proximal muscle weakness
2. If symptomatic, it is postulated that skewed inactivation of the normal X-chromosome has occurred (the Lyon hypothesis) and there is increased transcription by the mutated dystrophin gene
3. Rarely some carriers develop severe weakness

Neuropathology

1. Histologic features are similar to BMD (Less severe)
2. Immunostaining for dystrophin reveals its absence, reduced or mosaic pattern. Some patients may have normal staining

Laboratory Evaluation

1. Serum CK elevations can occur early in life but is an insensitive marker of carrier status. In general, elevated CK levels are demonstrated in less than 50% of carriers; a normal CK level does not rule out carrier status
2. Genetic testing is the most reliable method of determining carrier status. The detection of dystrophin gene mutations in affected male relatives determines the at-risk females. Sporadic mutations in a DMD affected patient may occur from a germline mosaicism. In this situation, the mutation

will involve only a percentage of the oocytes (germ cells). The recurrence rate in germline carriers is dependent on the number of affected oocytes has been estimated to be approximately 14%

3. An X-linked contiguous gene syndrome involving congenital adrenal hypoplasia, glycerol kinase deficiency, muscular Duchenne dystrophy and intellectual disability has been described

IL1RAPL (X-Linked Interleukin-1 Receptor Accessory Protein-Like 1)

General Characteristics

1. Contiguous gene syndromes are illnesses caused by deletions of adjacent genes
2. Glycerol kinase deficiency is caused by a partial deletion of p21
3. The gene order for the contiguous loci is pter-AHC-GKD-DMD-centromere
4. Microdeletions can span these contiguous genes that produces a different phenotype from that produced by mutations in the individual genes (DMD, GK, AHC)

Clinical Manifestations

1. Children with combined DMD and GKD suffer:
 - a. Muscular weakness
 - b. Episodic nausea, vomiting and stupor (GKD deficient)
 - c. If there are mutations in the DAX1 gene (causing congenital adrenal hypoplasia) there may be associated life threatening adrenal insufficiency. These mutations also cause:
 - i. Addisonian hyperpigmentation
 - ii. Hypogonadotropic hypogonadism/cryptorchidism
 - iii. Hyperkalemia
 - iv. Hyponatremia
 - v. Hypoglycemia

Neuropathology

1. Defects in glycerol kinase cause defects in glycolysis, gluconeogenesis and triglyceride metabolism
2. Defects in DAX1 (dosage-sensitive sex reversal AHC, X-chromosome gene 1)
 - a. A member of the nuclear hormone receptor superfamily
 - b. Regulates the transcription of genes that are essential for development of the adrenal glands
3. Mutations in the 3' portion of the dystrophin gene involve the glycerol kinase locus. Most of these patients have DMD although BMD can occur

Laboratory Evaluation

1. GKD causes elevation of serum triglycerides
2. AHC:
 - a. Decreased serum gonadotrophin level
 - b. Poor response of serum cortisol levels to ACTH stimulation
 - c. The patients with either DMD or BMD phenotypes:
 - i. Diagnosis of X-chromosome can be accomplished by DNA amplification through PCR

Outliers of DMD and BMD*General Characteristics*

1. This is a term for the clinical phenotype of children who manifest signs and symptoms between DMD and BMD

Clinical Manifestations

1. Are able to walk after the age of 12, but are wheelchair bound by age 15
2. In early childhood they can lift their head against gravity
3. They may develop a cardiomyopathy
4. Slight cognitive impairment in some patients

Neuropathology

1. Some dystrophin is present which is smaller in size

Laboratory Evaluation

1. Similar to BMD

LGMD (Limb Girdle Muscular Dystrophies)**Overview**

Limb girdle muscular dystrophies comprise Mendelian disorders that manifest progressive weakness and deterioration of proximal girdle muscles. Frequently these may be heart, respiratory and other muscle involvement. The clinical course and the phenotypic expression are variable. There are forms with a rapid onset and progression to very mild forms with minimal proximal weakness that allow for normal activities and life span. At present, there are 31 loci that have been characterized (8 autosomal dominant and 23 autosomal recessive). The use of next generation sequencing technology will accelerate the discovery of new LGMD genes.

Autosomal Dominant LGMD**Overview**

In general, the autosomal dominant forms of LGMD have an adult onset and are less severe than autosomal recessive forms. They account for less than 10% of LGMD patients. The phenotype may be present with mutations in genes that cause other disorders such as myotilin, lamin A/C or caveolin muscle disease.

LGMD1A*General Characteristics*

1. LGMD1A is caused by mutations in the myotilin (MYOT) gene located in chromosome 5q22.3-31.3. The DNA involved is a 2.2 kb and contains 10 exons

Clinical Manifestations

1. It may present in early or late adult life

2. Early involvement of scapular, humeral and pelvic muscles; rarely distal leg and arm weakness can be more profound than girdle proximal weakness
3. Affected muscles are atrophic
4. Contractures of the elbows and heel cords may occur early
5. Some patients develop nasal and dysarthric speech
6. Calf hypertrophy is rare in distinction from dystrophinopathies and sarcoglycanopathies
7. Patients may develop cardiomyopathy

Neuropathology

1. LGMD1A is caused by mutations in the myotilin gene; spontaneous mutations are common and therefore there may be a negative family history of muscle disease
2. Muscle biopsy:
 - a. Rimmed vacuoles with or without inclusions (nemaline rods)
3. Electron microscopy:
 - a. Prominent Z-line streaming
4. Histologic features may be similar to autosomal dominant hereditary inclusion body myopathy and myofibrillar myopathy

Laboratory Evaluation

1. Serum CK is normal or minimally elevated
2. EMG:
 - a. Myopathic pattern

LGMD1B*General Characteristics*

1. LGMD1B is caused by mutations in lamina A/C (LMNA) gene located in chromosome 1q11-21
2. There is overlap between LGMD1B and Emery-Dreifuss muscular dystrophy (EDMD); the severe forms of EDMD, those with childhood onset, have missense mutations while LGMD1B is associated with truncating mutations (haploin sufficiency)

Clinical Manifestations

1. The usual presentation is hip and shoulder girdle weakness; some patients may have a predilection for humeral peroneal muscle involvement
2. A severe cardiomyopathy is associated that causes:
 - a. Atrioventricular defects that have been associated with sudden death and may require a pacemaker
 - b. Dilated cardiomyopathy
3. Some patients may only have the cardiomyopathy

Neuropathology

1. Muscle biopsy:
 - a. Variation in fiber size
 - b. Increased endomysial connective tissue
 - c. Occasional rimmed vacuoles
2. Electron microscopy:

- a. Myonuclei demonstrate loss of peripheral heterochromatin
- b. Detachment of the heterochromatin from the nuclear envelope, altered interchromatic structure and a decreased number of nuclear pores
- 3. Immunocytochemistry:
 - a. Normal emerin and lamin A/C in the nuclear membrane
 - b. Normal dystrophin, sarcoglycan and emerin

Laboratory Evaluation

- 1. Serum CK may be normal or greatly elevated
- 2. EMG:
 - a. Myopathic pattern

LGMD1C

General Characteristics

- 1. LGMD1C is caused by mutations in the caveolin-3 gene in chromosome 3p25; spontaneous mutations occur

Clinical Manifestations

- 1. A variable phenotype
- 2. The illness may present in childhood or in adult life
- 3. Proximal girdle weakness
- 4. A subgroup has only exertional myalgias
- 5. Calf hypertrophy
- 6. Unusual signs and symptoms include:
 - a. Rippling muscle disease
 - b. Distal weakness of the anterior tibialis or gastrocnemius muscles
 - c. Asymptomatic hyperCKemia

Neuropathology

- 1. Muscle biopsy:
 - a. Non-specific myopathic features
 - b. Caveolin-3 is a muscle-specific protein and the major component of caveolae membrane in muscle cells; there may be reduced quantity of caveolin in the sarcolemma. The caveolins are essential in the formation of caveolar membranes. Caveolar membranes may function:
 - i. As scaffolding proteins that organize and concentrate caveolin interacting lipids and proteins
 - ii. A component of the organization of signaling complexes and interaction with sodium channels (possibly related to the demonstration of rippling muscles)
- 2. Normal quantities of dystrophin, sarcoglycan and merosin

Laboratory Evaluation

- 1. Serum CK is increased 3 to 25 times normal
- 2. EMG:
 - a. Rippling muscle disease
 - b. Myopathic pattern

LGMD1D

General Characteristics

- 1. LGMD1D has been mapped to chromosome 7q36.3; it is caused by a heterozygous missense mutation in the DNAJB6 gene (desmin). The DNAJ family is characterized by an amino acid stretch called the "J-domain"
- 2. The encoded protein functions as a molecular chaperone in a variety of cellular processes that include protein folding and oligomeric protein complex assembly
 - a. DNAJB6 heterozygous mutations are located in the GLY/Phe domain and cause decreased clearance of misfolded protein
- 3. The phenotype may overlap with myofibrillar myopathy

Clinical Manifestations

- 1. The lower limbs are more severely affected predominantly in the soleus, adductor magnus, semimembranosus, and biceps femoris. The rectus femoris gracilis and sartorius muscles as well as the muscles of the anterolateral lower leg are relatively spared
- 2. Onset is from 25–50 years of age
- 3. No cardiac or respiratory involvement
- 4. Patients may be able to walk throughout life
- 5. Symptoms in the upper limbs manifest late
- 6. DNAJB6 mutations may also cause a distally predominant myopathy

Neuropathology

- 1. The DNAJB6 protein is located in the Z-line and interacts with BAG3
- 2. Muscle biopsy:
 - a. Autophagic vacuoles and protein aggregation are demonstrated
 - b. The protein aggregates contain:
 - i. DNAJB6 protein with its ligands MLF1 and HSAP1
 - ii. Desmin
 - iii. AB-crystallin, myotilin and filamin C. These proteins also aggregate in myofibrillar myopathy

Laboratory Evaluation

- 1. Mildly elevated serum CK levels
- 2. EMG:
 - a. Myopathic pattern

LGMD1E

General Characteristics

- 1. Originally linked to chromosome 6q23; it may be considered a form of autosomal dominant desminopathy or myofibrillar myopathy
- 2. Also known as dilated cardiomyopathy type 1F (CMD1F)

Clinical Manifestations

- 1. Onset is the second or third decade
- 2. There may be a family history of sudden death
- 3. Progressive proximal muscle weakness
- 4. Dilated cardiomyopathy with conduction defects
- 5. A childhood onset family has been described

Neuropathology

1. Dystrophic changes
2. Perinuclear or subsarcolemmal granulofilamentous inclusions. Congophilic inclusions have been noted in some childhood patients

Laboratory Evaluation

1. Normal or slightly elevated serum CK levels
2. EMG:
 - a. Myopathic pattern

LGMD1F*General Characteristics*

1. LGMD1F is caused by a frame shift mutation in the transportin 3 (TNPO3) gene on chromosome 7q32.1-82.2. The frame-shifted TNPO3 protein is located around the nucleus

Clinical Manifestations

1. Patients with an early onset have a more severe phenotype with a rapid progressive course
2. Adult onset patients:
 - a. Slower progression of weakness
 - b. Lower limb muscles are atrophied with predominant involvement of the vastus lateralis and iliopsoas muscles
 - c. Other features include:
 - i. Dysphagia
 - ii. Arachnodactyly
 - iii. Respiratory insufficiency
 - iv. No cardiac involvement

Neuropathology

1. Muscle biopsy:
 - a. Increased fiber size variability, fiber atrophy, and acid phosphatase positive vacuoles
 - b. Immunofluorescence showed accumulation of myofibrils, ubiquitin-binding protein aggregates and autophagosomes
 - c. Electron microscopy:
 - i. Autophagosome vacuoles
 - ii. Disarray of myofibrillar components due to rod-like granular structures
 - iii. Findings are felt to demonstrate disarrangement of the cytoskeletal network

Laboratory Evaluation

1. Serum CK is 1–3x normal
2. EMG:
 - a. Myopathic pattern

LGMD1G*General Characteristics*

1. LGMD1G has been mapped in Brazilian and Uruguayan families to chromosome 4p21

2. The gene is HNRPDL that encodes the ANRPDL protein that is involved in RNA processing of proteins. The ribonucleoprotein is involved in mRNA biogenesis and metabolism

Clinical Manifestations

1. Late onset
2. Proximal limb girdle weakness
3. Progressive finger and toe flexion limitations

Neuropathology

1. Muscle biopsy (one patient)
 - a. Myopathic pattern
 - b. Rimmed vacuoles

LGMD1H*General Characteristics*

1. The LGMD1H locus has been mapped to chromosome 3p23-25.1 in a 4-generation Italian family

Clinical Manifestations

1. Onset is during the fourth-fifth decade with variable expressivity as to age and severity
2. Slowly progressive proximal weakness of both upper and lower extremities
3. An earlier onset is noted in a group of patients with calf hypertrophy

Neuropathology

1. Muscle biopsy:
 - a. Subsarcolemmal accumulation of mitochondria
 - b. Multiple mitochondrial DNA deletions

Laboratory Evaluation

1. A subgroup of patients had high CK and serum lactate levels
2. EMG:
 - a. Myopathic pattern

Autosomal Recessive LGMD**Overview**

The autosomal recessive limb girdle muscular dystrophies are much more common than the autosomal dominant forms. Their cumulative prevalence is 1:15,000 of the population. There are regional differences that depend on the degree of consanguinity and carrier distribution. The recessive genes in which there is loss of function mutations in both alleles cause LGMD2 (LGMD 2A-2H) and LGMD2L. Some other genes have mutations that are associated with LGMD or a complex disorder. Some variations in ordinary LGLMD gene mutations are associated with phenotypic forms of LGMD such as LGMD2A-2U.

LGMD2A*General Characteristics*

1. Has a worldwide distribution. It is the most common LGMD in those of eastern European, Spanish, and Italian ancestry and in Brazil
2. LGMD2A is caused by mutations in the Calpain 3 gene (CAPN3). The gene spans 53 kb of genomic sequence and is located at chromosome 15q15.2
3. There are heterozygotes (1:100) with varying CAPN3 mutations
4. Calpains are non-lysosomal cysteine proteases modulated by the concentration of calcium ions. They consist of a large and small subunit. One gene encodes the small subunit while there are several that encode the large subunit. Calpains target proteins and modify their function

Clinical Manifestations

1. The onset is variable and can occur from early childhood to mid-adult-life
2. Pelvic girdle muscles are usually affected initially and include:
 - a. Gluteus maximus
 - b. Thigh adductors
 - c. Hamstrings
 - d. Gluteus medius
 - e. Psoas (less severely)
3. Approximately 2–5 years after the onset of lower extremity weakness, the latissimus dorsi, serratus anterior, rhomboids, pectoralis major and the biceps brachii are affected
4. Muscles that are relatively spared include:
 - a. Deltoid and brachioradialis
 - b. Neck muscles
 - c. Distal leg muscles
 - d. Supra- and infraspinatus
 - e. Brachialis
 - f. Forearm muscles
5. Facial muscles extraocular and pharyngeal muscles are spared
6. Axial muscles may be weak and are associated with slight scoliosis
7. Abdominal muscles are weaker than paraspinal muscles
8. Contractures occur early at the elbows and calves (may be similar to EDMD)
9. Calf hypertrophy is rare, which is a strong differential point from dystrophinopathies, sarcoglycanopathies, and LGMD2I
10. Reflexes are markedly decreased or absent
11. Progression is variable among different kinships but is usually steadily progressive
12. Earlier onset correlates with faster progression of symptoms and signs
13. Approximately 50% of patients are unable to walk by age 20 although some are ambulatory in late life
14. Respiratory function is minimally involved, there is no cardiomyopathy and no cognitive loss

Neuropathology

1. Muscle biopsy:
 - a. Variation in fiber size with an increase of endomysial connective tissue
 - b. Lobulated muscle fibers on NADH histochemistry (not specific)
 - c. Western blot reveals reduced calpain-3 (20% of biopsies may be normal)
 - i. Secondary deficiency in calpain-3 may be demonstrated in dysferlinopathies and titinopathies
 - d. An eosinophilic infiltrate has been noted in some biopsies

Laboratory Evaluation

1. Serum CK levels may be 20x normal in children but decrease with disease progression
2. Children may demonstrate peripheral eosinophilia
3. EMG:
 - a. Myopathic pattern
4. Skeletal muscle MRI:
 - a. Predilection for severe involvement of posterior thigh muscles
 - b. Fat and connective tissue replaces normal muscles

Limb Girdle LGMD2B*General Characteristics*

1. LGMD2B is caused by missense or null alleles of the dysferlin gene (DYSF) located on chromosome 2p13.2
2. The protein is involved in calcium mediated sarcolemma resealing
3. LGMD2B is the second most frequent LGMD2 in many countries; accounting for 15–25% of patients
4. Mutations of the dysferlin gene cause:
 - a. Miyoshi myopathy
 - b. LGMD2B
 - c. Some distal myopathies with anterior tibial muscle weakness

Clinical Manifestations

1. Onset is in the late teens or early twenties although it has been reported to occur in middle age
2. Has a variable phenotype:
 - a. Proximal limb girdle weakness
 - b. Early involvement of the posterior calf muscles (Miyoshi myopathy)
 - c. Anterior tibial muscle weakness
 - d. Combinations of the various patterns
3. The most common initial pattern is the Miyoshi phenotype that demonstrates atrophy and weakness of the gastrocnemius and soleus muscles. The involvement of calf muscles may be asymmetric
4. Unusual presentation is with paraspinal involvement that causes rigid spine syndrome or a lax spine with hyperlordosis or kyphosis

5. A typical pattern of muscle weakness is gastrocnemius/soleus and subsequently gluteal and hamstring muscles and finally distal arm muscles. Less commonly proximal hip girdle then shoulder girdle weakens. A subgroup of patients has early anterior tibial muscle involvement. There may be atrophy and weakness of the gastrocnemius and soleus muscles in both the “limb girdle” and “anterior tibial” phenotypes. A helpful differential point in the dysferlinopathies is loss of the Achilles reflex early that is often the most preserved reflex in other LGMDs. In general, the progression of illness is slow but there is variability both intra- and interfamilially. A few patients have had a rapid onset and progression of the disease

Neuropathology

1. Muscle biopsy:
 - a. Variable fiber size, scattered necrotic and regenerating fibers and increased endomysial fibers
 - b. Immunostaining reveals decreased sarcolemmal dysferlin
 - c. Western blot on either muscle or white cells determine a primary dysferlin deficiency
 - d. There may be a mononuclear infiltrate in the endomysial connective tissue and around blood vessels. The inflammatory cells do not invade non-necrotic fibers that are in contrast to polymyositis
 - e. Deposition of membrane attack complexes on the sarcolemma of non-necrotic fibers that occurs in dysferlinopathies that demonstrate inflammation
 - f. Electron microscopy:
 - i. Reduplication of the basal lamina
 - ii. Disruption of the sarcolemma
 - iii. Invaginations or papillary defects of the muscle membrane
 - iv. Subsarcolemmal vesicles
 - v. Recent studies demonstrate:
 1. Dysferlin has an association with calcium (Ca^{2+}) signaling proteins in the transverse (T) tubular system
 2. It may also function besides its role in repair of the sarcolemma as a t-tubule protein that stabilizes stress-induced Ca^{2+} signaling

Laboratory Evaluation

1. Serum CK levels are often 25–200 times the normal value
2. Western blot analysis of white blood cells may demonstrate dysferlin
3. EMG:
 - a. Myopathic pattern

Sarcoglycan Mutations

Overview

The sarcoglycans are N-glycosylated transmembrane proteins that have a short intracellular domain, a single transmembrane region, and a large extracellular domain that contains a clus-

ter of cysteines. Mutations of the four genes that encode alpha, beta, gamma and delta sarcoglycans cause LGMD2D, 2E, 2C, and 2F, respectively. They form a tetrameric complex that is part of the dystrophin-associated proteins. The sarcoglycan complex (SGC) is a subcomplex within the dystrophin glycoprotein complex (DGC) that is essential for connecting the cytoskeleton to the extracellular matrix and protecting damage to the sarcolemma membrane from shearing forces generated with muscle contraction. In general, they have a childhood onset, a phenotype similar to the intermediate form of Duchenne/Becker dystrophinopathies and may involve both cardiac and respiratory musculature in some forms.

The sarcoglycanopathies are approximately 10% of the LGMDs. The frequency of occurrence is alpha sarcoglycan 6.6%, B sarcoglycan 3.1%, gamma sarcoglycan 1.5%, and delta J (SM) sarcoglycan at less than 1%.

LGMD2C, LGMD2D, LGMD2E and LGMD2F

General Characteristics

1. LGMD2C
 - a. Mutation in the gamma-sarcoglycan gene; located in chromosome 13q12.12
 - b. Common in the Maghreb and India
 - c. Patients may have absence of gamma-sarcoglycan with small amounts of the other non-mutated sarcoglycans
2. LGMD2D
 - a. Mutations of the alpha-sarcoglycan gene cause LGMD2D
 - b. The gene has 10 exons and is located at chromosome 17q21.33
 - c. The gene has a “dystroglycan type” cadherin-like domain
3. LGMD2E
 - a. The beta-sarcoglycan gene is located on chromosome 4q11
4. LGMD2F
 - a. The delta-sarcoglycan gene is the largest LGMD gene and one of the largest in the human genome. Mutations cause LGMD2F

Clinical Manifestations

1. In general, the clinical manifestations of these sarcoglycan mutations manifest the same clinical features as the intermediate dystrophinopathies:
 - a. Some children have an early onset with a severe phenotype that resembles DMD. A subgroup has a later onset with a slower progression suggestive of BMD
 - b. A proximal “limb-girdle” phenotype is seen early
 - c. Cardiomyopathy may occur

Neuropathology

1. Muscle biopsy:
 - a. There is normal dystrophin

2. The proteins of the sarcoglycan complex function as a unit. A mutation of any of the sarcoglycans destabilizes the complex and decreases the expression level of the other proteins
3. The clinical severity of the illness is determined by the type of mutation and the level of functional protein expression

LGMD2H

General Characteristics

1. LGMD2H and sarcotubular myopathy are allelic disorders
2. Mutations have been described in Manitoba Hutterite and Italian families
3. The disease is caused by mutations in the tripartite-motif containing gene 32 (TRIM32) located on chromosome 9q31-q33
4. The gene codes for a ubiquitous E3 ubiquitin ligase that localizes to cytoplasmic bodies

Clinical Manifestations

1. Onset is between 8–27 years of age
2. Slow progressive proximal muscle weakness and atrophy
3. Walking is preserved into the fourth decade
4. The D487N mutation in TRIM32 causes sarcotubular Myopathy

Neuropathology

1. Muscle biopsy:
 - a. Dystrophic features
 - b. Some type 2 fibers contain small vacuoles that are positive for sarcoplasmic reticulum associated ATPase. The vacuoles are adjacent to T-tubules and are membrane bound

Laboratory Evaluation

1. Serum CK levels are five to 50 times normal
2. EKG and ECHO changes have been described

LGMD2I

General Characteristics

1. LGMD2I is caused by mutations in the fukutin-related protein gene located in chromosome 19q13.32
2. Mutations in the FKRP gene also cause:
 - a. Congenital muscular dystrophy MDC1C which demonstrates:
 - i. Secondary laminin alpha 2 deficiency
 - ii. Abnormal glycosylation of alpha-dystroglycan
3. The mutation in the fukutin-related protein gene causes defects in the extracellular part of the dystrophin-utrophin associated complex
4. FKRP is located in rough endoplasmic reticulum
5. The mutation that causes CMGIC:
 - a. Produces mislocalization of the protein and alpha-dystroglycan is not processed

- b. The mutation that causes LGMD2I either affects the active site of the protein or its Golgi site localization
6. Fukutin (in chromosome 9q31) and FKRP:
 - a. Are involved in O-manno-sylglycan synthesis of alpha-dystroglycan. FKRP is involved in the initial step of its synthesis
 - b. It is possible that the mutant protein derived from FKRP gene mutation is retained in the ER (endoplasmic reticulum)

Clinical Manifestations

1. LGMD2I has a worldwide distribution and is the most common LGMD in England, Netherlands and Northern Europe
2. Onset may be in infancy (MDC1C to the fourth decade)
3. Patterns of weakness and the cause are variable
4. Some patients have predominant pelvic girdle weakness while others have proximal arm and neck flexor weakness
5. There may be calf hypertrophy
6. Fifty percent of patients develop a dilated cardiomyopathy and respiratory muscle weakness

Neuropathology

1. Muscle biopsy:
 - a. Non-specific dystrophic changes are noted
 - b. Immunostaining:
 - i. Normal dystrophin and sarcoglycan
 - ii. Decreased alpha-dystroglycan and rarely merosin

Laboratory Evaluation

1. In some younger patients the CK may be 10–30 times the normal value but may be normal in older patients
2. EMG:
 - a. Myopathic patterns

LGMD2J

General Characteristics

1. The titin gene (TTN) is very complex and encodes the largest protein of the human genome
2. It is located in chromosome 2q31 and has 363 exons. The protein encoded has 38, 138 amino acids and a length of 2 microns
3. Titin is a giant sarcomeric protein that comprises a continuous filament system in myoblasts. It spans from the sarcomere 2 disc to the M-band
4. Various mutations in TTN cause:
 - a. LGMD2J
 - i. A homozygous mutation in the TTN gene
 - ii. 11-6p mutation in the last titin exon causes tibial muscular dystrophy
 - iii. 2-bp insertion in exon 32.6 causes autosomal dominant dilated cardiomyopathy
 - b. Other titinopathies include:
 - i. Tibial muscular atrophy (TMD)

- ii. UDD myopathy
- iii. Early onset myopathy with fatal cardiomyopathy
- c. A French nonsense mutation in titin located in Mex6 has a milder phenotype than the usual FIN mutation that causes LGMD2J

Clinical Manifestations

1. Most patients manifest with autosomal dominant UDD type distal myopathy
2. Heterozygous mutations in the gene cause late adulthood weakness of the anterior tibial muscles
3. Some patients have a childhood onset of limb girdle weakness
4. A subgroup of patients have predominant biceps forearm and hand involvement
5. Patients have been described with weakness of the posterior calf compartment without anterior tibial muscle involvement
6. Truncating TTN mutations have been identified in 5 patients with the phenotype of congenital centronuclear myopathy

Neuropathology

1. Dependent on the specific phenotypic variant

Laboratory Evaluation

1. Dependent on the specific variant

LGMD2K

General Characteristic

1. LGMD2K is caused by mutations in the POMT1 gene
2. The gene is located in chromosome 9q34

Clinical Manifestations

1. Specific missense mutations in the POMT1 gene cause congenital muscular dystrophies
2. Mutations with residual enzyme activity cause the LGMD phenotype

Neuropathology

1. Decreased with congenital muscular dystrophies (Walker-Warburg phenotype); dystroglycan glycosylation

Laboratory Evaluation

1. Discussed with Walker-Warburg congenital muscular dystrophy (MDDGC1)

LGMD2L

General Characteristics

1. LGMD2L is caused by mutations in the anoctamin-5 gene (ANO5) located in chromosome 11p14.3
2. Anoctamins are calcium activated chloride channels
3. The disease is most frequent in Northern Europe and accounts for 10–20% of LGMD in this region

4. Penetrance is thought to be incomplete as females are less often affected than males
5. LGMD2L is allelic with:
 - a. AD gnathodiaphyseal dysplasia
 - b. AR distal Myopathy

Clinical Manifestations

1. Onset is in adulthood
2. There is asymmetric muscle involvement with prominent quadriceps atrophy
3. Pain occurs following exercise
4. There is no contracture, cardiomyopathy or respiratory involvement
5. Macular dystrophy has been described in two siblings
6. Patients usually maintain the ability to walk for several decades
7. Upper extremity strength is minimally affected (biceps brachii)
8. Miyoshi pattern of muscle weakness occurs in some patients
9. Recessive mutations in Anoctemin-5 have been found in three French Canadian LGMD2L families and one Finnish and one Dutch non-dysferlin family

Neuropathology

1. Muscle biopsy:
 - a. Myopathic pattern with variations in fiber size, central nuclei, fiber splitting, and degeneration of muscle fibers
 - b. An increase of intrafascicular and interfascicular connective tissue
 - c. In 2–40% of fibers regeneration was detected
 - d. 31% of biopsies demonstrated inflammatory changes
 - e. Approximately 10% of patients demonstrated rimmed vacuoles
2. Muscle wasting is predominant in quadriceps, hamstrings, and medial gastrocnemius muscles

Laboratory Evaluation

1. EMG:
 - a. Myopathic pattern
2. Serum CK levels are 300–10,000 normal values
3. Muscle MRI:
 - a. Asymmetric variable fatty replacement of the posterior compartment with involvement also of the adductor magnus. Semimembranosus and semitendinosus
 - b. Moderate to severe atrophy of the medial gastrocnemius and soleus muscles

LGMD2M

General Characteristics

1. LGMD2M is caused by mutations in the fukutin gene (FKTN) located at chromosome 9q31.2
2. One missense mutation causes the limb girdle phenotype; mutations in both alleles is associated with Walker-Warburg syndrome, muscle-eye-brain disease (MEB) or congenital muscular dystrophies

Clinical Manifestations

1. Onset is early childhood
2. Patients are hypotonic
3. Symmetric and diffuse muscle involvement that may be exacerbated by febrile illness
4. The CNS is not involved and patients have normal intelligence
5. They have spinal rigidity
6. Contractures
7. Respiratory muscle weakness

Neuropathology

1. Dystrophic features on muscle biopsy
2. WWS, FCMD, MEB disease have severe migrational and developmental alterations in the brain

Laboratory Evaluation

1. Serum CK levels are 5–20 times normal
2. EMG:
 - a. Myopathic pattern

LGMD2N*General Characteristics*

1. LGMD2N is caused by mutations in the POMT2 gene that is located on chromosome 14q24
2. POMT2 is a second O-mannosyltransferase that overlaps with POMT1 expression
3. O-mannosyltransferase 1 (POMT1) a glycosyltransferase, is complexed with POMT2, another O-mannosyltransferase, that catalyzes the first step in O-mannosylation. N-acetylglucosamine is transferred to the O-mannose of glycoproteins by the enzyme O-mannose B-1, 2-N-acetylglucosaminyl transferase (POMGnT1) in the post-translational glycosylation of α -dystroglycans
4. Glycosylation of α -dystroglycan is essential for its binding to merosin
5. In addition to a pivotal role in skeletal muscle, abnormal glycosylation of α -dystroglycan causes defects in neuronal migration that one found in Fukuyama type muscular dystrophy (FCMD), WWS, MEB disease, MDC1C and MDC1D

Clinical Manifestations

1. POMT2 mutations usually cause WWS or MEB disease
2. The phenotype of LGMD2N is that of LGMD without brain involvement

Neuropathology

1. Muscle biopsy
 - a. Dystrophic pattern

Laboratory Evaluation

1. High serum CK levels
2. Myopathic EMG pattern

LGMD2O*General Characteristics*

1. LGMD2O is caused by mutations in the POMGnT1 gene located on chromosome 1p32

Clinical Manifestations

1. The usual mutations in the POMGnT1 cause WWS or MEB disease
2. The milder mutations are associated with LGMD phenotype without brain involvement

Neuropathology

1. Muscle biopsy:
 - a. Dystrophic features

Laboratory Evaluation

1. High serum CK
 - a. EMG:
 - i. Myopathic pattern

LGMD2P*General Characteristics*

1. LGMD2P is caused by alterations of the dystroglycan gene (DAG1) which is located in chromosome 3p21.31
2. In general, the dystroglycanopathies are caused by mutations in the genes associated with the glycosylation of α -dystroglycan. In this instance the gene itself is mutated

Clinical Manifestations

1. Usual phenotype is that of LGMDs
2. A missense mutation in the gene has been reported to cause cognitive impairment
3. One patient with compound heterozygous missense mutations presented with hyperCKemia and mild proximal weakness

Neuropathology

1. Muscle biopsy:
 - a. Dystrophic pattern
2. Missense mutation of the dystroglycan gene

Laboratory Evaluation

1. High serum CK
2. EMG:
 - a. Dystrophic pattern

LGMD2Q*General Characteristics*

1. LGMD2Q is caused by mutations in the Plectin (PLEC1) gene located in chromosome of 8q243
2. LGMD2Q occurs from a homozygous 9-bp deletion that affects a muscle-specific transcript plectin 1. Other mutations in the gene cause epidermolysis bullosa simplex, EBS-muscular dystrophy with a myasthenic syndrome, EBS with pyloric atresia and EBS-Ogna3 type
3. Plectin is a widely expressed giant cytolinker protein

Clinical Manifestations

1. Early onset and slowly progressive phenotypic LGMD
2. Usually no cranial muscle involvement
3. An Iranian family with ptosis and ophthalmoparesis without skin lesions has been described

Neuropathology

1. Plectin's absence in skeletal muscle
 - a. Ultrastructural evaluation in patients with EBS (epidermolysis bullosa simplex)- MD(muscular dystrophy)
 - i. Widening and vacuolization adjacent to the sarcolemma
 - ii. Disorganization of Z-lines
 - iii. Disrupted filamentous bridge between Z-lines
 - b. Postulated that fiber specific plectin expression is associated with the desmin-cytoskeleton, Z-lines and myocyte membrane linkage
 - c. Plectin may function as:
 - i. Organizer of intermediate filament networks
 - ii. Scaffolding platforms for muscle signaling proteins
 - d. No skin pathology in LKGM2Q

Laboratory Evaluation

1. EMG:
 - a. Myopathic pattern
2. High serum CK levels

LGMD2R*General Characteristics*

1. LGMD2R is caused by mutations in the Desmin gene (DES) located in chromosome 2q35
2. It is a member of the intermediate filament (IF) protein gene family which is muscle-specific
3. Desmin is the major class III IF protein in striated and smooth muscle cells
4. Desmin mutations are associated with different phenotypes that include:
 - a. Limb-girdle muscular dystrophy
 - b. Scapuloperonal pattern
 - c. Generalized myopathy
5. A meta analysis of patients with 40 different heterozygous desmin mutations demonstrated:
 - a. Combined distal and proximal weakness in 67% of patients
 - b. Distal and proximal myopathies occurred in 27% of patients
 - c. Desmin mutations account for 2% of pure dilatative cardiomyopathy
 - d. Desminopathies have been described in diverse ethnic groups in both men and women

Clinical Manifestations

1. Onset in the teens or twenties
2. Progressive proximal muscle weakness and non-specific atrophy of both the upper and lower extremities
3. A-V conduction block but no cardiomyopathy

Neuropathology

1. Immunofluorescent staining and Western blot analysis show that the cytoskeletal network formation of mutant desmin is preserved. In the AD desminopathies ultrastructure evaluation reveals disruption of myofibrillar organization, formation of myofibrillar degradation products and dislocation or aggregation of membranous organelles

Laboratory Evaluation

1. CK most often is normal
2. EMG:
 - a. With desminopathy there is a myopathic pattern, but frequent positive sharp waves, fibrillation potentials and pseudomyotonic/myotonic discharges occur

LGMD2S*General Characteristics*

1. LGMD2S is caused by mutation in the transport protein particle complex 11 (TRAPPC11) gene in chromosome 4q35
2. Mutations have been identified in a consanguineous family and five Hutterite patients
3. A splice site mutation in the foie gras domain has been demonstrated of TRAPPC11 in the Hutterite patients

Clinical Manifestations

1. Infantile hyperkinetic movements
2. Ataxia
3. Cognitive impairment
4. Limb girdle proximal myopathy
5. Hip dysplasia and scoliosis
6. Muscle pain

Neuropathology

1. TRAPPC11 encodes a component of the multiprotein TRAPP complex that is involved in anterograde membrane transport from the endoplasmic reticulum to the ER-to-Golgi intermediate compartments
2. Mutations cause alteration in TRAPP complex composition, in Golgi morphology and cell trafficking. Golgi organelles are fragmented in some patients
3. Defects of the secretory pathway

Laboratory Evaluation

1. Elevated CK
2. EMG:
 - a. Myopathic pattern

LGMD2T*General Characteristics*

1. LGMD2T is caused by mutations in the GPP-mannose pyrophosphorylase B (GMPPB) gene that is located in chromosome 3p21
2. The LGMD phenotype has been reported in 3 patients
3. This mutation has been associated primarily with congenital muscular dystrophies due to decreased glycosylation of alpha-dystroglycan

Clinical Manifestation

1. LGMD phenotype of muscle weakness
2. Microcephaly
3. Cognitive impairment
4. Exercise intolerance

Neuropathology

1. Muscle biopsy:
 - a. Dystrophic pattern

Laboratory Evaluation

1. Increased serum CK
2. EMG:
 - a. Myopathic pattern

LGMD2U*General Characteristics*

1. LGMD2U is caused by a loss of function recessive mutations in the gene isoprenoid synthase (ISPD) in chromosome 7p21
2. The mutations disrupt dystroglycan mannosylation

Clinical Manifestations

1. Mutations in ISPD and the TMEM5 gene cause cobblestone lissencephaly:
 - a. A cortical dysplasia that is caused by neuroglial overmigration into the subarachnoid space
 - b. The extra cortical layer is either agyric or has multiple small gyri “cobblestone” in appearance
2. Walker-Warburg phenotype or “cobblestone lissencephaly” is caused by null alleles of ISPD
3. The allele causing LGMD is manifest by:
 - a. Progressive limb girdle weakness
 - b. The ability to walk is lost in the early teenage years similar to DMD
 - c. Muscle pseudohypertrophy that includes the tongue
 - d. There is cardiac and respiratory muscle involvement

Neuropathology

1. Reduction of functional glycosylation of α -dystroglycan
2. Muscle biopsy:
 - a. Dystrophic pattern

Laboratory Evaluation

1. EMG:
 - a. Myopathic pattern (in those with LGMD phenotype)
2. MRI:
 - a. Structural characteristics of WWS in those with this phenotype that includes:
 - i. Cobblestone lissencephaly
 - ii. Eye malformations
 - iii. Hypoplastic cerebellum and brainstem
 - iv. Hydrocephalus

LGMD2V*General Characteristics*

1. Mutations in the acid alphaglucohydrolase gene (GAA) that is located in chromosome 17q25.3
2. GAA mutations cause glycogen storage disease type 2

Clinical Manifestations

1. The infantile form of Pompe disease presents with massive accumulation of glycogen in muscle heart and liver
2. Infantile Pompe disease:
 - a. Floppy infant
 - b. Enlarged tongue
 - c. Heart failure
 - d. Respiratory involvement
3. Late onset Pompe disease:
 - a. May present from the second to the seventh decade
 - b. Progressive proximal muscle weakness, the lower limbs being more severely affected
 - c. Quantitative assessment of lingual strength reveals that it is diminished in late onset Pompe's disease

Neuropathology

1. Muscle biopsy:
 - a. Mild vacuolar myopathy of glycogen storage within skeletal and smooth muscle
 - b. Degenerating and regenerating fibers
2. Transmission electron microscopy:
 - a. Lysosomal glycogen storage within skeletal, cardiac and vascular smooth muscle cells

Laboratory Evaluation

1. Measurement of alphaglucohydrolase activity in cultured fibroblasts if the dried blood spot test demonstrates decreased enzyme activity
2. Genetic testing
3. EMG:
 - a. Increased insertional and spontaneous activity manifested by positive sharp waves, fibrillation potentials, complex repetitive discharge and occasional myotonic discharges
 - b. Myopathic MUAP
4. MRI/CT evaluation:
 - a. Early and severe involvement of the adductor magnus and semimembranosus muscles with later involvement of the long head of the biceps femoris, semitendinosis and anterior thigh muscles
5. EKG evaluation:
 - a. Left axis deviation
 - b. Short PR interval
 - c. Large QRS complexes
 - d. Inverted T-waves
 - e. ST depression
 - f. Wolff-Parkinson-White syndrome
6. ECHO cardiography:
 - a. Hypertrophic cardiomyopathy

LGMD2W*General Characteristics*

1. LGMD2W is caused by mutations in the LIM and senescent cell antigen-like-containing domain protein2 (LIMS2/PINCH2) gene located in chromosome 2q14
2. LIMS2 encodes a focal adhesion protein which interacts with ILK (integrin-linked kinase) which is essential for protein-protein interactions with the extracellular matrix

Clinical Manifestations

1. Childhood onset of LGMD
2. Macroglossy
3. Calf enlargement
4. In the third decade, patients developed decreased cardiac ejection fraction with global left ventricular dysfunction
5. Over time, patients develop severe quadriparesis with minimal facial involvement
6. A triangular tongue

Neuropathology

1. Unavailable

Laboratory Evaluation

1. Unavailable

Congenital Muscular Dystrophy**Overview**

Congenital muscular dystrophies are a clinically and genetically heterogeneous group of inherited muscle diseases whose major categories include:

1. Disorders associated with mutations in genes that encode structural proteins in the basal lamina, extracellular matrix or the sarcolemmal proteins that bind the basal lamina
2. Glycosylation defects of α -dystroglycan
3. Disorders due to selenoprotein 1 mutations

Muscle weakness occurs from birth to early infancy, the affected infants appearing “floppy” due to poor muscle tone and decreased spontaneous movements. Affected children often have delay or arrest of gross motor milestones in conjunction with joint or spinal rigidity. Generally, there is progressive weakness, joint contractures, spinal deformities, and respiratory compromise. Characteristic of the dystroglycanopathies are cognitive impairment, structural brain or eye abnormalities and seizures. The laminin alpha-2-deficient subtype has characteristic white matter abnormalities but no major cognitive defects.

In the autosomal recessive subtype, the siblings of an affected patient have a 25% chance of inheriting the disease, a 25% chance of being unaffected and not a carrier and a 50% chance of being an unaffected carrier.

In the autosomal dominant forms of the disease, 50% of the children of affected patients will inherit the disease. The

risk to siblings of a patient with an apparent de novo mutation is low, but not zero because a parent may harbor a germline mosaicism.

Congenital muscular dystrophy with genetic defects of structural proteins of the basal lamina or extracellular matrix.

Congenital Muscular Dystrophy with Laminin Merosin Deficiency*General Characteristics*

1. MDC1A is caused by mutations in the LAMA2 gene located in 6q21-6q22
2. Merosin is present in the basal lamina of myelinated nerves that is postulated to interfere with myelinogenesis and hypomyelinations in the central and peripheral nervous systems
3. Merosin binds to α -dystroglycan and A7BID integrin. Mutations may disrupt the dystrophin-glycoprotein complex
4. Mutations that alter the α -2 subchain of merosin markedly depress expression of the A7BID integrin with no or minimal effect on the dystroglycan or sarcoglycan complexes on the sarcolemma
5. Absent or decreased merosin occurs in approximately 30–40% of patients with congenital muscular dystrophy
6. There are patients with partial merosin deficiency as occurs with dystrophinopathies and sarcoglycanopathies
7. Patients may have secondary deficiency from glycosylation deficiency alterations that occur with the alpha-dystroglycanopathies

Clinical Manifestations

1. MDC1A infants have hypotonia, delayed, or arrested motor milestones and difficulty feeding
2. Neck, shoulder, and hip girdle muscles are progressively involved
3. Calf hypertrophy may be evident early in the clinical course
4. Respiratory insufficiency and orthopedic complications that include diffuse joint contractures and spinal rigidity become manifest
5. Nocturnal mechanical ventilation or continuous ventilation with tracheostomy may be required in early stages or in patients 10–15 years of age
6. Most children are unable to walk although rarely a patient can stand and walk with assistance
7. Children develop typical myopathic facies and in late disease a subset develop ophthalmoparesis
8. Some children develop a cardiomyopathy
9. Patients with partial merosin deficiency present in childhood with a DMD phenotype or in early adulthood with a BMD or LGMD phenotype
10. Intelligence is normal in most children
11. Approximately 20–30% of patients develop epilepsy
12. A small group of patients with MDC1A have epilepsy, occipital agyria and cognitive disability

Neuropathology

1. Muscle biopsy:
 - a. Variation in fiber size
 - b. Increased endomysial connective tissue
 - c. Decreased or absent merosin

Laboratory Evaluation

1. Serum CK levels are usually markedly elevated in merosin negative infants; partial merosin deficient patients have normal or minimally elevated levels
2. Brain MRI:
 - a. Diffuse white matter hyperintensities on T2-weighted sequences in children older than six years of age
 - b. Occipital polymicrogyria/agyria
 - c. Hypoplasia of the pons and/or cerebellum (rarely)
 - d. Patient with partial merosin deficiency may or may not demonstrate cerebral hypomyelination
3. Visual and somatosensory evoked potentials
 - a. Delayed latencies
4. EMG:
 - a. Slow nerve conduction velocities

Merosin-Positive Chronic MDC*General Characteristics*

1. Merosin-positive MDC are genetically heterogeneous
 - a. MDIB maps to chromosome 1Q42
2. Some partial merosin deficiency patients have mutations in glycosyltransferases that cause a secondary α -dystroglycanopathy
3. Mutations of the α -alpha 7' subunit of the integrin gene mapped to chromosome 12q13 have been described in three patients

Clinical Manifestations

1. α -alpha 7' subunit of integrin gene mutations:
 - a. Congenital onset of weakness and hypotonia
 - b. Delayed motor milestones
 - c. Cognitive deficits were demonstrated in one child
2. Secondary deficiency of alpha-laminin-2:
 - a. AR inheritance; mapped to chromosome 1q42
 - b. Deficiency of laminin alpha 2 in muscle
 - c. Clinical Manifestations from one family from the United Arab Emirates:
 - i. Generalized muscle hypertrophy
 - ii. Rigidity of the spine
 - iii. Contractures of the Achilles tendons
 - iv. Severe diaphragmatic muscle involvement that caused early respiratory failure
 - v. No cognitive deficit

Neuropathology

1. Muscle biopsy (α -alpha 7' subunit of integrin gene):
 - a. Mild variation of fiber size
2. Slight elevation of serum CK
3. MRI of the brain:
 - a. Normal

The Collagen VI-Deficient Congenital Muscular Dystrophies*General Characteristics*

1. The collagen deficient CMDs were formerly known as Ullrich and Bethlem Myopathy
2. Collagen V is an extracellular matrix protein composed of three chains. They are encoded by three genes COL6A1 and COL6A2 that map to chromosome 21q22.5 and COL6A3 that maps to chromosome 2q37
3. Recent evidence supports the classification that Ullrich CMD and Bethlem myopathy are a clinical continuum that can clinically be categorized as:
 - a. Early onset and severe:
 - i. Walking is not achieved
 - b. Moderate progressive:
 - i. The ability to walk is achieved and then lost
 - c. Mild:
 - i. The ability to walk is maintained into adulthood
4. The myopathies are caused by the genes that encode the three chains that compose collagen VI:
 - a. Homozygous premature termination codon-causing mutations in the triple helix domains cause the early severe phenotype (formerly Ullrich MCD); mutations in COL6A2 and COL6A3
 - b. Dominant de novo inframe exon skipping mutations and glycine missense mutations cause the moderate progressive phenotype (formerly Bethlem myopathy)
 - c. Mutations may be seen in COL6A1, COL6A2 and COL6A3 genes

Clinical Manifestations

1. Weakness at birth or early infancy
2. Contractions of the proximal joints
3. Hyperextensibility of the distal joints
4. Abnormal protuberant calcanei
5. Delayed motor milestones
6. No cognitive deficits

Neuropathology

1. Muscle biopsy:
 - a. Variation in muscle fiber size
 - b. Scattered degenerating and regenerating fibers
 - c. Increased endomysial connective tissue
 - d. Immunohistochemistry:
 - i. Collagen VI is present in the interstitial tissue but absent from the sarcolemma
2. Electron microscopy:
 - a. Interstitial collagen VI does not bind normally to the basal lamina surrounding muscle fibers

Laboratory Evaluation

1. Serum CK may be normal or only slightly elevated
2. EMG:
 - a. Myopathic pattern

Dystroglycanopathies

Overview

The dystroglycanopathies have a wide phenotypic spectrum that may present as LGMD or severe weakness with associated cognitive impairment, eye and brain involvement. Mutations in seven genes ISPD, POMT1, POMT2, POMGNT1, FKTN, FKRP and LARGE cause the alpha-dystroglycan-related muscular dystrophies. The proteins encoded by these genes are involved in both O-mannosylation and glycan chain synthesis and placement on alpha-dystroglycan. These proteins include:

1. Isoprenoid synthase that is involved in early O-mannosylation
2. The glycosyltransferases that are encoded by POMT1, POMT2, and POMGNT1
3. Proteins that are involved in a specific glycan epitope critical for laminin binding that are encoded by FKTN, FKRP and LARGE

Recent evidence supports the concept that mutations in any of these seven genes can cause wide phenotypic variations. Mutations in FKTN and FKRP may cause WWS to CMD, LGMD, elevated creatine kinase, and exercise intolerance with normal intelligence and no structural defects on MRI.

Glycosylation of alpha-dystroglycan is essential for normal binding to merosin as well as normal CNS neuronal migration.

Fukayama Congenital Muscular Dystrophy

General Characteristics

1. FCMD is caused by mutations in the fukutin gene which maps to chromosome 9q31
2. Fukutin is localized to the cis-golgi compartment and is involved in post-translational glycosylation of α -dystroglycan
3. Normal α -dystroglycan is essential as well for neuronal CNS migration and differentiation

Clinical Manifestations

1. FCMD is the most common congenital muscular dystrophy in Japan
2. Infants present with proximal greater than distal weakness and hypotonia
3. There are decreased fetal movements and an increased incidence of abortions of affected fetuses
4. Approximately 50% of children demonstrate pseudohypertrophy of calf muscles
5. Decreased muscle stretch reflexes are noted
6. Some children are born with arthrogryposis which continues to progress
7. 50% of children have seizures
8. Delayed motor and mental milestones
9. Severe cognitive impairment
10. The majority of patients can never stand or walk
11. Death occurs between 10–12 years of age from respiratory failure

Neuropathology

1. Muscle biopsy:
 - a. Dystrophic pattern
 - b. An occasional patient may demonstrate inflammatory features
 - c. Structural brain abnormalities include:
 - i. Microcephaly
 - ii. Lissencephaly
 - iii. Cortical dysplasia
 - iv. Pachygyria
 - v. Polymicrogyria
 - vi. Hydrocephalus

Laboratory Evaluation

1. The serum CK level is elevated 10–50 times normal
2. MRI/CT of the brain:
 - a. Structural abnormalities of migrational disorders
 - b. Hypomyelination
3. EEG:
 - a. Generalized slowing and epileptic activity

Walker-Warburg Syndrome

General Characteristics

1. Gene mutations in POMT1, POMT2 fukutin and FKRP all cause WWS
2. Mutations in POMT1 gene that maps to chromosome 9q31-11 cause 20% of patients with WWS
3. A homozygous loss of function frame shift mutation in the DA1 gene causes absence of both α -alpha and β -dystroglycan and also can cause the WWS

Clinical Manifestations

1. WWS is the most severe cerebro-ocular dysplasia and has a life expectancy of less than three years
2. Infants have generalized weakness, hypotonia and may be blind due to ocular malformations
3. The ocular manifestations of WWS syndrome include:
 - a. Unilateral or bilateral microcornea or microphthalmia
 - b. Hypoplastic or absent optic nerves
 - c. Coloboma with retinal involvement
 - d. Cataracts
 - e. Iris hypoplasia or malformation
 - f. Shallow anterior chamber angle with glaucoma
 - g. Retinal dysplasia or detachment
 - h. In patients with a less severe phenotype only high myopia or optic disc pallor may be manifest
 - i. Iridolental synechia
 - j. Seizure disorder
 - k. Mild LGMD phenotype with or without cognitive impairment

Neuropathology

1. Structural brain abnormalities include:
 - a. Cobblestone lissencephaly

- b. Polymicrogyria
 - c. Hydrocephalus
 - d. Hypomyelination of subcortical white matter
 - e. Hypoplasia of the brainstem and cerebellar vermis
 - f. Cerebellar cysts
2. White matter abnormalities may regress over time
 3. There may be partial absence of the corpus callosum and hypoplasia of the pyramidal tracts
 4. Immunostaining:
 - a. Reduced immunostaining for α -dystroglycan on the sarcolemmal membrane
 5. Muscle biopsy:
 - a. Dystrophic pattern

Laboratory Evaluation

1. Serum CK levels are elevated
2. Brain MRI:
 - a. Structural defects from migrational disorders (noted in neuropathology section)
 - b. Hydrocephalus
 - c. Negative in the LGMD phenotype
3. EEG:
 - a. Generalized slowing
 - b. Epileptic features

Muscle-Eye-Brain Disease (MEB)

General Characteristics

1. MEB is caused by mutations in the O-mannase-B1-2-N-acetylglucosaminyl transferase (POMGnT1) gene that map to chromosome 1p32-p34
2. The enzyme catalyzes the transfer of N-acetylglucosamine to O-mannos of glycoproteins
3. Mutations may also cause LGMD2M

Clinical Manifestations

1. MEB has brain and eye defects as well as muscle weakness, but the phenotype is less severe
2. Infants are weak and motor development is slow, many children can sit and stand and rarely walk
3. Severe cognitive impairment
4. The eye abnormalities include progressive myopia, glaucoma, and cataracts
5. In one series of patients 12 patients from 10 families demonstrated severe hypotonia at birth with varying stages of spasticity as the disease progressed

Neuropathology

1. Frontoparietal pachygyria
2. Polymicrogyria
3. Vermis hypoplasia
4. Cysts
5. Pontine hypoplasia
6. Abnormal midline structures

Laboratory Evaluation

1. Elevated serum CK levels

2. MRI of the brain:
 - a. Frontoparietal pachygyria
 - b. Hypoplasia of pons and cerebellum
 - c. Abnormal midline structures

MDC1C

General Characteristics

1. MD1C is caused by mutations that map to chromosome 19q13.3
2. The gene encodes the protein FKRP that localizes in the rough endoplasmic reticulum
3. The protein is involved in an early step in the synthesis of O-mannosylglycan of alpha-dystroglycan
4. Evidence supports the concept that FKRP is a Golgi resident type II transmembrane protein

Clinical Manifestations

1. FKRP-related myopathies are common in both English and Northern European populations
2. The age of onset is congenital to the fourth decade
3. Phenotypes include:
 - a. Similar to MDC1A
 - b. WWS/MEB
 - c. LGMD2I
 - d. Elevated creatine kinase
 - e. Exercise intolerance without cognitive impairment and a normal brain MRI
4. There is early involvement of cardiac and respiratory muscles
5. One of the mutations with the most phenotypic variability

Neuropathology

1. Reduction of alpha-dystroglycan glycosylation

Laboratory Evaluation

1. Serum CK levels are elevated at 10–75 times normal
2. Echocardiography:
 - a. May demonstrate a dilated cardiomyopathy
3. Pulmonary function tests:
 - a. Reduced forced vital capacity and inspiratory pressure generation
4. Brain MRI:
 - a. Microcephaly
 - b. Cerebellar atrophy and cysts
 - c. Hypoplasia of the vermis
 - d. Demyelinating white matter

MDC1D

General Characteristics

1. MDC1D is caused by mutation in the LARGE gene which maps to chromosome 22q12
2. It is a bifunctional glycosyltransferase with xylosyltransferase (Xyl-T) and glucuronyl transferase (GlcA-T) activity

3. LARGE-dependent modification of α -dystroglycan by the addition of the polysaccharide-repeating unit [3-xylase- α -1, 3-glucuronic acid –B1-Jn] is essential for α -dystroglycan to function as a receptor for proteins in the extracellular matrix
4. Patients with increased severity of disease have fewer LARGE glycan repeats

Clinical Manifestations

1. Global developmental delay
2. Generalized weakness
3. Cognitive impairment
4. Motor milestones are delayed but patients may be able to walk

Neuropathology

1. Experimental evidence demonstrates a correlation between LARGE glycan extension and its binding capacity (α -DG) to extracellular matrix ligands

Laboratory Evaluation

1. Serum CK levels are mild to moderately elevated
2. Variable MRI structural abnormalities

Congenital Muscular Dystrophy with Selenoprotein N1 Mutations (SEPN1)

Rigid Spine Syndrome

General Characteristics

1. SEPN1 has been mapped to chromosome 1p35-36 in some patients with rigid spine syndrome
2. SEPN1 mutations also cause:
 - a. Multiminicore myopathy
 - b. Congenital fiber-type disproportion myopathy
 - c. A desminopathy with Mallory body-like inclusions
3. Selenoprotein N1 is an endoplasmic reticulum glycoprotein:
 - a. The protein contains a selenocysteine (sec) residue at its active site
 - b. The selenocysteine is encoded by the UGA codon that signals translation termination. Mutations cause a stop signal rather than translation termination

Clinical Manifestations

1. The rigid spine phenotype:
 - a. Hypotonia in infancy
 - b. Proximal weakness
 - c. Delayed motor milestones
2. Progressive limitation of spine mobility
3. Thoracic spinal lordosis with S-shaped thoracic scoliosis
4. Progressive respiratory insufficiency that is exacerbated by diaphragmatic weakness
5. Early nocturnal hypoventilation prior to adulthood
6. Contractures of the knees and elbows (similar to EDMD and collagen V1-deficient MDC)
7. Medial thigh wasting in adults

Neuropathology

1. Muscle biopsy:
 - a. Variability of fiber size
 - b. Increased central nuclei
 - c. Type 1 fiber predominance
 - d. Moth eaten and lobulated fibers on NADH-TRstains
2. Multiple minicores (subset of patients)
3. Cytoplasmic Mallory bodies (subset of patients)
4. Increased desmin expression, sarcoplasmic and intranuclear tubulofilamentous inclusions (features of myofibrillar myopathy) in another subset of patients
5. Endomysial fibrosis occurs in axial musculature that includes paraspinous and rectus abdominus muscles

Laboratory Evaluation

1. Serum CK levels are normal to slightly elevated
2. EKG:
 - a. Conduction alterations
3. EMG:
 - a. Myopathic MUAPs
 - b. Rare abnormal spontaneous activity and normal insertional activity
4. MRI of muscle:
 - a. Selective involvement of the sartorius and major adductor muscles in the thigh

Differential Diagnosis of Congenital Muscular Dystrophies

MDC1A

1. Laminin-X-2 chain (Merosin deficiency in chromosome 6q22-23)
2. Neck, shoulder, hip girdle weakness
3. Contractions
4. Normal intelligence
5. Seizures
6. White matter changes on MRI

Merosin-Positive Classic MDC

1. Some partial merosin deficiencies map to chromosome 1q42
2. More benign

Ullrich Disease

1. Contractions of the proximal joints
2. Hyperextensive distal joints
3. Protruberant calcanei
4. Normal intelligence

Fukuyama Congenital Muscular Dystrophy

1. Allelic to LC and 2L; fukutin (chromosome 9q31-33)
2. Proximal > distal weakness at birth
3. Calf pseudohypertrophy (50%)
4. Arthrogryposis (some children)
5. Severe brain structural abnormalities (Microcephaly, dysplasia and lissencephaly)

Walker-Warburg Syndrome

1. DOnT1; (chromosome 9q3c)
2. Severe generalized weakness and hypotonia in infancy
3. Ocular malformation
4. Migrational and developmental abnormalities
5. Hypoplasia of the brain stem and veins
6. Seizures

Muscle-Eye-Brain Disease

1. POMGnT1 (chromosome 1p32)
2. MEB is less severe than WWS
3. Slow motor development
4. Eye abnormalities (glaucoma, cataracts)
5. Cognitive impairment
6. Hypoplasia of the vermis and pons; abnormalities of the midline structure

MDC1C

1. MDC1C is allelic to LGMD2I; mutation in the gene FKRP that maps to 19q13
2. Northern European ancestry
3. Onset is from infancy to the fourth decade
4. Weakness similar to MDC1A (rare WWS phenotype)
5. Early cardiac and respiratory muscle involvement

MDC1D

1. Mutation of the LARGE gene (chromosome 22q12-13.1)
2. Generalized weakness, cognitive impairment and developmental delay
3. Nystagmus (one patient)

Rigid Spine Syndrome

1. Selenoprotein (chromosome 1p35-36)
2. Rigid spine muscular dystrophy manifests in infancy
3. Hypotonia, proximal weakness and delayed milestones
4. Limited spine mobility with scoliosis and contracture of the knees and elbows
5. Respiratory involvement from rib cage restriction and diaphragm weakness
6. Similar phenotype is seen with:
 - a. EDMD
 - b. Ullrich CMD
 - c. Bethlem myopathy
 - d. Scapuloperoneal syndrome

LMNA-Related Congenital Muscular Dystrophy*General Characteristics*

1. LMNA-related congenital muscular dystrophy is caused by mutations in the LMNA gene that maps to chromosome 1q22
2. The gene encodes prelamin A and lamin C
3. There is a wide spectrum of disorders caused by mutations in the LAMA gene that cause:
 - a. Muscular dystrophy
 - b. Cardiomyopathy
 - c. Partial lipodystrophy
 - d. Progeria syndromes

4. The "laminopathies" primarily affect mesenchymal tissue (striated muscle, bone, and fibrous tissue) although recent work has identified functions for nuclear lamins in the CNS
5. The nuclear lamina is a meshwork of proteins underneath the nuclear envelope
6. L-CMD has been postulated to be an early onset variant of Emery-Dreifuss muscular dystrophy, but recent work has identified several de novo dominant mutations that have not been identified in the milder forms of ED muscular dystrophy

Clinical Manifestations

1. Presentation within the first six months of life with poor head control or progressive loss of head control after the ability to sit or walk has been acquired
2. Progressive weakness and hypotonia of axial-cervical muscles
3. Sequential proximal weakness of the upper limb associated with distal lower limb involvement
4. Sequentially there is head lag, thoracic and lumbar rigidity, lower limb contractures with talipes equinovarus; contractures do not occur in the upper extremities
5. Respiratory insufficiency occurs from restrictive lung disease due to muscle weakness. Severely affected patients may require mechanical ventilation prior to two years of age
6. Facial muscles are spared

Neuropathology

1. Lamins are the main proteins of the nuclear lamina and are the ancestors of intermediate filament proteins
2. They form complexes with intra-cellular proteins of the inner nuclear membrane as well as with transcriptional regulators, histones, and chromatin modifiers
3. The exact mechanism of how LMNA mutations cause muscular dystrophy has not been determined but studies in fibroblasts suggest that they cause a weakening of the structural support network in the nuclear envelope

Neuropathology

1. Muscle biopsy:
 - a. Dystrophic changes
 - b. Some children demonstrate non-specific myopathic changes

Laboratory Evaluation

1. Serum CK levels are mildly to moderately increased
2. EMG:
 - a. Myopathic pattern

Rare Congenital Muscular Dystrophies

Integrin Alpha-7 Deficiency

General Characteristics

1. Congenital muscular dystrophy with integrin-alpha-7 deficiency is caused by mutations in the ITGA7 gene that maps to chromosome 12q13.2
2. This CMD has been described in three patients with phenotypic variation
3. Integrin alpha-7/beta-1 is a receptor for the basal membrane proteins laminin-1 and laminin-2
4. It is expressed primarily in striated muscle and is thought to function in muscle maintenance through mechanical links between muscle fibers and the basal membrane. It may also have a role in muscle differentiation and migration during myogenesis

Clinical Manifestations

1. Neonatal hypotonia
2. Proximal muscle weakness and atrophy
3. Cognitive deficit
4. Scoliosis
5. Delayed motor milestones
6. Respiratory muscle weakness and dyspnea
7. One patient has been described with congenital hip dislocation and torticollis

Neuropathology

1. Muscle biopsy:
 - a. Dystrophic pattern
 - b. Absence of integrin alpha-7 staining

Laboratory Evaluation

1. EMG:
 - a. Myopathic pattern
2. CK is mild to moderately elevated

Integrin Alpha 9 Deficient Congenital Muscular Dystrophy

General Characteristics

1. Integrin alpha 9 deficient congenital muscular dystrophy is caused by mutations in the ITGA9 gene that map to chromosome 3p21.3
2. This CMD overlaps with collagen V1-deficient CMD
3. The mutation has been described in the French-Canadian population in Quebec
4. This integrin is a heterodimeric integral membrane glycoprotein composed of an alpha and beta chain
5. The encoded protein with its beta 1 chain forms an integrin that is a receptor for:
 - a. VCAM1
 - b. Cytotactin
 - c. Osteopontin
6. The integrin:
 - a. Participates with different ligands to effect cell adhesion in the extracellular matrix
 - b. Ligands include:
 - i. Extradomain A (EDA) fibronectin
 - ii. Tenascin C
 - iii. ADAMs
 - iv. Osteopontin
 - v. VEGF
 - vi. EMELINI

Clinical Manifestations

1. Presents with hypotonia
2. Distal hyperlaxity localized to metacarpal phalanges as opposed to the fingers
3. Scoliosis
4. Normal intelligence
5. Proximal weakness
6. Distinguishing features from COLA VI deficiency (that are seen in COLA VI deficiency) are:
 - a. Spine rigidity
 - b. High arched palate
 - c. Prominent calcaneus
7. Maintain the ability to walk into later decades
8. Some respiratory deficit

Neuropathology

1. Muscle biopsy:
 - a. Dystrophic changes

Laboratory Evaluation

1. CK is normal to mildly elevated
2. EMG:
 - a. Myopathic pattern

SYNE1-Related CMD

General Characteristics

1. SYNE1 (spectrum repeat-containing nuclear envelope protein 1) is causative
2. The gene encodes enaptin (nesprin-1) a nuclear envelope protein that is found in myocytes and synapses
3. The protein functions in the maintenance of nuclear organization and structural integrity by tethering the cell nucleus to the cytoskeleton. It interacts with the nuclear envelope and with F-actin in the cytoplasm
4. Mutations in the gene are associated with autosomal recessive spinocerebellar ataxia as well as CMD. Two unrelated probands with Emery-Dreifuss muscular dystrophy have been shown to have two different heterozygous mutations in the gene

Clinical Manifestations

1. Study of a Palestinian consanguineous family demonstrated:
 - a. Bilateral clubfoot

- b. Decreased fetal movements
- c. Delayed motor milestones
- d. Progressive motor decline after the first decade
- 2. Emery-Dreifuss phenotype in two unrelated probands
- 3. Two Japanese patients:
 - a. Adult onset of SCAR8
- 4. Nesprin-1 mutation:
 - a. Adducted thumbs
 - b. Severe cognitive deficits
 - c. Congenital muscular dystrophy phenotype
 - d. Cerebellar hypoplasia

Neuropathology

- 1. Muscle biopsy (Palestinian patients):
 - a. Variation in muscle fiber size
 - b. No necrosis or fibrosis
- 2. The basic pathology may be uncoupling of the nucleoskeleton and cytoskeleton by a dominant-negative effect

Laboratory Evaluation

- 1. Muscle biopsy:
 - a. Myopathic pattern
- 2. MRI:
 - a. Cerebellar hypoplasia in spinocerebellar ataxia AR phenotype and with some patients with nesprin-1 mutations

CHKB-Related Muscle Disease (Megaconial CMD)

General Characteristics

- 1. Congenital megaconial type muscular dystrophy has been mapped to chromosome 22q13.33
- 2. Choline kinase β -catalyzes the phosphorylation of choline by ATP with Mg^{2+} that produces phosphocholine and ADP. This is the initial step in the enzymatic pathway for choline in the synthesis of phosphatidylcholine
- 3. Japanese, Turkish, British, French and one African American patient have had detected mutations of the CHKB gene. All patients have a homogeneous phenotype

Clinical Manifestations

- 1. Early onset muscle wasting
- 2. Severe cognitive disability
- 3. Dilated cardiomyopathy and other cardiac defects in a subset of patients

Neuropathology

- 1. Muscle biopsy:
 - a. Reveals mitochondrial structural abnormalities:
 - i. Enlargement of the mitochondria at the muscle fiber periphery
 - ii. Depletion of mitochondria at the fiber center
 - iii. Most biopsies had no detectable choline kinase activity and decreased amounts of phosphatidylcholine

- iv. Mutations cause loss of function deficits
- v. Electron microscopy:
 - 1. Central mitochondria were subject to autophagy and had no cytochrome C oxidase

Laboratory Evaluation

- 1. EMG:
 - a. Myopathic pattern
- 2. Echocardiography:
 - a. Dilated cardiomyopathy

Congenital Muscular Dystrophy of Unknown Cause

Overview

These patients have a subtype of CMD that does not have a phenotypic resemblance to known subtype and their genes have not been identified.

- 1. CMD with cerebellar cysts, hypoplasia, or dysplasia
- 2. CMD with cognitive deficits and minimal ventriculomegaly or minor white matter abnormalities
- 3. CMD with normal intelligence and a normal MRI
- 4. CMD with cognitive deficits, microcephaly, cerebellar hypoplasia, feeding problems and severe myoclonic seizures

Differential Diagnosis of CMD by the Medical History

- 1. Central nervous system involvement manifest by delay in obtaining motor milestones and psychomotor development
- 2. Dystroglycanopathies
- 3. Laminin alpha-2 of life stages:
 - a. L-CMD
 - b. Hypotonic infants with laminin alpha-2 deficiency
- 4. A slowly progressive course with severe respiratory insufficiency in the first decade:
 - a. Non-ambulatory:
 - i. Laminin alpha-2 deficiency
 - ii. Collagen VI deficient CMD
 - iii. L-CMD
 - iv. Dystroglycanopathy
 - b. Ambulatory:
 - i. SEPN1-related CMD

Development of Skeletal Complications

- 1. Diffuse proximal and distal joint contractions, spinal stiffness, paravertebral muscle rigidity and scoliosis:
 - a. Collagen VI-deficient CMD (formerly Ullrich/Bethlem myopathy)
 - b. Laminin alpha-2 deficiency
 - c. Late-stage L-CMD
 - d. Dystroglycanopathies
- 2. Selective involvement of the spine:
 - a. SEPN1-related CMD
 - b. Early in the course of laminin alpha-2-deficiency in children that are able to walk
 - c. Collagen VI-deficient CMD

- d. L-CMD
- 3. Rapid developing course with loss of head control (dropped head syndrome):
 - a. L-CMD

Severe Cervicoaxial Hypotonia and Progressive Stiffness with Congenital Head Lag

- 1. SEPN1-CMD

Differential Diagnosis by Family History

- 1. Most congenital muscular dystrophies are autosomal recessive. In non-consanguine small nuclear families often, only one individual is affected
- 2. Collagen VI deficient CMD and all L-CMD patients have de novo autosomal dominant mutations and have only one occurrence in a family

Differential Diagnosis of CMD by the Physical Examination

- 1. Muscle pseudohypertrophy:
 - a. Dystroglycanopathies
- 2. Diffuse joint contractures:
 - a. Laminin alpha-2 deficiency
 - b. Collagen VI-deficient CMD
- 3. Distal hyperlaxity:
 - a. Collagen VI-deficient CMD
- 4. Skin manifestations that include hypertrophic scars or keloids:
 - a. Collagen VI-deficient CMD
- 5. Spinal stiffness without limb joint contractures:
 - a. SEPN1-related CMD
- 6. Axial hypotonia and weakness that precedes spinal rigidity:
 - a. Early laminin alpha-2 deficiency
 - b. L-CMD
 - c. Collagen VI-deficient CMD
- 7. Cardiac involvement:
 - a. L-CMD-arrhythmias
 - b. Cardiomyopathy with the dystroglycanopathies
 - c. Right heart failure from pulmonary hypertension in any CMD with respiratory insufficiency
- 8. Nocturnal hypoventilation or respiratory failure in a patient that can walk:
 - a. SEPN1-related CMD
 - b. Rarely collagen VI-deficient CMD
- 9. Location of the spinal deformity:
 - a. Thoracic kyphosis:
 - i. Collagen VI-deficient CMD
 - b. Thoracic lordosis:
 - i. Laminin alpha-2 deficiency
 - ii. SEPN1 related CMD
 - iii. L-CMD
 - iv. Dystroglycanopathies (late stage)
 - c. Lumbar hyperlordosis may occur in all subtypes

Differential Diagnosis of CMD by the Neurologic Examination

- 1. Occipital frontal circumference abnormalities:
 - a. Macrocephaly with laminin alpha-2 deficiency
 - b. Dystroglycanopathies may have micro- or macrocephaly
- 2. Muscle pseudohypertrophy of calves and tongue:
 - a. Dystroglycanopathies
- 3. Structural brain lesions and white matter demyelination:
 - a. Pyramidal signs and cognitive deficits:
 - i. Dystroglycanopathies
 - b. Seizure (routine treatment):
 - i. Laminin alpha-2 deficiency
 - c. Refractory seizures:
 - i. MEB (POMGNT1 subtype)
 - d. Cognitive deficits with behavioral disorder:
 - i. MEB (POMGNT1 subtype)

Differential Diagnosis of CMD by Serum CK Level

- 1. Normal merosin expression have normal or minimally elevated CK levels and include:
 - a. Collagen VI-deficient CMD
 - b. SEPN1-related CMD
 - c. L-CMD
- 2. Primary merosin deficiencies have high CK levels (>4x normal) and include:
 - a. Laminin alpha-2 deficiency
 - b. Dystroglycanopathies (secondary merosin deficiency)

Differential Diagnosis of CMD by Neuroimaging

- 1. Brain MRI:
 - a. Laminin alpha-2 deficiency:
 - i. Abnormal white matter is detected after six months of age
 - b. Dystroglycanopathies:
 - i. Brain stem hypoplasia
 - ii. Cerebellar cysts
 - iii. Hydrocephalus
 - iv. Migrational defects (lissencephaly or polymicrogyria)
- 2. Muscle imaging in spinal rigidity:
 - a. Specific patterns of muscle degeneration, normal merosin of skin or muscle and normal CK levels differentiate:
 - i. Collagen VI deficient CMD
 - ii. SEPN1-related CMD
 - iii. L-CMD

These parameters are normal in patients with spinal rigidity from:

- 1. RYR1 mutations
- 2. Acid maltase
- 3. DNM2

Differential Diagnosis of Rare Congenital Muscular Dystrophies

1. Congenital MD with Joint Hyperlaxity
2. Congenital MD with CNS atrophy and absent large myelinated peripheral nerve axons
3. Walker-Warburg syndromes
 - a. The gene disorders generally produce abnormal glycosylation of α -dystroglycan
 - b. The systems that are affected are:
 - i. Brain
 - ii. Muscle
 - iii. Eye
 - c. Mutations in:
 - i. POMT1 (chromosome 9q34)
 - ii. POMT2 (14q24)
 - iii. POMGnT1 (1p34)
 - iv. Fukutin (9q31)
 - v. FKR1 (19q13)
 - vi. LARGE (22q12)
 - vii. ISPD (7p21)
 - viii. GTDC3 (3p22)
 - ix. TMEM5 (12q14.2)
 - x. B3GALNT2 (1q42)
 - xi. SGK196 (8p11)
 - xii. B3GNT1 (11q13)
 - xiii. GMPPB (3p21)
4. Congenital muscular dystrophy with familial junctional epidermolysis bulbosa
5. Congenital muscular dystrophy with mitochondrial (mitochondrial) structural abnormalities
6. Congenital muscular dystrophy with early spine rigidity
7. Congenital muscular dystrophy with respiratory failure and muscular hypertrophy
8. Early-onset myopathy with areflexia, respiratory distress and dysphagia
9. Congenital muscular dystrophy with muscle hypertrophy
10. Scleroatonic muscular dystrophy (Ullrich)
11. Congenital muscular dystrophy with mental retardation and abnormal glycosylation
12. Congenital muscular dystrophy with adducted thumbs, ophthalmoplegia and mental retardation
13. Congenital muscular dystrophy and myasthenic syndrome

Regional Muscular Dystrophies

Facioscapulohumeral Muscular Dystrophy (FSHD)

General Characteristics

1. There are two forms of FSHD. FSHD1 and FSHD2 that have an identical phenotype but different genetic and epigenetic mechanisms
2. 95% of FSHD patients have autosomal dominant FSHD1

3. The incidence of FSHD is approximately 4 per million and its prevalence is 50 patients per million persons
4. There is a variable degree of clinical penetrance and a significant proportion of affected family members are unaware that they have the disease

Clinical Manifestations

1. The onset is usually between 3 and 44 years of age
2. The orbicularis oculi, zygomaticus, and orbicularis oris are affected early. Patients may be unable to close their eyes against resistance and may sleep with their eyes open
3. A horizontal smile, weak lip puckering, and a prominent Bell's phenomena appear early
4. Facial muscles are often asymmetrically involved
5. Extraocular muscles and those of mastication are typically unaffected
6. Other muscles affected early in the course of the illness are:
 - a. Serratus anterior
 - b. Rhomboids
 - c. Middle trapezius
 - d. Latissimus dorsi
- e. Weakness of these muscles cause:
 - i. Upward and lateral rotation of the scapular that includes scapular winging
 - ii. Weakness of the sternocostal head of the pectoralis major causes horizontal and downward displacement of the clavicles. Combined with internal rotation of the upper arms there is horizontal rather than the normal vertical position of the anterior axillary fold
 - iii. There is weakness and atrophy of the biceps brachii and relative sparing of forearm muscles. Wrist extensors are weaker than wrist flexors
 - iv. A subset of patients only manifests scapular winging or a limb-girdle muscle phenotype
 - v. There can be striking unilateral involvement of affected muscle groups
 - vi. The tibialis anterior is often the first muscle of the lower extremity to be affected and rarely a patient may present with foot drop. The gastrocnemius muscle is usually normal
 - vii. Pelvic muscle girdle involvement may occur which produces a hyperlordic posture and a waddling gait
 - viii. Approximately 20% of patients have severe difficulty walking and require a wheelchair
 - ix. Abdominal muscles are often involved which produces a positive Beever's sign (movement up or down of the umbilicus when the patient flexes the head against resistance); the direction of movement depends on relative weakness of the upper or lower rectus abdominal musculature
 - x. Sensation is intact to all modalities

- xi. Reflexes are diminished or absent, reflecting the degree of muscle wasting
- xii. A subgroup of patients suffers a late exacerbation of weakness in affected muscles that had been stable for a long time
- xiii. Severe progressive respiratory muscle weakness occurs in 1% of patients. This is exacerbated by kyphoscoliosis, severe extremity weakness, and wheelchair dependency
- xiv. Rare patients manifest cardiac signs and symptoms that include:
 - 1. Supra or ventricular arrhythmias
 - 2. Conduction defects
 - 3. May require a pacemaker

Clinical Variants

1. Infantile onset FSHD:
 - a. Severe weakness that is manifest in the first two years of life
 - b. Wheelchair dependence by 9 to 10 years of age
2. Coats' disease:
 - a. Facioscapulohumeral weakness
 - b. Sensorineural hearing loss
 - c. Retinal telangiectasia
3. Infants:
 - a. May present with severe facial diplegia similar to Moebius syndrome

Neuropathology

1. There are two forms of FSHD. FSHD1 and FSHD2 are phenotypically similar but have a different genetic and epigenetic basis. Autosomal dominant FSHD that accounts for 95% of patients is caused by chromatin relaxation induced by a macro-satellite repeat D4Z4 located on the 4q subtelomere; FSHD1 patients have 1–10 D4Z4 repeat units. The chromatin relaxation causes abnormal expression of Dux4, a retrogene that induces muscle apoptosis and inflammation, two allelic variants 4qA and 4QB have been identified that lie distal to the last D4Z4 unit. 4qA has a functional polyadenylation consensus site. Only D4Z4 contractions in this allele cause disease because this Dux4 transcript is polyadenylated and translated into a functional protein. FSHD2 is a digenic disease in which two mutations are required for the full expression of the disease phenotype. One mutation has no or only a slight deleterious effect. Chromatin relaxation of the D4Z4 locus is caused by heterozygous mutations in the SMCHD1 gene that encodes an essential protein for chromatin condensation. These patients have to have at least one 4qA allele to express functional Dux4 transcripts. There may be additive effects of FSHD1 and FSHD2 mutations as patients with D4 contraction and those with SMCHD1 mutations have a severe clinical phenotype. In summary, both forms of FSHD cause aberrant epigenetic regulation

of the chromosome 4q35 D4Z4 macrosatellite. Both variants of FSHD, type 1 caused by large deletions of heterochromatin and mutations in chromatin regulatory proteins (FSHD2) cause relaxation of epigenetic repression and thus increased expression of the pathogenic Dux4 gene that is encoded within the distal D4Z4 repeat. However, there are individuals with the genetic background that would predict FSHD who remain asymptomatic. Recent studies have demonstrated that the epigenetic status of the distal 4qA D4Z4 repeat correlates with the FSHD phenotype. Hypomethylation of DNA is seen in FSHD-affected patients, unaffected individuals have hypermethylation and non-manifesting individuals demonstrate intermediate methylation. The stability of epigenetic repression upstream of Dux4 expression is a major regulator of the disease

2. Muscle biopsy:
 - a. Variation in muscle fiber size
 - b. Atrophic and hypertrophic fibers
 - c. Scattered necrotic and regenerating fibers
 - d. Increased endomysial connective tissue
 - e. Increased internal nuclei
 - f. A subset of patients has an active mononuclear inflammatory infiltration of the endomysium that is similar to that of polymyositis
 - g. A membrane attack complex may be demonstrated on the sarcolemma of non-necrotic muscle fibers

Laboratory Evaluation

1. Serum CK levels may be normal or moderately elevated
2. EMG:
 - a. Myopathic pattern
3. Genetic testing:
 - a. 95% of patients have large deletions in the D4Z4 region (FSHD1)
 - b. FSHD2 has mutations in the SMCHD1 gene
 - c. False positives occur from non-pathologic contractions from the 4qB allele or complex 4q-10q rearrangements

Scapuloperoneal Muscular Dystrophy

General Characteristics

1. Scapuloperoneal muscular dystrophy has been linked to mutation in the desmin gene mapped to chromosome 2q35 (a form of MFM) and to chromosome 12 in another family. It is autosomally dominantly transmitted
2. Mutations in the DES gene also cause desmin related myopathy and a form of dilated cardiomyopathy

Clinical Manifestations

1. Peroneal weakness and atrophy accompanied by bilateral foot drop and talipes equinovarus is the usual initial presentation
2. Scapular weakness occurs within the first two decades of life. Weakness is frequently asymmetric

3. A subset of patients demonstrates hypertrophy of the extensor digitorum brevis
4. Ankle contractures may be severe
5. Scapular muscle weakness is similar to that of FSHD although humeral musculature is relatively spared. The peroneal muscles are more atrophic and weaker than those of FSHD
6. Facial weakness can occur but is much less severe than that of FSHD
7. The muscle weakness is slowly progressive
8. Dysphagia and gynecomastia have been reported from the kindred first reported by Kaeser. Phenotypic variability of the Kaeser large multigenerational kindred included:
 - a. Scapuloperoneal phenotype (12%)
 - b. LGMD phenotype (60%)
 - c. Distal phenotypes 18%
 - d. Cardiac and respiratory involvement occurred in 41% of affected patients

Neuropathology

1. Fiber size variation
2. Atrophic and hypertrophic fibers
3. Split fibers
4. Necrotic and regenerating fibers
5. Increased endomysial connective tissue
6. Some patients have inclusions that are similar to those seen in MFM

Laboratory Evaluation

1. Serum CK levels may be normal to moderately elevated:
 - a. EMG: Decreased CMAPs in severely affected muscles
 - b. Rare fibrillation potentials
 - c. Myopathic pattern
 - d. Normal motor and sensory nerve conduction velocities

X-Linked Emery-Dreifuss Muscular Dystrophy

General Characteristics

1. X-linked Emery-Dreifuss muscular dystrophy is caused by mutations in the (STA) gene that maps to chromosome Xq28 that encodes the protein emerin
2. Emerin is located on the inner nuclear membrane of cardiac, skeletal and smooth muscle
3. The carboxy terminal tail of emerin attaches it to the inner nuclear membrane and the remainder of the protein extends into the nucleoplasm
4. Emerin is a member of the nuclear LAP family which is composed of the intermediate filaments lamins A, B and C. They are attached to the nucleoplasmic surface of the inner nuclear membrane and bind laminin-associated proteins. These include LAP1, LAP2 and lamin B receptors that are localized to the inner nuclear membrane. The LAP2, lamin B receptors and lamins also attach to chromatin and augment its binding to the nuclear membrane
5. Mutations in emerin may disorganize the nuclear lamina and heterochromatin

Clinical Manifestations

1. Early contractures of the Achilles tendons, elbows, and posterior cervical musculature
2. Progressive muscle weakness that affects the humeroperoneal distribution early
3. Cardiomyopathy with conduction defects
4. The contractures are evident in early childhood or by teenage years
5. Patients may toe walk early due to heel cord contractures
6. Reduced spinal column mobility with difficulty flexing their neck and axial musculature
7. Contractures may precede weakness that is a differential point of EDMD and the other dystrophies with prominent contractures
8. Children are normal at birth
9. Pes cavus foot deformity
10. Patients can walk into the third decade
11. There is no calf hypertrophy
12. Muscle stretch reflexes are decreased or absent early in the course of the illness
13. Severe cardiac conduction defects are evident by the end of the second or the early third decade and include:
 - a. Syncope
 - b. First-degree A–V block
 - c. Complete heart block
 - d. Sudden death
14. Male carriers do not have weakness or contractures, but they may develop the arrhythmias

Neuropathology

1. Muscle biopsy:
 - a. Fiber size variation
 - b. Type 1 fiber atrophy
 - c. There may be type 4 or type 2-fiber predominance
 - d. Central nuclei
 - e. Muscle fiber splitting
 - f. Increased endomysial fibrosis
2. Immunostaining:
 - a. Absent emerin
 - b. Abnormal lamin A/C and lamin B2 or the nuclear membrane
3. Electron microscopy:
 - a. Focal absence of peripheral heterochromatin between the nuclear pores
 - b. Irregular and uniform thickening of the nuclear lamina and compaction of heterochromatin in areas of heterochromatin detachment

Laboratory Evaluation

1. Serum CK may be normal to moderately increased
2. EMG:
 - a. Myopathic MUAPs
 - b. Normal motor and sensory conduction velocities
3. EKG:
 - a. Sinus bradycardia

- b. Prolonged PR interval
- c. Conduction blocks
- d. Total permanent auricular paralysis

Autosomal Dominant EDMD2

General Characteristics

1. Autosomal dominant inheritance
2. EDMD2 and LGMD1B are allelic disorders
3. The disorders are caused by mutations in the lamin A/C gene that map to chromosome 1q11-23
4. Hereditary dilated cardiomyopathy is caused by mutations of the rod domain of the LMNA gene. Conduction alterations occur with or without skeletal muscle weakness
5. De-novo mutations may account for over 70% of cases
6. Alternative splicing of the laminin A/C RNA transcripts produces laminins A and C
7. LMNA genes encode the lamins that are intermediate filament proteins; these form a meshwork of filaments that underlie the inner nuclear membrane. The function of the lamin network has been postulated to include:
 - a. Interaction with signaling proteins and transcription factors
 - b. Structural integrity of the nuclear membrane
8. Additional genes that have been associated with EDMD are SYNE1 (spectrin repeat containing nuclear envelope protein1) and SYNE2
9. These genes encode nesprin-1 and -2 that are multi-isomeric, spectrin-repeat proteins that bind emerin and lamins that form a network that link the nucleoskeleton to the INM, the outer nuclear membrane, organelles in the membrane as well as the sarcomere and the actin cytoskeleton SYNE1 is mapped to chromosome 6q24 and SYNE2 is mapped to chromosome 14q22

Clinical Manifestations

1. Affected members have a later onset of the disease than patients with X-linked EDMD
2. The disease starts between ages 7 and 42
3. Similar manifestations as patients with X-linked EDMD

Neuropathology

1. Similar to X-linked EDMD

Laboratory Evaluation

1. Serum CK may be normal to moderately elevated
2. EMG:
 - a. Myopathic pattern
3. EKG:
 - a. Conduction defects

Autosomal Recessive EDMD3

General Characteristics

1. A rare disorder reported in only a few families
2. Mutations in the LMNA gene are causative

Clinical Manifestations

1. Early onset of extremity contractures and severe rigidity of the spine
2. Onset is within the first two years of life
3. No cardiac abnormalities
4. Children were unable to walk by age 8

Neuropathology

1. Muscle biopsy:
 - a. Dystrophic changes

Laboratory Evaluation

1. EMG:
 - a. Myopathic pattern
2. Moderate elevation of CK
3. EKG:
 - a. Normal

Bethlem Myopathy

General Characteristics

1. Bethlem myopathy is caused by heterogeneous autosomal dominant mutations of the genes COL6A1, COL6A2, and COL6A3
2. The alpha 1 and alpha 2 subunits of collagen VI map to chromosome 21q while the α -3 subunit is encoded from COL6A3 that is mapped to chromosome 2q37
3. Two patients have had a Bethlem myopathy phenotype who were compound heterozygotes for a truncating and missense mutation that mapped to the COL6A2 gene
4. As noted earlier Ullrich congenital muscular dystrophy can be caused by mutations in any of the genes that encode the subunits of collagen type VI. Mutations are both homozygous (recessive) and heterozygous (dominant)
5. Two additional phenotypes have recently been described:
 1. limb girdle; 2. autosomal recessive myosclerosis in one family with mutations in the COL6A2 gene
6. Glycine substitutions in the conserved Gly-s-y motif in the triple helical (TH) domain of collagen VI are the most common mutations in the collagen VI myopathies
7. In one large series intermediate phenotypes between the severe Ullrich and more benign Bethlem phenotype were the most common

Clinical Manifestations

1. Onset is at birth or during early childhood
2. Decreased fetal movements may be ascertained and infants may demonstrate generalized hypotonia
3. Delay of motor milestones
4. Weakness may only become evident in early adulthood
5. There is variability of phenotypic expression within affected families
6. Proximal greater than distal weakness, legs are more affected than the arms, and extensor musculature is more affected than flexor

7. There is mild neck and axial muscle involvement
8. No cranial muscle involvement
9. Contractures of the elbows and interphalangeal joints and plantar contractures of the ankles often occur prior to muscle weakness
10. Rarely there is proximal shoulder and hip girdle weakness without contractures
11. Muscle stretch reflexes are usually reduced
12. Recent study has demonstrated heart involvement in approximately 10% of patients
13. Respiratory insufficiency occurs with diaphragmatic muscle involvement
4. Restricted extensor neck muscle weakness may remain for years although there may be concurrent upper thoracic involvement demonstrated radiographically or by EMG
5. A positive family history has been documented in two kinships that only involved women
6. In addition to myasthenia gravis and ALS dropped head/bent spine has been described in:
 - a. Monophasic inflammatory myopathy restricted to paraspinal muscles
 - b. Dysferlinopathies
 - c. Myotonic dystrophy
 - d. Late onset nemaline myopathy

Neuropathology

1. A myopathic pattern on muscle biopsy with variation of fiber size, fiber splitting, central nuclei, and endomysial fibrosis
2. Histochemistry reveals lobulated moth-eaten type one fibers on NADH-TR staining

Laboratory Evaluation

1. Serum CK is normal or only mildly elevated
2. EKG (in approximately 10% of patients):
 - a. Atrial fibrillation
 - b. Intraventricular conduction delay
 - c. Supraventricular tachycardia
 - d. Right bundle branch block
 - e. Q waves in V1, V6 and AVL
3. Echocardiology:
 - a. Decreased ejection fraction
 - b. Ventricular dilatation
4. Respiratory function tests:
 - a. Reduced vital capacity
 - b. A subset of patients requires mechanical ventilation

Bent Spine/Dropped Head Syndrome

General Characteristics

1. There are several neuromuscular disorders primarily amyotrophic lateral sclerosis and myasthenia gravis that manifest severe neck extensor weakness
2. This syndrome pertains to patients with weakness that is restricted to the cervical, upper thoracic and paraspinal musculature

Clinical Manifestations

1. Onset begins after 60 years of age and progresses to head drop on the chest
2. This syndrome pertains to patients with weakness that is restricted to the cervical, upper thoracic and paraspinal musculature
3. There may be severe kyphoscoliosis from thoracic paraspinal muscle involvement that causes the bent spine posture when standing. The posture returns to normal on recumbency. This does not occur in patients with fixed spinal contracture

Neuropathology

1. Muscle biopsy (cervical paraspinal muscles):
 - a. Fiber size variability
 - b. Atrophic and hypertrophic fibers
 - c. Increased central nuclei
 - d. Fiber splitting
 - e. Some fibers have rimmed vacuoles
 - f. Rare endomysial inflammation
 - g. Moth eaten fibers
 - h. Increased endomysial connective tissue
 - i. Proximal muscle biopsies may be normal or demonstrate similar but less severe myopathic changes
 - j. Ragged red fibers and cytochrome C-oxidase negative fibers may be seen, but may be just age related

Laboratory Evaluation

1. Serum CK levels are normal to mildly elevated
2. Monoclonal gammopathy may occur in patients with the late-onset nemaline myopathy phenotype
3. EMG:
 - a. Short duration, small amplitude MUAPs with early recruitment are demonstrated in cervical and thoracic paraspinal muscles
 - b. Normal motor and sensory conduction velocities
 - c. Fibrillation potentials and positive sharp waves may be seen in cervical and thoracic paraspinal muscles
 - d. Extremity EMG is usually normal

Oculopharyngeal Muscular Dystrophy

General Characteristics

1. Oculopharyngeal muscular dystrophy is caused by expansion of GCG repeats within the poly (A) binding protein nuclear gene (PABPN1) that maps to chromosome 14q11.1. The gene expansion is usually 8–13 repeats
2. Homozygous expansions may present at an earlier age and have a more severe phenotype
3. Patients with a polymorphism (7GCG repeats) heterogeneous for the GCG repeat also have a more severe phenotype
4. A late onset phenotype may be seen in patients with homozygous polymorphisms (7GCG repeats)

5. The encoded protein is in dimeric and oligomeric states and is a component of the process of polyadenylation of mRNA. It is bound to the polyadenylated mRNA complex that is then transported through the nuclear pores into the cytoplasm. Once in the cytoplasm, the PABPN1 encoded protein detaches from the mRNA and is transported back to the nucleus. The mRNA undergoes translation
6. It is postulated that the GCG expansion repeats in the polyalanine domains of the PABPN1 gene encode a protein that is misfolded. The proteins are ubiquitinated, but do not undergo proteasomal degradation. The misfolded proteins accumulate as intranuclear tubulofilamentous inclusions that are seen on electron microscopy
7. There is a correlation with increased numbers of myonuclear inclusions and phenotypic severity

Clinical Manifestations

1. Onset is the fourth to sixth decade
2. Presenting feature is increasing ptosis
3. The ptosis is usually bilateral but is often asymmetric
4. Extraocular muscles are involved in approximately 50% of patients
5. There is no pupillary involvement and complaints of diplopia are rare
6. Approximately 25% of patients may have dysphagia as their initial presentation
7. Progressive weight loss and weakness supervenes
8. In a subset of patients there is facial weakness, masticatory and laryngeal involvement
9. The gag reflex may be impaired
10. The neck and proximal muscles may be slightly involved and there is a distal muscle variant
11. There is no sensory loss
12. Muscle stretch reflexes are decreased or absent

Neuropathology

1. Muscle biopsy:
 - a. Variation in fiber size
 - b. Degeneration and regenerating muscle fibers
 - c. Central nuclei
 - d. Increased endomysial connective tissue
 - e. Rimmed vacuoles are common
 - f. Electron microscopy:
 - i. In approximately 10% of patients, there are inclusions in the muscle fiber nuclei
 - ii. The inclusions are tubulofilamentous with an outer diameter of 8.5 μm , and inner diameter of 3 μm and may be 0.25 μm in length. They form tangles or palisades
 - iii. Inclusions may also occur in the cytoplasm that is also seen in inclusion body myositis, hereditary inclusion body myopathy and some distal myopathies
 - g. There are reports of abnormal mitochondrial number and structure in some patients

Oculopharyngeal Muscular Dystrophy Variants

1. Infantile or early childhood variant:
 - a. Ptosis, ophthalmoparesis, generalized muscle weakness with respiratory involvement
 - b. Distal myopathy variant:
 - i. Primarily in Japanese patients
 - ii. Earlier onset than classic OPMD
 - iii. Onset in the first decade of life

Laboratory Evaluation

1. Serum CK levels are normal or only slightly increased
2. Swallowing studies reveal impaired pharyngeal and esophageal function
3. EMG:
 - a. Myopathic pattern
4. The clinical variants are similar to classic OPMD

Distal Myopathy (Muscular Dystrophies)

Overview

Molecular genetic studies support the concept that distal myopathies are forms of muscular dystrophy. Some distal myopathies are allelic to specific types of LGMD as evidenced by tibial myopathy and LGMD2J (titin mutations) and Miyoshi myopathy and LGMD2B (dysferlin mutations). There is also an overlap of some distal myopathies with variants of hereditary inclusion body myopathy and myofibrillar myopathy. In general, they manifest distal progressive atrophy and weakness of the extremities and myopathic features on muscle biopsy. They form specific entities based on clinical features that include mode of inheritance, age of onset and muscle histology and CK levels.

In the distal myopathies: 1. there are no monogenetic classical phenotypes; 2. there are no phenotypes with different genotypes and 3. there are phenotypes with different genotypes that are usually associated with non-distal muscular clinical manifestations.

Welander Distal Myopathy

General Characteristics

1. Welander distal Myopathy is caused by heterozygous mutations in the TIA1 gene that map to chromosome 2p13
2. A subset of patients has a homozygous mutation that causes a more severe phenotype
3. The myopathy is seen predominately in Sweden and Finland
4. The myopathy is autosomal dominant

Clinical Manifestations

1. The onset is usually in the fifth decade; rare patients have been reported with onset prior to age 30
2. Weakness is initially in the wrist and finger extensors and slowly progresses to the ankle dorsiflexors to a greater degree than plantar flexors

3. In approximately 10% of patients, weakness is first noted in the distal lower extremities or simultaneously in the arms and legs
4. There is no sensory loss
5. Muscle stretch reflexes are lost in the biceps brachii and at the Achilles tendon

Neuropathology

1. Muscle biopsy:
 - a. Variability in fiber size
 - b. Increased central nuclei
 - c. Split fibers
 - d. Increased endomysial connective tissue in long standing patients
 - e. Rimmed vacuoles occur in scattered fibers
2. Electron microscopy:
 - a. 15–18 Nm cytoplasmic and nuclear filaments may be detected that are similar to those noted in IBM, ICBM and OPMD
 - b. Disruption of myofibrils
 - c. Z-disc derived material, similar to that seen in MFM, accumulates
 - d. Sural nerve biopsy:
 1. Moderate loss of small diameter myelinated fibers

Laboratory Evaluation

1. Serum CK is normal or only slightly increased
2. EMG:
 - a. Early recruitment of small amplitude, short duration MUAPs
 - b. Quantitative EMG supports a myopathy
 - c. Motor and sensory conduction velocities are normal
3. A subgroup of patients have decreased temperature and vibration threshold by QST (quantitative sensory testing)

Udd Distal Myopathy

General Characteristics

1. Tibial muscular dystrophy is caused by heterozygous mutation in the gene that encodes the muscle protein titin (TTN)
2. Homozygous mutation in the gene causes LGMD type 2J
3. The gene maps to chromosome 2q31-33
4. Dominant mutations cause a late onset distal myopathy while recessive mutations of the titin gene cause early onset LGMD2J

Clinical Manifestations

1. Usual presentation is after 35 years of age
2. Presenting sign is weakness of the anterior compartment of the leg with unilateral or bilateral foot drop
3. Weakness begins in the toe extensors and then gradually progresses to involve the anterior tibialis muscle
4. The proximal leg muscles and the intrinsic hand and wrist extensors are affected

5. Rare patterns of weakness include:
 - a. Arms are affected to a greater degree than the legs
 - b. The gastrocnemius and soleus muscles are affected and the anterior tibialis is spared
 - c. LGMD phenotype
6. Facial muscles are spared; rarely bulbar weakness occurs
7. Normal sensation
8. Decreased Achilles muscle stretch reflexes

Neuropathology

1. Muscle biopsy:
 - a. Non-specific myopathic pattern
2. The protein is attached to the Z-line in the M-line of the sarcomere
3. Functions include the structural attachment of the myosin filaments with the Z-disc; possible role in myofibrillar genesis

Laboratory Evaluation

1. The serum CK is normal or minimally increased
2. EMG:
 - a. Early recruitment of small amplitude, brief duration MUAP
 - b. Motor and sensory conduction velocities are normal
 - c. Fibrillation potentials and positive sharp waves occur

Markesbery-Griggs Distal Myopathy

General Characteristics

1. Markesbery-Griggs distal myopathy is caused by mutations in the ZASP gene that maps to chromosome 10q22.3-23.2
2. The core of skeletal muscle Z-discs is composed of actin filaments from neighboring sarcomeres that are cross-linked by α -actinin hemodimers
3. Z-disc-associated alternatively spliced, PDZ motif-containing protein ZASP/Cypher interacts through its PDZ domain with Z-disc proteins that include: 1. α -actin, 2. motilin and 3. other Z-disc proteins
4. ZASP protein directly interacts with skeletal muscle actin filament through its actin-binding domain between the modular PDZ and LIM domains
5. Alternative splicing of this region imparts each isoform with unique actin-binding domains
6. Expression of mutant ZASP causes Z-disc disruption and F-Actin accumulation that is similar to what is seen in myofibrillar myopathy

Clinical Manifestations

1. Late onset autosomal dominant distal myopathy that has initial anterior compartment lower extremity weakness and atrophy
2. A subset of patients develops proximal leg and wrist/finger extensory weakness
3. Cardiomyopathy is common

Neuropathology

1. Muscle biopsy:
 - a. Rimmed vacuoles
 - b. Disruption of skeletal muscle Z-discs and an accumulation of myofibrillar degradation products

Laboratory Evaluation

1. CK is mildly elevated
2. EMG:
 - a. An irritative myopathy

Nonaka Distal Myopathy (Autosomal Recessive Inclusion Body Myopathy)*General Characteristics*

1. Nonaka myopathy is an autosomal recessive illness caused by a mutation in the GNE gene that encodes UDP-N-acetylglucosamine-2-epimerase/N-acetylmannosamine kinase
2. The gene maps to chromosome 9p13.3
3. This myopathy is allelic to autosomal recessive inclusion body myopathy
4. The disease occurs worldwide but the largest ethnic cluster is in Jews that originated from Iran and the Middle East. A similar number patients has been reported from Japan

Clinical Manifestations

1. The initial presentation is usually weakness and atrophy of the anterior compartment of the lower extremities
2. Foot drop occurs in the second or third decade
3. The posterior leg compartments and the distal upper extremities are affected early in the disease course, but to a lesser degree
4. Proximal arm and leg muscles and the neck are gradually involved
5. The quadriceps muscle is relatively spared even to adulthood
6. There are no sensory signs or symptoms
7. Extraocular and bulbar muscles are spared
8. There is a report of a patient with asymmetric hand weakness presentation

Neuropathology

1. Muscle biopsy:
 - a. Non-specific myopathic changes
 - b. Rimmed vacuoles with acid phosphatase-positive autophagocytic activity have been described
2. Absent inflammatory cell infiltrate
3. Electron microscopy:
 - a. 15–18 nm intranuclear and cytoplasmic tubulofilaments that is similar to those seen in sporadic IBM

Laboratory Evaluation

1. The serum CK is normal or minimally elevated
2. EMG:

- a. Needle evaluation in weak muscles demonstrates positive sharp waves
- b. Early recruitment of low amplitude, brief duration MUAPs

Miyoshi Distal Myopathy*General Characteristics*

1. Miyoshi muscular dystrophy is caused by homozygous mutation in the dysferlin gene. It is an autosomal recessive illness and maps to chromosome 2p13.2
2. Mutation in the dysferlin gene also causes LGMD2B

Clinical Manifestations

1. The onset is in young adulthood
2. There is weakness of distal extremity musculature of both upper and lower extremities with sparing of the intrinsic hand muscles
3. There is predominant atrophy and weakness of the gastrocnemius and soleus muscles that later spreads to involve the thigh and gluteal muscles
4. Patients are unable to stand on their tiptoes, have difficulty climbing stairs and walking
5. Decreased ankle muscle stretch reflexes

Neuropathology

1. Muscle biopsy:
 - a. Dystrophic features
 - b. Active muscle fiber necrosis and regeneration
 - c. Disorganization of the intermyofibrillar network
 - d. Usually dysferlin reduction is less than 20% of normal

Laboratory Evaluation

1. Elevated serum CK (35–200x normal)
2. EMG:
 - a. Myopathic pattern

Laing Distal Myopathy*General Characteristics*

1. Laing distal myopathy has been linked to mutations in the slow beta cardiac MyHC1 gene or MyH7 gene that maps to chromosome 14q

Clinical Manifestations

1. The onset is in young adulthood with weakness and atrophy of the anterior compartment
2. When anterior compartment weakness occurs that includes the extensor hallucis longus muscle the “hanging toe” sign is prominent
3. The age of onset may be between 4 and 25 years
4. Over time, weakness spreads to the neck flexors and finger extensors. The shoulder and hip girdle musculature may be affected
5. Hand intrinsic muscles and finger flexors are spared
6. An infantile form has been reported

Neuropathology

1. MyHC is the most prominent myosin isoform of type 1 muscle fibers
2. Muscle biopsy:
 - a. Non-specific myopathic pattern
 - b. No rimmed vacuoles
 - c. Large deposits of myosin heavy chain (MyHC) are demonstrated in subsarcolemmal areas of type 1 muscle fibers

Laboratory Evaluation

1. The serum CK may be normal or only mildly elevated
2. EMG:
 - a. Small amplitude, brief duration polyphasic MUAPs are demonstrated in distal > proximal muscles
 - b. Occasional fibrillation potentials and positive sharp waves are seen
 - c. There are normal motor and sensory conduction velocities

Distal Myopathy with Vocal Cord Paralysis and Pharyngeal Weakness*General Characteristics*

1. Distal Myopathy with vocal cord paralysis has been mapped to chromosome 5q31

Clinical Manifestations

1. Autosomal dominant inheritance has been determined for this myopathy in one large kindred
2. The onset is in the fourth to sixth decade with weakness of the anterior tibial musculature
3. After limb muscle weakness, there is involvement of the vocal cords and pharyngeal musculature

Neuropathology

1. Non-specific myopathic pattern with rimmed vacuoles on muscle biopsy
2. Electron microscopy:
 - a. No filamentous inclusions

Laboratory Evaluation

1. EMG:
 - a. Mixed neuropathic and myopathic characteristics
 - b. In some patients, there is mild slowing of conduction velocities
2. The serum CK is normal or moderately increased

Myofibrillar Myopathy (MFM)*General Characteristics*

1. Myofibrillar Myopathy is a compilation of muscle diseases that are clinically and genetically heterogeneous but have electron microscopic evidence of myofibrillar disruption and desmin accumulation in muscle fibers

2. A major component of the pathogenesis of MFM is disruption of the Z-disc. Mutations have been described in proteins important to Z-disc function and integrity in:
 - a. Desmin
 - b. α - β crystalline
 - c. Myotilin
 - d. Filamin-C
 - e. ZASP (Z-band alternatively spliced PDX motif containing protein)
3. Most familial cases are autosomal dominant although autosomal recessive and possible X-linked heritability have been described
4. Desmin gene mutations which maps to chromosome 2q35 have been reported in autosomal dominant MFM and also in some sporadic patients
5. Other gene mutations that produce the MFM phenotype includes:
 - a. Mutations in the α - β -crystalline gene that map to chromosome 11q21-23 have been described in some autosomal dominant kinships
 - b. Myotilin gene mutations that map to chromosome 5q22-31. Some patients with late-onset MFM are allelic to LGMD1A
 - c. Missense mutations in the ZASP gene that maps to chromosome 10q22.3-10q23.1; dominant inheritance occurs in greater than 50% of these patients. The Markesbery-Griggs distal myopathy also is due to mutations in the ZASP gene
 - d. Mutations in the selenoprotein N-gene (SEPNI) that maps to chromosome 1p36 cause autosomal recessive MFM with Mallory-body-like inclusions. Mutations of SEPNI gene also cause congenital muscular dystrophy with the rigid spine phenotype and multi/minicore myopathy
 - e. Nonsense mutations in the filamin-L gene (FLNC) that maps to chromosome 7q32 cause autosomal-dominant phenotype of MFM
 - f. Antiapoptotic BCL2-associated athanogene 3 may cause the phenotype

Clinical Manifestations

1. MFM is associated with a wide spectrum of clinical phenotypes
2. Onset is usually between 25–45 years of age; patients have been described in infancy or late adulthood
3. Phenotypic variants include:
 - a. Facioscapulohumeral
 - b. Scapuloperoneal
 - c. Weakness can be predominately proximal, distal, or generalized
4. Facial and pharyngeal muscles may be affected in some patients
5. Spinal rigidity occurs in a subset of patients
6. Cardiomyopathy occurs with both arrhythmias and congestive heart failure that in severe patients requires heart transplantation or pacemaker insertion

7. There may be smooth muscle involvement with intestinal pseudo-obstruction
8. Respiratory insufficiency may develop
9. Patients with desminopathy, α - β -crystallinopathy or Bag3opathies have an infantile or juvenile disease onset
10. Cardiac involvement is common and may be the only manifestation of desminopathy

Specific Clinical Manifestations of Gene Defects That Cause Myofibrillar Myopathy

1. Alpha- β -crystallin gene
 - a. Autosomal dominant type that maps to chromosome 11q21-23
 - b. Infantile and adolescent form with rapid progression
2. Titan gene:
 - a. Mutations in the titin gene that maps to chromosome 2q31.2
 - b. Associated with hereditary early respiratory failure
3. Myotilin gene:
 - a. Missense mutation in the myotilin gene that maps to chromosome 5q22-31
 - b. The late onset patients that are allelic to LGMD1A manifest:
 - i. Late onset distal > proximal weakness
 - ii. Polyneuropathy
 - iii. Cardiopathy
4. ZASP gene:
 - a. Missense mutations in the ZASP gene that maps to chromosome 10q22.3-10q23.2 demonstrate:
 - i. Dominant inheritance
 - ii. Distal > proximal weakness
 - iii. Onset is between 44–73 years of age
 - iv. A subset has a cardiomyopathy with arrhythmias or a low ejection fraction
 - v. Some patients develop a polyneuropathy
5. Selenoprotein N gene (SEPN1):
 - a. Mapped to chromosome 1p36 were associated with autosomal recessive MFM
 - b. They manifested axial weakness, respiratory insufficiency
 - c. Rigidity of the spine
6. Filamin-C gene (FLNC):
 - a. Nonsense mutations in the FLNC gene that maps to chromosome 7q32 are associated with autosomal dominant subtype of MFM
 - b. Patients initially present with proximal muscle weakness that subsequently involve distal and respiratory muscles
7. BAG3 gene:
 - a. Myofibrillar Myopathy-6 is caused by heterozygous mutations in the BAG3 gene (BCL2-associated antho-gene 3) that map to chromosome 10q26.11
 - b. Patients manifest in the first decade:
 - i. Rapidly progressive generalized and proximal muscle weakness
 - ii. Respiratory insufficiency (restrictive)
 - iii. Cardiomyopathy
 - iv. Skeletal abnormalities due to muscle weakness cause scoliosis
 - v. Contractures of the Achilles tendon and limited spine mobility in a subgroup of patients

Neuropathology

1. Desmin is an intermediate filament protein that is prominent in skeletal, cardiac and smooth muscle
2. It functions to link the Z-band with the sarcolemma and the nucleus
3. The intermediate filament network stabilizes the muscle fiber and also is important during mitosis and muscle regeneration
4. Mutated desmin filaments form from insoluble aggregates that block the genesis of the normal filamentous network
5. Alpha- β -crystalline acts as a molecular chaperone and in concert with desmin functions in the construction of the intermediate filament network
6. Myotilin is a Z-disc protein and interacts with α -actinin, actin, and filamin-C in myofibrillar construction
7. ZASP protein is expressed in both skeletal and cardiac muscle binds to α -actinin at the Z-disc that cross-links thin filaments of adjacent sarcomeres
8. Selenoproteins play a role in the regulation of oxidative stress and calcium homeostasis. Filamin-C is involved in the formation of the Z-disc and binds actin. It also binds gamma- and L-sarcoglycan at the sarcolemmal membrane. It is postulated to play a role in signaling from the sarcolemma to the myofibril

Muscle Biopsy

1. Variability in fiber size
2. Central nuclei
3. Occasional type 1 fiber predominance
4. Hyaline structures and non-hyaline structures are the two major types of lesions seen on light and electron microscopy

Hyaline Structures on EM

1. Hyaline structures resemble cytoplasmic, spheroid or Mallory bodies
2. Non-hyaline structures:
 - a. Are dark green amorphous areas demonstrated with the Gomori Trichrome stain
 - b. On EM:
 - i. The non-hyaline lesions are foci of myofibrillar destruction. They consist of disrupted myofilaments, Z-disc-dense material, dense Z-disc structures and straining of the Z-disc. There may be an accumulation of 14–20 nm tubulofilaments that are typically seen in IBM

Immunohistochemistry

- Both hyaline and non-hyaline lesions contain desmin and other proteins
- Non-hyaline lesions contain desmin, dystrophin, gelsolin, N terminus of B-amyloid precursor protein and NCAM. They are depleted of actin, α -actinin, myosin, titin and nebulin
- Hyalin structures consist of:
 - Compacted and degraded components of thick and thin filaments
 - Histochemically hyaline structures react to: 1. actin; 2. α -actinin; 3. myosin; 4. dystrophin; 5. gelsolin; 6. filamin-C and 7. the N-terminus of amyloid-beta precursor protein
- Both granular and non-granular lesions react for alpha- β -crystalline, L-1 antichymotrypsin and ubiquitin
- Affected muscle fibers abnormally express cyclin-dependent kinase that includes CDC/CDK in the cytoplasm (CDC2, CDK2, CDK4 and CDK7)

Nerve and Intramuscular Nerve Biopsies Reveal (on a Subset of Patients)

- Enlarged axons with the accumulation of intermediate neurofilaments
- Axonal spheroids (subset of patients)

Laboratory Evaluation

- The serum CK may be normal to slightly elevated
- EMG:
 - Complex repetitive discharges, early recruitment of short-duration small amplitude polyphasic MUAPs
 - Increased insertional activity with positive sharp waves, pseudomyotonic potentials
 - Long duration, large amplitude MUAPs may be seen in chronic patients
 - Most often nerve conduction velocities are normal although in a subset of patients, low amplitude of motor and sensory potentials and decreased conduction velocities occur
- EKG:
 - Arrhythmias and conduction blocks
- Echocardiography:
 - Reveals a dilated or hypertrophic cardiomyopathy

Hereditary Inclusion Body Myopathy**General Characteristics**

- Autosomal recessive inclusion body myopathy is caused by homozygous or compound heterozygous mutations in the GNE gene that map to chromosome 9p13.3
- There are autosomal dominant forms of the disease and autosomal recessive forms; h-IBM is allelic to Nonaka distal myopathy
- Autosomal recessive h-IBM has been extensively studied in Iranian Jews but has been found in other Middle Eastern Jewish populations as well as non-Jews

GNE Involved in the Post-Translational Glycosylation of Proteins**Clinical Manifestations**

- H-IBM presents in the second or third decade with foot drop from anterior tibial muscle involvement
- There is slow, but progressive weakness of the iliopsoas, thigh adductors, and glutei
- The quadriceps is usually spared or is minimally affected in contrast to sporadic IBM
- The neck flexors and proximal arm muscles can be affected which may be asymmetric
- Severity of the weakness is variable and some patients are able to walk for decades while others are wheelchair bound early in the course of the illness
- Autosomal dominant h-IBM has predominantly limb girdle pattern of weakness although distal muscles may occasionally be affected. There is no involvement of extraocular or bulbar musculature. Deep tendon stretch reflexes are normal
- There may be a familial predisposition for s-IBM in some patients that is confused with hereditary forms
- Variant with cerebral hypomyelination:
 - Infantile onset
 - Autosomal recessive inheritance
 - Progressive proximal greater than distal weakness
 - The legs are affected to a greater degree than the arms
 - Normal intelligence
 - Leukoencephalopathy by MRI
 - EMG demonstrates mildly slow conduction velocities

Neuropathology

- Muscle biopsy:
 - Autosomal recessive and dominant h-IBM have similar biopsy findings as are noted with s-IBM except that there is no endomysial inflammation of non-necrotic muscle fibers
 - Fiber size variability
 - Central nuclei
 - Fiber splitting
 - Rimmed vacuoles:
 - The vacuoles are autophagic and are characterized by an accumulation of ubiquitinated and congophilic multiprotein aggregates that contain amyloid- β
 - Recent studies have demonstrated that there is no activation of the unfolded protein response in hereditary GNE inclusion body myopathy that occurs in the sporadic form of the disease
- Electron microscopy:
 - Abnormal accumulation of 15–18 nm tubulofilaments in the nuclei and cytoplasm of muscle fibers

Laboratory Evaluation

- Serum CK levels are normal or only minimally elevated
- EMG:

- a. Fibrillation potentials, positive sharp waves and complex repetitive discharges
- b. Small amplitude brief duration polyphasic MUAPs
- c. There may also be large amplitude, long duration polyphasic MUAP

Hereditary Inclusion Body Myopathy and Paget's Disease of Bone and Dementia (IBMPFDI)

1. IBM with Paget's disease and frontotemporal dementia (IBMPFDI) is caused by heterozygous mutations in the VCP gene that map to chromosome 9p13.3
2. It is an autosomal dominant disorder with incomplete penetrance
3. Nineteen missense mutations have been identified
4. It is allelic with:
 - a. Familial ALS
 - b. Familial spastic paraparesis
 - c. Distal myopathy and dementia
 - d. CMT2

Clinical Manifestations

1. A high degree of intrafamilial variability
2. Onset is in the 3rd and 4th decades
3. Its major features are:
 - a. Muscle weakness (90%)
 - b. Osteolytic bone lesions similar to those of Paget's disease (51%)
 - c. Frontotemporal dementia (32%)
4. Onset may be variable manifesting as back pain, weakness, or dementia
5. The mean age of onset is 43 years of age (3–66 years)
6. Adult onset of proximal and distal muscle weakness that may be variable in degree and asymmetric in pattern within families
7. Respiratory muscles are involved (vital capacity 29–70% of normal) that progress and may cause respiratory insufficiency
8. Scapular winging from supra- and infraspinatus weakness
9. Rarely face and tongue involvement
10. Posterior neck muscle weakness with dropped head (rare)
11. Camptocormia
12. Slow progression over 1 to 2 decades with severe weakness and death in the 40th–60th years
13. Bone disease:
 - a. Paget's disease occurs in 43–49% of patients
 - b. The spine is the most common location but lesions occur in the hip, skull, pelvis
14. Pain in involved bony locations
15. Onset at a mean age of 42 (29–61 years)
16. Lumbar lordosis
17. Dementia:
 - a. Occurs in 30%–37% of patients
 - b. Onset is 52–54 years (mean; range 39–62 years)

18. Cardiomyopathy:
 - a. Occurs occasionally late in the course of the disease
 - b. Congestive heart failure from dilated cardiomyopathy
19. Rarely there are associated:
 - a. Liver disease
 - b. Cataracts
 - c. Sensorimotor polyneuropathy

Neuropathology

1. Muscle biopsy:
 - a. Non-specific myopathic pattern
 - b. Increased endomysial connective tissue
 - c. Rimmed vacuoles
 - d. VCP staining inclusions in the sarcoplasm and myonuclei
 - e. Electron microscopy:
 - i. Tubulofilamentous inclusions
2. Brain pathology:
 - a. Cortical atrophy
 - b. Widespread cortical and subcortical neuronal loss
 - c. Ubiquitin and TDP-43 positive intranuclear inclusions
3. VCP belongs to the AAA-ATPase super family and its functions include:
 - a. Cell-cycle control
 - b. Membrane fusion
 - c. Ubiquitin proteasome degradation pathways
4. The mutated protein causes:
 - a. Increased levels of ubiquitinated cell proteins
 - b. Sensitization to proteasome stress
 - c. Decreases degradation of proteins by the endoplasmic reticulum associated degradation (ERAD) mechanisms
 - d. Increase the formation of aggregates
 - e. Upregulation of autophagy related proteins

Laboratory Evaluation

1. Serum CK levels are normal in 80% of patients or mildly increased
2. Serum alkaline phosphatase is elevated with Paget's disease
3. EMG:
 - a. Low amplitude, polyphasic, short duration MUAPs
 - b. Fibrillations and positive sharp waves
 - c. Chronic denervation changes are seen in long standing patients
4. Muscle MRI:
 - a. Widespread degenerative changes that include axial musculature
5. Skeletal x-ray:
 - a. Compatible with Paget's disease of bone
6. Echocardiography:
 - a. Dilated cardiomyopathy late in the course of the illness
7. Variant syndromes:
 - a. Familial ALS
 - b. Distal myopathy
 - c. Progressive spastic paraparesis
 - d. CMT2 sensory motor neuropathy

Myopathy with Paget's Disease of Bone with or Without Cognitive Deficit or Motor Neuron Disease (IBMPDID2)

General Characteristics

1. IBMPDID2 is caused by mutations in the heterogeneous nuclear ribonucleoprotein A2/B1 (HNRNPA2B1) gene that maps to chromosome 7p15.2 which is autosomal dominant
2. The disease has been described from 1 US family with 5 patients
3. The HNRNPA2 protein is the most abundant isoform
4. The mutation is missense and is located in the prion-like domain of the genes

Clinical Manifestations

1. Onset is in the 3rd to 5th decades
2. Weakness is distal in the lower extremities and affects the ankles and toes
3. Proximal muscles are affected in the upper extremity that causes scapular winging from supra and infraspinatii weakness
4. A slowly progressive process with atrophy of the affected muscles
5. 100% of patients have Paget's disease of bone that may be severe, widespread and affects long bones
6. Cognitive deficiency occurs in 40% of patients
7. Motor neuron disease occurs in approximately 40% of patients

Neuropathology

1. Muscle biopsy:
 - a. Variation in fiber size
 - b. Central nuclei
 - c. Increased endomysial connection tissue
 - d. Rimmed vacuoles
 - e. TDP-43 inclusions
 - f. The protein is localized to the nucleus to a greater degree than the cytoplasm and binds RNA
 - g. In the cytoplasm there are mRNA granules that contain untranslated mRNAs
 - h. The mutated protein assembles into self-seeding fibrils that are recruited to stress granules

Laboratory Evaluation

1. Serum CK may be normal to high
2. Serum alkaline phosphatase is high
3. EMG:
 - a. Myopathic pattern
4. Skeletal x-rays:
 - a. Paget's disease of bone

Myopathy with Paget's Disease of Bone (IBMPFD3)

General Characteristics

1. Mutation in the heterogeneous nuclear ribonucleoprotein A1 (HNRNPA1) gene that maps to chromosome 12q13.13 dominant

2. The mutation is missense and is located in the prion-like domain
3. Protein functions are:
 - a. RNA-binding
 - b. Packaging of pre-mRNA into hnRNP particles
 - c. Essential in the mechanism of assembly of ribonucleo-protein granules

Clinical Manifestations

1. Onset in childhood with clumsiness
2. Myopathy occurs in 100% of patients:
 - a. Initial weakness is in the iliopsoas muscle
 - b. Foot dorsiflexors are subsequently involved
 - c. Subsequent spread to the abdominal wall
 - d. Arms are usually spared except for slight scapular winging
 - e. The weakness is progressive and most patients are wheelchair bound in the 5th or 6th decade
3. Paget's disease (50% of patients)
4. Normal cognition

Neuropathology

1. Muscle biopsy:
 - a. Variation on fiber size
 - b. Central nuclei
 - c. Rimmed vacuoles
 - d. TDP-43 inclusions
2. Involved in the transport of poly (A) mRNA from the nucleus to the cytoplasm. The disease-mutated protein exacerbates the abnormal protein into self-seeding fibrils

Laboratory Evaluation

1. Serum CK normal to mildly elevated
2. Alkaline phosphatase is normal to 8x normal
3. EMG:
 - a. Myopathic

HNRNPA1 Variant Syndrome

1. ALS 20

Hereditary IBM Type 3

General Characteristics

1. h-IBM type 3 is caused by heterozygous, compound heterozygous or homozygous mutations in myosin heavy chain II a (MYHC2A) gene or the MYH2 gene that maps to chromosome 17p13
2. Autosomal dominant and autosomal recessive inheritance has been reported
3. The protein encodes MyHC11a that is expressed in type 2A muscle fibers

Clinical Manifestations (AD Form)

1. Congenital joint contractures that disappeared during early childhood

2. Proximal muscle weakness
3. External ophthalmoplegia
4. Adults have progressive muscle weakness that starts between 30 to 50 years of age
5. Patients may not progress during childhood
6. Autosomal recessive form:
 - a. Onset in childhood
 - b. Reported from 16 patients from 8 Arab families
 - c. Mild proximal limb girdle weakness
 - d. Neck flexor weakness
 - e. Facial weakness
 - f. Variable extraocular muscle involvement
 - g. Slowly progressive course
 - h. Patients develop myopathic facies, nasal voice
 - i. High arched palate
 - j. Some patients develop scapular winging, scoliosis, and intrinsic hand muscle weakness

Neuropathology

1. Muscle biopsy:
 - a. Rimmed vacuoles
 - b. Tubulofilamentous inclusions (15–21 nm size)
 - c. Dystrophic changes
 - d. In some patients, there were hypotrophic type 2 fibers

Laboratory Evaluation

1. Serum CK normal to mildly elevated
2. EMG:
 - a. Myopathic

Myopathy with Early Respiratory Failure

General Characteristics

1. Titin (TTN) gene that maps to chromosome 2q31.2
2. Autosomal dominant missense mutation whose deficit in the encoded protein is located in the myosin-binding component of the A-band
3. Primarily seen in English and Swedish patients

Clinical Manifestations

1. The onset is variable and most common in the 4th to 5th decade (18–71 years)
2. Weakness is variable:
 - a. Distal weakness occurs in 30% proximal in 40% of patients
 - b. Legs > arms
3. Leg weakness encompasses distal and proximal muscles that include the tibialis anterior
4. Arm weakness involves the wrist flexors and extensors as well as the deltoid; weakness may be diffuse
5. Axial muscle weakness
6. Strong ankle extensor
7. Mild facial muscle involvement in some patients
8. Weakness is symmetric in 90% of patients
9. The course is slowly progressive. The progression is proximal legs to shoulders. There may be quadriceps

sparing. Patients often require non-invasive nocturnal ventilator support

10. Respiratory failure:
 - a. Vital capacity and FEV1L 75% of predicted values at presentation with progressive deterioration
11. No contractures
12. No cardiac involvement
13. Some patients demonstrate calf hypertrophy

Neuropathology

1. Muscle biopsy:
 - a. Variability of fiber size
 - b. Central nuclei
 - c. Fiber splitting
 - d. Myofibrillar pathology
 - e. Eosinophilic inclusions; cytophilic inclusions may contain amyloid-beta desmin, SMI-31 binding proteins
 - f. Cytophilic bodies (in 95% of patients):
 - i. Stain for F-actin
 - ii. “Necklace” pattern
 - g. Vacuoles (rimmed in 50% of patients)
 - h. Type 1 fiber predominance in 50% of patients
 - i. Reduced calpain-3
 - j. Electron microscopy

Laboratory Evaluation

1. Serum CK normal to slightly elevated
2. EMG:
 - a. Myopathic with irritative features
 - b. Normal nerve conduction velocities
3. MRI of muscle:
 - a. Selective early involvement of the semitendinosus and obturator externus
 - b. The proximal part of the muscle is more severely involved
 - c. Adductor longus muscle is spared
 - d. Tibialis anterior is most severely involved with relative sparing of the gastrocnemius and soleus muscles
 - e. Moderate involvement of the supra- and infraspinus, the serratus anterior, subscapularis and trapezius muscles

Myopathy with Ringed Muscle Fibers

General Characteristics

1. Sporadic inheritance

Clinical Manifestations

1. Onset in the third decade
2. Weakness in the quadriceps and ankle dorsiflexors
3. Progression occurs in 1 to 5 years

Neuropathology

1. Muscle biopsy:
 - a. Variation in fiber size

- b. Central nuclei
- c. Increased endomysial connective tissue
- d. Rings in the outer sarcoplasm, the middle annular myofibrils with a normal central myofibril

Laboratory Evaluation

1. Serum CK is normal
2. EMG:
 - a. Myopathic with irritable features

Distal Myopathy (MPD3)

General Characteristics

1. Two possible gene loci that map to chromosome 8p22-q11 and 12q13-q22
2. Described in a single Finnish family

Clinical Manifestations

1. Onset between 32 to 45 years of age with clumsiness of the hands or legs
2. Leg involvement includes the tibialis anterior, extensor digitorum longus, gluteus medius and tibialis flexor longus
3. Arm involvement includes opponens pollicis, first dorsal interosseous, abductor digiti minimi
4. The involvement may be asymmetric and progresses to involve the proximal limb muscles, infraspinatus, triceps, and proximal leg muscles
5. Patients are able to walk throughout the illness

Neuropathology

1. Muscle biopsy:
 - a. Variation in fiber size
 - b. Severe endomysial fibrosis
 - c. Rimmed vacuoles
 - d. Cytoplasmic inclusion bodies

Laboratory Evaluation

1. Serum CK is normal or minimally elevated
2. EMG:
 - a. Myopathic pattern

Distal Myopathy with Spared Anterior Leg Muscles (Williams Distal Myopathy)

General Characteristics

1. Williams distal myopathy is caused by heterozygous mutations in the FLNC gene that map to chromosome 7q32.1
2. The mutations are missense and dominant; they occur in the actin-binding domain
3. The disease is allelic with:
 - a. Myofibrillar myopathy
 - b. Distal myopathy with upper limb predominance

Clinical Manifestations

1. Onset of the disease is at birth to 30 years of age
2. It has been described in Australian and Italian families

3. The phenotype is variable within families and some family members are asymptomatic
4. Arm involvement includes forearm pronators, finger flexors and intrinsic hand muscles
5. Leg muscle involvement includes the ankle evertors and plantar flexors (calf atrophy)
6. There is sparing of the anterior leg compartment and the posterior arm musculature
7. There is distal muscle wasting
8. Cramps and deep muscle pain with exercise
9. Deep muscle stretch reflexes demonstrate absent ankle reflexes
10. Cardiomyopathy has been reported in two patients
11. There is no respiratory involvement
12. A slowly progressive course but patients are able to walk throughout the illness

Neuropathology

1. Muscle biopsy:
 - a. Variation in fiber size
 - b. Internal muscle architecture is disrupted in some biopsies
 - c. There are neomyofibrillar aggregates, vacuoles, or inflammation
 - d. Dysferlin is normal

Laboratory Evaluation

1. Serum CK is normal or minimally increased
2. EMG:
 - a. Myopathic pattern
3. Muscle MRI:
 - a. Involvement of posterior and lateral leg muscles
 - b. Some asymmetry of involvement

Distal Myopathy with Upper Limb Predominance

General Characteristics

1. FLNC mutation with variant syndrome:
 - a. A frame shift mutation produces a stop codon
 - b. Haploinsufficiency of filamin-C
 - c. Autosomal dominant with partial penetrance

Clinical Manifestations

1. Onset between 20–54 years of age with weakness of the fingers and foot extensors
2. Distal weakness is greater than proximal
3. Arms are affected prior to legs in some patients
4. Finger extensors and interossei may be severely affected
5. There is sensory loss in 40% of patients
6. Pes cavus in 20%, hypertension in 30% and cardiomyopathy in 10% of patients
7. Atrophy of distal arms and legs

Neuropathology

1. Muscle biopsy:

- a. Fiber size variability
- b. Necrosis with pyknotic nuclear clumps
- c. Type 1 fiber predominance
- d. Few myofibrillar aggregates or none demonstrated
- e. Electron microscopy:
 - i. Myofibrillar disorganization

Distal Nebulin Myopathy

General Characteristics

1. Distal nebulin myopathy is caused by missense often homozygous mutation in the NEB gene that maps to chromosome 2q23.3. It is an autosomal recessive disease
2. Its encoded protein is postulated to have a role in the regulation of thin filament length and muscle contraction
3. Allelic with rod myopathy

Clinical Manifestations

1. The onset may be in childhood or rarely in adults
2. Weakness is distal and demonstrates the “hanging big toe” sign
3. There is extensor finger weakness. The index finger is spared
4. Neck flexor weakness
5. Patients are slender
6. The pattern of weakness resembles that of Laing myopathy

Neuropathology

1. Muscle biopsy:
 - a. Rods and cores may be demonstrated but are not prominent
 - b. A childhood onset patient demonstrated both cores and rods
2. Electron microscopy:
 - a. Z-line streaming
 - b. Minor rod changes

Laboratory Evaluation

1. Serum CK is normal
2. EMG:
 - a. Myopathic pattern
3. Muscle MRI:
 - a. Predominant distal involvement of the anterior compartment

Nephropathic Cystinosis

General Characteristics

1. Nephropathic cystinosis is caused by missense mutations in the CTNS gene that maps to chromosome 17p13.2
2. Cystinosis is classified as lysosomal storage disorder because of the intralysosomal localization of stored cysteine
3. Intracellularly cystine is compartmentalized with acid phosphatase and is membrane bound
4. There are multiple systemic effects of the illness

Clinical Manifestations

1. Age of onset is from the first year of life to adulthood
2. Infants have a failure to thrive
3. Multiple systems are involved that include:
 - a. Skeletal:
 - i. Short stature
 - ii. Frontal balding
 - iii. Hypophosphatemic rickets
 - b. Eyes:
 - i. Retinopathy
 - ii. Corneal cystine crystal deposition
 - c. Renal:
 - i. Fanconi syndrome that leads to renal failure
 - d. Endocrine:
 - i. Hypothyroidism
 - ii. Insulin dependent diabetes mellitus
 - iii. Delayed puberty
 - iv. Skin:
 - 1. Pigmentary alterations
 - 2. Hypohidrosis
 - v. CNS:
 - 1. Cognitive impairment
 - 2. Visual spatial processing defects
 - 3. Cerebral atrophy
 - vi. Muscle:
 - 1. Distal weakness and wasting
 - 2. Dysphagia

Neuropathology

1. Muscle biopsy:
 - a. Variation in fiber size
 - b. Rimmed vacuoles that are acid phosphatase positive
 - c. Cystine deposition in muscle fibers

Laboratory Evaluation

1. Increased cystine deposition in leukocytes
2. Urine proteinuria, glycosuria and microscopic hematuria
3. Blood hyponatremia, hypokalemia, and hypophosphatemia
4. Carnitine deficiency
5. Generalized aminoaciduria

Early Onset Distal Weakness

General Manifestations

1. Early onset distal weakness is caused by a missense mutation in Kelch-like homologue 9 gene that maps to chromosome 9p22 which is autosomal dominant
2. The KLHL9 protein complexes with cullin 3 and is involved in the ubiquitin dependent protein degradation pathway
3. Described in a German family

Clinical Manifestations

1. The onset is between 8 to 16 years of age

2. Weakness of the intrinsic hand muscles and distal leg muscles
3. Atrophy of the anterior tibialis muscles
4. Proximal muscles are normal
5. Late in the disease course, there is distal sensory loss in the extremities
6. A prolonged course and patients are able to walk throughout life

Laboratory Evaluation

1. CK is usually mildly elevated
2. EMG:
 - a. Motor nerve conduction velocities are normal; occasionally there is prolonged distal latency
 - b. Sensory conduction velocities are normal
 - c. Fibrillation potentials and large polyphasic motor unit potentials are seen in affected distal muscles

Neuropathology

1. Muscle biopsy:
 - a. Variation in fiber size

Distal Weakness, Hoarseness, Hearing Loss (CPNMHH)

General Characteristics

1. CPNMHH is caused by a mutation in the MyH14 gene that maps to chromosome 19q13.33
2. It is an autosomal dominant missense mutation
3. It is allelic with autosomal dominant deafness (DFNAI)
4. The mutation affects microRNA (mR-199)
5. Described in a Korean family

Clinical Manifestations

1. The onset is between 5 and 13 years of age
2. Distal muscle weakness that is followed by progressive atrophy of affected muscles
3. Lower extremities are affected to a greater extent than the upper
4. The weakness is seen first in the anterior lower leg compartment and then the posterior
5. Thigh muscles become involved at approximately 40 years of age
6. Most patients have foot deformity
7. Loss of muscle stretch reflexes
8. No sensory loss
9. 53% of patients developed hoarseness but none had dysphagia or vocal cord paralysis
10. Late onset sensorineural hearing loss was noted in 45% of patients

Neuropathology

1. Muscle biopsy:
 - a. Variation in fiber size
 - b. Fiber type grouping
 - c. Two patients demonstrated subsarcolemmal accumulation of enlarged mitochondria with rectangular or elongated rhomboidal paracrystalline inclusions by EM

Laboratory Evaluation

1. Serum CK varied from normal to 2.5 times normal
2. EMG:
 - a. Fibrillation potentials in affected muscles
 - b. Low amplitude CMAP
 - c. Normal nerve conduction velocities

Congenital Myopathies

Overview

The congenital myopathies are diverse skeletal muscle diseases that most often present at birth or early infancy. The natural history of a large pediatric cohort of 125 patients revealed that the genetic basis could be determined in approximately 80% of patients and mutations in the RYR1 gene was the most common. Approximately 70% of patients had a neonatal or infantile onset. Approximately 30% required mechanical ventilation at birth and 25% needed nasogastric alimentation. Twelve percent of patients died within the first year and had mutations in ACTA1, MTM1 or KLHL40 genes. All patients with RYR1 mutations survived. Patients with recessive mutations required gastrostomy more than those with dominant mutations. Approximately 75% of patients were able to walk although this milestone was acquired late in 60% of patients. Approximately 10% of patients lost the ability to walk. Bulbar involvement occurred in 40% of patients. Scoliosis of varying degree occurred in those who were able to walk and in 40% of patients who could not. Respiratory impairment occurred in 64% of patients and approximately 50% of these patients required nocturnal non-invasive ventilation.

The congenital myopathies usually present in infancy with generalized weakness and hypotonia. Motor milestones and development are delayed. Progressive weakness may gradually develop. The disorders are inherited in autosomal dominant, autosomal recessive or in an X-linked pattern. There is frequent intrafamilial variation in both presentation and severity. Mutations in many different genes may cause similar pathology and mutations in the same gene may result in different pathologies. Recent studies suggest that there are five major mechanisms that cause congenital myopathies which include:

1. Sarcolemmal and intracellular membrane remodeling and excitation-contraction coupling
2. Mitochondrial distribution and function
3. Myofibrillar generation of force
4. Atrophy
5. Autophagic mechanisms

In the past, congenital myopathies were classified according to their clinical features and microscopic structural differences on muscle biopsy. Next generation sequencing techniques is revealing a genetic diagnosis in these patients as a basis for diagnosis.

Central Core Myopathy (CCD)*General Characteristics*

1. Central core disease (CCD) and its variants are caused by heterozygous, homozygous or compound heterozygous mutations in the ryanodine receptor RYR1 gene that maps to chromosome 19q13.2
2. Biallelic mutation in the RYR1 gene causes minicore myopathy with external ophthalmoplegia

Clinical Manifestations

1. The onset is usually at birth or in early childhood with generalized weakness and hypotonia
2. There is considerable variability of weakness both inter- and infrafamily
3. The muscle weakness is stable or slowly progressive
4. Motor milestones are delayed
5. Proximal muscles of the leg as more affected than the arms
6. A wide-based hyperlordotic gait and Gowen's sign may be seen
7. There may be neck flexor and mild facial weakness
8. There is no extraocular muscle weakness or ptosis that are distinguishing clinical signs from centronuclear and nemaline myopathies
9. Muscle hypertrophy, atrophy, or contractures are usually not appreciated
10. Muscle stretch reflexes are normal or slightly reduced
11. Skeletal abnormalities include:
 - a. Pes plavus and cavus
 - b. Kyphoscoliosis
 - c. Congenital hip dislocation
12. Respiratory muscle involvement with nocturnal hypoxemia may occur
13. Patients are at risk for malignant hyperthermia

Neuropathology

1. Cores may be eccentric and multiple within a muscle fiber
2. In central core disease, the cores extend the entire length of the muscles
3. Cores are regions of sarcomeric disorganization without mitochondria and lack oxidative activity
4. In multicore disease, the multicores are in both type I and type II fibers and also have less mitochondria and lack of oxidative activity in the core lesion
5. Electron microscopy:
 - a. Changes in the sarcoplasmic reticulum and t-tubules
 - b. Structured cores demonstrate streaming of the Z-band but the sarcomeres are preserved
 - c. Unstructured cores have myofibrillary disruption
 - d. Cores contain desmin, dystrophin, actin, α -actinin, gelsolin, nebulin, myotilin, amyloid-beta precursor protein, NCAM and cyclin-dependent kinesin

Laboratory Evaluation

1. The serum CK level is normal or minimally elevated

2. EMG:

- a. Fibrillation potentials and positive sharp waves may occur in affected muscles
- b. Myopathic MUAPs with early recruitment
- c. Some long duration, polyphasic MUAPs

Multiminicore Myopathy (MmD)*General Characteristics*

1. MmD is inherited primarily as an AR disease with some patients mapping to the selenoprotein N1 gene on chromosome 1p36. Other patients show AD and sporadic inheritance

Clinical Manifestations

1. Onset is in infancy with hypotonia and weakness
2. Delayed motor milestones are seen but most patients are able to walk
3. Generalized proximal muscle weakness
4. A subset of patients may have predominant distal hand weakness
5. Skeletal abnormalities include: 1. muscle contractures; 2. kyphoscoliosis; 3. high arched palate and 4. clubfoot
6. Facial muscle weakness, ptosis, and occasionally ophthalmoparesis are manifest
7. Weakness may be slowly progressive
8. Neck extensor and axial musculature contraction leads to decreased spine mobility
9. Cardiomyopathy and respiratory insufficiency may develop over time. The respiratory involvement is disproportionate to the degree of scoliosis that may require mechanical ventilation

Neuropathology

1. Muscle biopsy:
 - a. Minicores are seen which are non-continuous along the length of the muscle fibers
 - b. The minicores occur in both type 1 and type 2 fibers
 - c. Variation in fiber size
 - d. Type 1 fiber predominance with atrophy
 - e. Increased endomysial connective tissue
 - f. Electron microscopy:
 - i. Myofibrillar disorganization is seen that is similar to that of central core disease
2. Patients have been described with mutations in the PYR1 gene that is seen in central core myopathy
3. The SEPN1 gene is also responsible for congenital muscular dystrophy with rigid spine deformity and some patients with myofibrillar myopathy
4. Two siblings have been reported with cofilin-2 gene mutations that map to chromosome 14q13 and demonstrated nemaline rods as well as minicores on muscle biopsy

Laboratory Evaluation

1. The serum CK level is normal or only minimally increased
2. EMG:

- a. Normal insertional and spontaneous activity
- b. Short duration, low amplitude early recruited MUAPs are seen
- c. Normal nerve conduction velocities
- 3. Pulmonary function tests:
 - a. Reduced forced vital capacity
- 4. Polysomnography:
 - a. Nocturnal desaturation with short apneic periods

Nemaline Myopathy

General Characteristics

1. The genetics of nemaline myopathy are heterogeneous with mutations in multiple genes that determine different phenotypes of the disease
2. Mutations in the nebulin gene (NEM2) is the most common and maps to chromosome 2q21.2-q22
3. Other genes that cause the syndrome are mutations in:
 - a. ACTA1 (AR/AD) that maps to 1q42
 - b. TMP3 (AR/AD) that maps to 1q21-1q23
 - c. TMP2 (AD) that maps to 9q13
 - d. TNNT1 (AR) that maps to 19q13
 - e. TMP1 (AR/AD) that maps to 15q21-23
 - f. CFL2-that maps to 14q12

Clinical Manifestations

1. There are three major clinical presentations of nemaline myopathy:
 - a. A severe infantile form
 - b. A slowly progressive form
 - c. Adult onset form

Infantile Form

1. Severe generalized weakness and hypotonia at birth
2. Absent motor and muscle stretch reflexes
3. Weak suck and cry
4. Mechanical ventilation is required for many patients
5. Arthrogryposis and neonatal respiratory insufficiency are associated with early mortality

Early Childhood

1. This is a non-progressive or very slowly progressive illness with both proximal and distal weakness and decreased muscle bulk
2. Delayed motor milestones
3. A subset of patients manifests a facioscapulohumeral pattern of weakness
4. Wide-based lordotic waddling gait
5. Slight facial and masticatory weakness
6. Dysmorphic features of high arched palate, micrognathia and narrow face
7. Skeletal abnormalities include:
 - a. Pectus excavatum
 - b. Kyphoscoliosis
 - c. Pes cavus
 - d. Clubbed feet
8. Diminished or absent deep muscle stretch reflexes

Adult Onset

1. Mild proximal and occasionally slight distal muscle weakness
2. Cardiomyopathy may predominate over muscle weakness in some patients
3. No dystrophic or skeletal abnormalities that are seen in the early onset forms

Neuropathology

1. Muscle biopsy:
 - a. Type 1 fiber predominance and hypotrophy is seen in the congenital forms
 - b. Modified Gomori trichrome stain demonstrates nemaline rods in the subsarcolemma and occasionally perinuclear areas
 - c. Electron microscopy:
 - i. Rod bodies are 3–6 μm in length and 1–3 μm in diameter
 - ii. Their density is similar to that of Z-discs
 - iii. Intranuclear rods are seen in all severe infantile patients but also can be seen in the milder adult onset patients
 - iv. Histochemistry analysis reveals that both the Z-discs and rods are immune-reactive for α -actinin
 - v. Rods are seen in:
 1. Tenotomy
 2. HIV associated myopathy
 3. Myofibrillar myopathy
 4. Myositis
 5. Hypothyroidism

Laboratory Evaluation

1. The serum CK is normal or only minimally increased
2. EMG:
 - a. Early recruitment of low amplitude short duration MUAPs
 - b. In severe infantile forms, there may be fibrillation potentials and positive sharp waves

Late Onset Nemaline Myopathy

General Characteristics

1. A sporadic disorder that in 50% of patients is associated with a monoclonal gammopathy of undetermined significance

Clinical Manifestations

1. Presents after the age of 40, but has been reported in the ninth decade
2. The weakness involves proximal or distal muscles but may be generalized
3. Isolated neck extensor weakness may cause the “dropped head” syndrome
4. In patients with associated gammopathy, respiratory insufficiency may be severe

Neuropathology

1. Rods are identified by both light and electron microscopy
2. Rods are short

Laboratory Evaluation

1. Serum CK levels are usually normal
2. EMG:
 - a. Increased insertional activity with positive sharp waves and fibrillation potentials
 - b. Early recruitment of brief duration low amplitude MUAP
 - c. Motor and sensory nerve conduction velocities are normal
3. Approximately 50% of patients have a monoclonal gammopathy of undetermined significance

Centronuclear Myopathy*General Characteristics*

1. There is genetic heterogeneity among the different type of centronuclear myopathy:
 - a. The severe neonatal type is caused by mutations in the myotubularin gene (MTM1) that maps to chromosome xp28
 - b. Late onset centronuclear myopathy is autosomal dominant and has been mapped to the DNM2 gene on chromosome 19p13.2. Several sporadic patients have also been linked to this locus and manifest the severe neonatal phenotype of this myopathy
 - c. Mutations in the DNM2 gene also cause autosomal dominant intermediate or D1-CMTB

Clinical Manifestations

1. Infantile-early childhood phenotype:
 - a. Maybe autosomally dominant or recessively inherited
 - b. Mild hypotonia and generalized weakness are detected in infancy
 - c. Motor milestones are delayed
 - d. Patients can walk but often have a wide-based hyperlordotic gait. Dysmorphic features include:
 - i. Narrow face and high arched palate
2. Ptosis and ophthalmoparesis are common and a differential point from other congenital myopathies
3. X-linked recessive myotubular myopathy:
 - a. A common form of centronuclear myopathy presents at birth with hypertonic, generalized weakness and often requires mechanical ventilation and nasogastric or gastroscopy tubes
 - b. Polyhydramnios is often present during pregnancy
 - c. Ptosis and ophthalmoparesis are noted in early childhood
 - d. Arthrogryposis may occur
4. A few manifesting females have been described with X-linked myotubularin deficiency:
 - a. They can present in adulthood
 - b. Childhood onset and some adult patients have:

- i. Axial and proximal weakness
 - ii. Bilateral ptosis
 - iii. External ophthalmoparesis
 - iv. Possible mechanism is skewed inactivation of the X-chromosome
- c. Childhood or less severe form that presents with:
 - i. Mild muscle weakness that is slowly progressive
 - ii. A variable pattern of muscle weakness occurs with some patients more affected proximally and others with more distal muscles involvement
 - iii. Facial muscles may be involved
 - iv. Ptosis and ophthalmoparesis is seen in some patients
 - v. A facioscapulohumeral phenotype has been described
 - vi. In the adult form of centronuclear myopathy, there are no facial dysmorphic features or skeletal abnormalities

Neuropathology

1. Muscle biopsy:
 - a. Central myonuclei that may form chains or occasionally there are nuclear clusters in the fiber center
 - b. Central nuclei occur in 25–95% of both type I and type II fibers
 - c. There is type 1 fiber predominance and hypotrophy; Type 2 fibers are normal
 - d. Electron Microscopy:
 - i. There are reduced myofibrils and an excess of mitochondria and glycogen granules in the center of muscle fibers that have peripheral nuclei

Laboratory Evaluation

1. The serum CK is normally or only minimally increased
2. EMG:
 - a. Increased insertional and spontaneous activity manifest by positive sharp waves, fibrillation potentials, complex repetitive discharges and myotonic discharges
 - b. Low amplitudes, short duration and increased recruitment of MUAPs
 - c. Some patients with dynamic 2 gene mutations have reduced amplitude and slow motor and sensory nerves conduction studies

Congenital Fiber-Type Disproportion (CFTD)*General Characteristics*

1. CFTD can be caused by mutations in the ACTA1, SEPN1, and TPM3 genes
2. Most patients are sporadic but others have been described with autosomal dominant or autosomal recessive inheritance

Clinical Manifestations

1. At birth, patients have generalized hypotonia and weakness associated with a weak cry and suck reflex

2. There is delay in acquiring motor milestones
3. Motor weakness is usually static. Patients have been reported with a progressive course marked by respiratory insufficiency
4. Dysmorphic fascies, high arched palate, congenital hip dislocation, kyphoscoliosis, arthrogryposis, and a rigid spine may be seen
5. Approximately 1/3 of patients may have CNS manifestations that have been postulated to be caused by impaired glycosylation of L-dystroglycan

Neuropathology

1. Muscle biopsy:
 - a. There is disproportion in the size and proportion of type 1 versus type 2 muscle
 - b. Type 1 fibers predominate in a number, but are only 15% the size of type 2 fibers that are normal or slightly hypertrophic
 - c. Type 1 fiber predominance and hypotrophy are found in:
 - i. Nemaline myopathy
 - ii. Centronuclear myopathy
 - iii. Congenital muscular dystrophies
 - iv. Spinal muscular atrophy
 - d. Electron microscopy:
 - i. Non-specific ultrastructural deficits

Laboratory Evaluation

1. The serum CK level is normal or only minimally increased
2. EMG:
 - a. There may be increased insertional and spontaneous activity
 - b. Nerve conduction velocities are normal
 - c. There may be early recruitment of MUAPs
 - d. The electrodiagnostic studies only be normal

Sarcotubular Myopathy

General Characteristics

1. Sarcotubular myopathy is allelic to LGMD2H
2. The mutation that is causative in the original Hutterite families is in TRIM32 that maps to chromosome 9q33.1
3. A subset of Hutterite patients (LGMD2I) have been described with mutations in the FKRP gene that map to chromosome 19q13
4. TRIM32 regulates skeletal muscle stem cell differentiation that is important for generation of processes of adult skeletal muscle during growth or following injury
5. TRIM32 may also play a role in the recognition of proteins that are targeted for ubiquitination

Clinical Manifestations

1. Patients may present in infancy or adulthood
2. Exertional myalgia
3. Proximal muscle weakness

4. Scapular winging and foot drop
5. Calf hypertrophy
6. Mild facial weakness
7. Depressed muscle stretch reflexes
8. South Dakota Hutterite families may have a scapuloperoneal phenotype

Neuropathology

1. Increased central nuclei
2. Fiber splitting
3. Fibers (primarily type 2) may have small vacuoles
4. Electron microscopy:
 - a. The vacuoles are adjacent to T-tubules and are membrane bound
 - b. The vacuoles may be empty or contain amorphous material
 - c. Immunostains reveal that vacuoles are positive for sarcoplasmic reticulum associated ATPase

Laboratory Evaluation

1. Serum CK levels may be normal or elevated to 20 times normal
2. EMG:
 - a. Myopathic pattern
 - b. Normal

Fingerprint Body Myopathy

General Characteristics

1. Most patients have sporadic inheritance although the disease has been reported in identical twins and in familial form

Clinical Manifestations

1. Onset is in infancy or early childhood
2. The infants have generalized hypotonia, weakness, and atrophy
3. Muscle strength is stable or progresses minimally
4. Some patients have cognitive deficits, febrile seizures, kyphoscoliosis, and pectus excavatum

Neuropathology

1. Muscle biopsy:
 - a. Type 1 fiber predominance and hypotrophy
 - b. Type 2 fiber hypertrophy
 - c. Type 1 fibers have decreased oxidative activity in the subsarcolemmal and perinuclear regions

Electron Microscopy

1. Fingerprint bodies appear as a complex lamellar body that resembles a finger print. They may be composed of cytoskeletal proteins

Laboratory Evaluation

1. Serum CK levels are normal or only minimally elevated
2. EMG:
 - a. Low amplitude short duration MUAPs
 - b. Normal insertional and spontaneous activity

Trilaminar Myopathy*General Characteristics*

1. Only one infant has been described
2. Genetics have not been determined

Clinical Manifestations

1. The infant was born with rigid axial and extremity muscles
2. Weak cry and suck reflexes
3. Joint contractures
4. Intact muscle stretch reflexes
5. Patients have delayed motor milestones and were able to walk

Neuropathology

1. Muscle biopsy:
 - a. Variability in fiber size
 - b. Approximately 25% of fibers were hypertrophic that demonstrated three concentric zones with a differential histochemical staining pattern:
 - i. The inner and outer zones stained with the Gomori trichome and NADH stains
 - ii. An inverse pattern was seen with ATPase staining
 - c. Electron microscopy:
 - i. Myofibrillar disorganization of the innermost zone that also was filled with mitochondria, glycogen granules and myofilaments
 - ii. The intermediate zone had Z-band streaming
 - iii. The outer zone demonstrated disorganized myofibrils, mitochondria, lipid droplets, and vesicles

Laboratory Evaluation

1. The serum CK was 40x normal
2. EMG:
 - a. The EMG and NCS were normal

Hyaline Body Myopathy (HBM)*General Characteristics*

1. Hyaline body myopathy is caused by missense mutations in the MYH7 gene that maps to chromosome 14q11.2. An autosomal dominant form of the disease has also shown a heterozygous mutation in the same gene
2. Mutations in MYH7 have been identified in a form of familial cardiomyopathy
3. The MYH7 gene encodes for slow beta cardiac MYH7 proteins although a cardiomyopathy does not occur in hyaline body myopathy
4. Normal MyHC is necessary for the assembly of thick filaments
5. Mutations in chromosome 3p22.2-p21.3 have been described with this phenotype

Clinical Manifestations

1. Onset may be in infancy to the fifth decade

2. Patients may have a limb girdle or scapuloperoneal phenotype
3. The disease is stable or demonstrates only a slight deterioration of muscle strength
4. Rarely there is a cardiomyopathy
5. Muscle stretch reflexes are preserved
6. Some adult patients have demonstrated calf hypertrophy
7. There is variability in clinical symptomatology within families

Neuropathology

1. Muscle biopsy:
 - a. Subsarcolemmal "hyaline bodies" are demonstrated with the Gomori trichome stains
 - b. Hyaline bodies occur in type 1 fibers that are hypotrophic and do not stain with oxidative enzyme or periodic acid Schiff stains, but are positive for myofibrillar ATPase
 - c. Some biopsies demonstrate angular fibers with type grouping
 - d. Some hyaline bodies are positive for slow myosin heavy chain MyHC activity
 - e. Electron microscopy:
 - i. Hyaline bodies are composed of granulomatous debris with fragments of sarcomeres that are surrounded by an area of sarcomere disorganization

Laboratory Evaluation

1. Serum CK levels are normal or minimally elevated
2. EMG:
 - a. Increased low amplitude, short duration polyphasic MUAPs
 - b. May be normal
 - c. Echocardiogram:
 - i. In a subset of patients, there is evidence of a dilated cardiomyopathy with a low ejection fraction

MYH2 Myopathy*General Characteristics*

1. Hereditary myosin myopathies are a group of muscle disorders with variable age at onset and variable phenotypes
2. They are caused by mutations in the skeletal muscle heavy chain MyHC genes. There are three major isoforms in adults that include:
 - a. MYHC1 is encoded by MYH7:
 - i. Expressed in slow type I muscle fibers and in heart ventricles
 - ii. MyHC II is encoded by MYH2 gene and is expressed in fast IIA muscle fibers
 - iii. MyHC that is expressed in fast IIB fibers
 - iv. The MYH2 gene has been mapped to chromosome 17p13.1
 - v. Homozygous, compound heterozygous, truncating and missense mutations have been demonstrated to cause these muscle disorders

Clinical Manifestations

1. Phenotype includes:
 - a. An autosomal recessive proximal myopathy with external ophthalmoparesis
 - b. Congenital arthrogryposis
 - c. Mild proximal weakness myalgias that begin in adulthood or early childhood (autosomal dominant)

Neuropathology

1. Many biopsies reveal rimmed vacuoles and tubulofilamentous inclusions similar to hereditary inclusion body type 3
2. Missense mutation has demonstrated small or absent type 2A muscle fibers
3. Muscle biopsy from long standing patients may demonstrate dystrophic changes. Variability of fiber size with increased perimysial and endomysial connective tissue without inflammation and necrosis has been described

Laboratory Evaluation

1. Serum CK levels may be minimally elevated
2. EMG:
 - a. Myopathic pattern
3. Muscle MRI (in recessive MYH2 missense mutation patients):
 - a. Diffuse fatty infiltration with predominant involvement of the medial gastrocnemius muscle of the lower leg
 - b. Predominant involvement of the semitendinosus gracilis and vastus lateralis in the thigh

CAP Myopathy*General Characteristics*

1. CAP myopathy is caused by mutations in the skeletal muscle isoform of the tropomyosin genes:
 - a. CAP myopathy-2 is caused by heterozygous mutation in the tropomyosin-2 gene (TPM2) that maps to chromosome 9p13
2. CAP myopathy-1 is caused by heterozygous mutation in the alpha tropomyosin 3 gene (TPM3) that maps to chromosome 1q21
3. Mutations affecting muscle isoforms of the tropomyosin genes cause a variety of disorders that include:
 - a. Nemaline myopathy
 - b. Core-rod myopathy
 - c. Congenital fiber type disproportion
 - d. Distal arthrogryposis
 - e. Escobar syndrome
4. There are at present thirty variants of TPM2 and 20 of TPM3; most are heterozygous and are associated with autosomal dominant disease

Clinical Manifestations

1. Neonatal onset with muscle weakness and hypotonia
2. Skeletal deformities
3. Decreased muscle stretch reflexes

4. The respiratory muscles are frequently affected
5. Patients with TPM2 mutations are less affected than those with TPM3 mutations
6. Five mutations in the TPM2 and one in TPM3 cause hypercontraction of muscles. The hypercontractible phenotypes have more limb joint and jaw contractions than those patients with the non-hyper contracture phenotype. Patients with the non-hyper contracture phenotype had axial contractures to a greater degree than the contractual phenotype

Neuropathology

1. Muscle biopsy:
 - a. Many muscle fibers contain a peripheral crescent that strongly stains for NADH-TR, PAS and phosphorylase
 - b. The "caps" contain fast myosin, desmin, tropomyosin, and alpha-actinin
2. Electron Microscopy:
 - a. Widened Z-bands
 - b. Disorganization of myofibrils
 - c. Lack of thick filaments

Laboratory Evaluation

1. The serum CK level is normal
2. EMG:
 - a. Myopathic MUAPs
 - b. Normal conduction in velocities

Zebra Body Myopathy*General Characteristics*

1. Zebra body myopathy is caused by mutations in the ACTA1 gene

Clinical Manifestations

1. Only a few patients have been reported
2. One patient presented with generalized muscle weakness and atrophy from birth
3. A second patient manifested severe hypotonia, dysphagia and asymmetric upper extremity weakness
4. Muscle weakness is stable or slightly progressive

Neuropathology

1. Muscle biopsy:
 - a. Central nuclei
 - b. Variability in fiber size
 - c. Occasional vacuoles
2. Electron Microscopy
 - a. The z-bodies are striae with a periodicity that appear as stripes
 - b. The density of the striae is similar to Z-discs
 - c. There may be streaming of the X-bands and Nemaline rods
3. Zebra bodies may be found in:
 - a. Myofibrillar myopathy
 - b. Cardiac muscle

Laboratory Evaluation

1. The serum CK can be 2–3 x normal
2. EMG:
 - a. Myopathic pattern
 - b. No abnormal insertional or spontaneous activity

Tubular Aggregate Myopathy*General Characteristics*

1. Autosomal dominant tubular aggregate myopathy may be caused by a heterozygous mutation in the STIM1 gene that maps to chromosome 11p15.4
2. Tubular aggregates are a non-specific finding that may be seen in disorders that include:
 - a. Alcohol and drug-induced myopathies
 - b. Hereditary periodic paralysis
 - c. Hyperthyroidism
 - d. Congenital slow channel myasthenia
 - e. Hypoxia
 - f. Some toxic myopathies
3. The STIM1 gene (stromal interaction molecule 1) encodes the main calcium sensor in the sarcoplasmic reticulum

Clinical Manifestations

1. There are various phenotypes associated with tubular aggregates:
 - a. Slowly progressive limb girdle weakness that begins in childhood or early adulthood
 - b. A form whose phenotype resembles congenital myasthenia and responds to acetylcholinesterase
 - c. Myalgias with exercise. The muscle bulk and strength are normal

Neuropathology

1. Tubular aggregates are located subsarcolemmally and are only in type 2 muscle fibers in patients with periodic paralysis and those with muscle pain with exercise. They are present in both fiber types in patients with the limb girdle phenotype
2. They appear as abnormal accumulations of densely packed single-walled or double-walled membrane tubules in muscle fibers
3. They are basophilic in A- and E-stain; they react to NADH-TR but not to SDH
4. Electron microscopy:
 - a. The aggregates are bundles of tubules of 60–80 nm in diameter

Laboratory Evaluation

1. Serum CK is normal or only minimally elevated
2. EMG:
 - a. Patients with the congenital myasthenic phenotype have a decremental response that corrects with pyridostigmine (improves)
 - b. Normal in those with muscle pain syndrome
 - c. Some patients demonstrate myopathic MUAPs and have fibrillation potentials
 - d. Motor and sensory NCS are normal

Reducing Body Myopathy*General Characteristics*

1. Sporadic or inherited missense mutations in four-and-a-half LIM to main protein 1 (FHL1) cause alteration in the expression of FHL1 protein and clinically heterogeneous myopathies
2. X-linked early onset severe myopathy has been mapped to Xq26.33
3. FHL1 mutations cause:
 - a. Reducing body myopathy (RBM)
 - b. Scapuloperoneal myopathy
 - c. X-linked myopathy with postural muscle atrophy (XM-PMA)

Clinical Manifestations

1. The infantile form may present with severe generalized weakness, hypotonia, and joint contractures. Patients may have ptosis. Deep tendon reflexes are depressed. Some patients have respiratory muscle involvement with increased mortality
2. Onset may be late childhood or as an adult:
 - a. There may be asymmetrical involvement of either proximal or distal muscles
 - b. Some patients develop contracture of the major joints, sclerosis and spinal rigidity
 - c. There is recently described adult onset involvement of the sternocleidomastoid and trapezius muscles

Neuropathology

1. Muscle biopsy:
 - a. “Reducing” bodies are characterized by their ability to reduce nitro blue tetrazolium mediated by menadione
 - b. They have no oxidative enzyme staining but some fibers demonstrate desmin at the periphery of some reducing bodies
 - c. There is type 1 fiber predominance
 - d. Reducing bodies are seen in both type 1 and type 2 fibers
 - e. Electron microscopy:
 - i. Reducing bodies are composed of electron dense granules associated with tubulofilaments
 - ii. Some biopsies reveal:
 1. Variation in fiber size
 2. Central nuclei
 3. Mild inflammation
 4. Rimmed vacuoles
 5. Reducing bodies in the majority of fibers

Laboratory Evaluation

1. Serum CK levels are usually normal or can be minimally elevated
2. EMG:
 - a. Myopathic pattern
 - b. NCS are normal

Myofibrillar Myopathies

General Characteristics

1. The myofibrillar myopathies (MFMs) are sporadic or inherited muscle disease
2. The six genes that have been identified with this disease include:
 - a. Alpha-B crystallin (CRYAB)
 - b. Myotilin gene mutations occur in both myotilinopathy and spheroid body myopathy
 - c. ZASP-related MFM is caused by mutations in the ZASP gene
 - d. FLNC-related MFM
 - e. BAG-3 related MFM
3. The causative genes encode sarcomeric Z-disc proteins:
 - a. Desmin
 - b. α - β crystallin
 - c. Myotilin
 - d. Z-band alternatively spliced PDD motif containing protein (ZASP)
 - e. Filamin C
 - f. Anti-apoptotic Bcl2-associated athanogene 3 (BAG-3). These genes account for approximately 50% of patients with MFM

Clinical Manifestations

1. Most patients have an adult onset with slow progression
2. Desminopathy, α - β crystallinopathy and BAG2opathies have an infantile or juvenile disease onset
3. Cardiomyopathy is characteristic in patients with desminopathies and may be the only sign
4. Respiratory symptoms occur in childhood patients with β -crystallinopathies
5. Early severe cardiac and respiratory insufficiency occur in Bag3-opathies

Neuropathology

1. Muscle biopsy:
 - a. Variability in fiber size
 - b. Central nuclei
 - c. Some biopsies demonstrate type 1 fiber predominance and related rimmed vacuoles
 - d. Hyaline and non-hyaline structures:
 - i. Central desmin and other proteins
 - e. Nerve and intramuscular nerve biopsy reveal:
 - i. Enlarged axons with accumulated intermediate neurofilaments and axonal spheroids

Laboratory Evaluation

1. Serum CK is normal or only minimally elevated
2. EMG:
 - a. Increased insertional and spontaneous activity with fibrillation potentials and positive sharp waves
 - b. Pseudomyotonic potentials
 - c. Complex repetitive discharges

- d. Early recruitment of short duration, low amplitude polyphasic MUAP
- e. In chronic patients, there may be long duration, large amplitude MUAPs
- f. Nerve conduction may have low amplitude and slow motor and sensory NCS
3. EKG:
 - a. Conduction defects and arrhythmias
 - b. Echocardiography:
 - c. Dilated or hypertrophic cardiomyopathy

Metabolic Myopathies

Overview

Primary metabolic myopathies may be classified according to their underlying biochemical defects of 1. carbohydrate, 2. lipid, 3. adenine nucleotide and 4. mitochondrial effects on the function of the muscle itself. Secondary metabolic defects of muscle occur in disorders of endocrine function on the thyroid, parathyroid or adrenal gland.

The immediate energy source for muscle contraction is derived from the hydrolysis of adenosine triphosphate (ATP). During rest, ATP production for muscles is derived from the metabolism of long chain fatty acids. Disorders that effect β -oxidation of fatty acids that occurs in mitochondria cause muscle weakness. In exercising muscle, ATP is generated from metabolism of carbohydrates as fatty acids and ketone bodies. The first forty-five minutes of exercise ATP is generated from glucose that is available or generated from glycogenolysis. After this period, there is a shift to fatty acid metabolism which accounts for approximately 70% of ATP production.

Glycogen is the primary sarcoplasmic source of carbohydrate while fatty acids are derived from adipose tissue and intracellular lipid stores. Carbohydrates can be metabolized both anaerobically and aerobically while fatty acids are metabolized only aerobically. During short periods of intense exercise, the carbohydrate utilized is from glycogen stores that is initiated by myophosphorylase. After glycogen stores are depleted, oxidation of fatty acids provides the source for ATP production. Increased blood concentration of β -hydroxybutyrate is a marker of fatty acid oxidation while increased concentration of blood lactate is a marker of anaerobic metabolism of glucose. The cytochrome system is essential for both aerobic and anaerobic muscle metabolism.

Disorders of Muscle Carbohydrate Metabolism

Type II Glycogenosis (Pompe Disease, Acid Maltase Deficiency, α -Glucosidase Deficiency)

General Characteristics

1. Pompe disease is caused by mutation in the α -glucosidase gene that maps to chromosome 17q25.2-q25.3

2. The incidence of infantile Pompe disease is 1 in 31,000 to 1 in 38,000 of the population
3. The incidence of the late onset form is 1 in 53,000 of the population

Clinical Manifestations

1. Infantile form:
 - a. Infants have generalized weakness and hypotonia
 - b. Cardiomegaly and mild to moderate hepatomegaly
 - c. The onset is during the first several months of life
 - d. Enlarged tongue
 - e. Feeding difficulties
 - f. The illness is usually fatal by two years of age from cardiorespiratory failure
2. Juvenile form:
 - a. Onset is in the first decade
 - b. Motor milestones may be delayed
 - c. There is progressive proximal greater than distal weakness
 - d. Hypertrophy of calf muscles, hyperlordosis and a waddling gait may be prominent
 - e. Rarely patients present with a rigid spine phenotype
 - f. Rare cardiomegaly, hepatomegaly and an enlarged tongue
 - g. Scapuloperoneal phenotype may occur
 - h. Respiratory insufficiency with apnea and nocturnal hypoxemia may occur in 10–33% of patients
3. Adult form:
 - a. Onset is in the third or fourth decade to 70 years of age
 - b. Proximal greater than distal weakness which may be asymmetric
 - c. The tongue and face may be involved
 - d. Muscle pain (particularly in the thigh) is a complaint in 50% of patients
 - e. Decreased muscle stretch reflexes
 - f. No cardiomegaly or hepatomegaly
 - g. A predilection for respiratory muscle involvement

Neuropathology

Muscle Biopsy

1. Glycogen filled vacuoles are seen within muscle fibers in the infantile form
2. In childhood and adult types, they are demonstrated in 25–75% of clinically affected muscles
3. In late onset disease there may only be non-specific muscle changes
4. The staining characteristics of vacuoles confirm that they are secondary liposomes filled with glycogen
5. Variation in fiber size, necrotic and regenerating fibers and splitting may be demonstrated
6. In late stages, there is endomysial connective tissue fibrosis and fiber atrophy
7. Some patients demonstrate neurogenic features of type grouping and group atrophy due to motor neuron degeneration from glycogen storage in anterior horn cells, bulbar nuclear and Schwann cells

8. The correlation between genotype and phenotype is close. Patients with the most severe phenotype have two pathogenic mutations, one in each GAS allele
9. Adult onset patients have higher levels of GAA activity
10. Alpha-glucosidase is a liposomal enzyme that cleaves the 1, 4 and 1, 6 linkages in glycogen, maltose and isomaltose. Enzyme deficiency causes glycogen accumulation
11. Mechanisms that cause pathology that have been suggested include:
 - a. Progressive expansion of glycogen-filled lysosomes with release of muscle destructive proteases
 - b. Increased muscle metabolism which has been demonstrated in approximately 1/3 of patients
 - c. Decreased mean protein balance

Laboratory Evaluation

1. Assay of α -glucosidase activity is possible in muscle, fibroblasts, leukocytes, lymphocytes and in the urine
2. Dried blood spot analysis
3. Serum CK is moderately increased in infantile forms but may be normal in adults
4. EMG
 - a. Increased insertional and spontaneous activity with positive sharp waves, fibrillation potentials, complex repetitive discharges and occasional myotonic discharges
 - b. Myopathic MUAPs
 - c. NCS are normal
 - d. In mild types of disease initial features may only be demonstrated in paraspinal muscles
5. MRI/CT of muscle:
 - a. Early and severe involvement of the adductor magnus and semimembranosus muscles; as the disease progresses there is fatty infiltration of the long head of the biceps femoris, semitendinosus and the anterior thigh muscles
 - b. In late stages there is selective sparing of the sartorius, rectus femoris, graciles and components of the vastus lateralis
6. EKG:
 - a. Left axis deviation, short PR interval, large QRS complexes, ST depression and persistent sinus tachycardia
 - b. Wolffe-Parkinson-White syndrome may be seen in both infantile and adult patients
7. Echocardiography:
 - a. Hypertrophic cardiomyopathy
8. Pulmonary function studies:
 - a. Restrictive deficits
 - b. Decreased forced vital capacity
 - c. Decreased maximal inspiratory and expiratory pressures
 - d. Diaphragmatic fatigue

Type III Glycogenosis (Debranching Enzyme Deficiency)*General Characteristics*

1. Mutations in the debranching enzyme gene AGL that maps to chromosome 1p21 causes both GSDIIIa and GSDIIIb
2. The differential expression of the AGL gene is caused by alternative splicing and differential RNA transcription
 - a. The enzyme has two catalytic functions, oligo-1, 4-1, 4-glucotransferase and amylo-1-6-glucosidase activities
 - b. Subsequent to phosphorylase shortening of the peripheral glycogen chain to four glucosyl units, the debrancher enzyme removes the remaining end in two stages:
 - i. The transferase activity moves a maltose unit to an acceptor chain
 - ii. The single remaining glucosyl unit then is hydrolyzed by the amylo-1-6 glucosidase which severs the branch

Clinical Manifestations

1. In GSDIIIa there is an enzyme deficiency in both the liver and muscle whereas in GSDIIIb the deficiency only occurs in the liver
2. Clinical Manifestations of GSDIIIa:
 - a. Onset of muscle weakness occurs in infancy or childhood but is not clinically manifest until the third or fourth decade
 - b. In approximately 50% of patients there is weakness and atrophy of distal extremity muscles particularly the peroneal and calf musculature
 - c. Toe walking associated with fibrotic heel cords is seen
 - d. A subgroup of patients has a superimposed sensorimotor neuropathy
 - e. Pseudohypertrophy of proximal muscle groups may occur
 - f. Respiratory muscles are involved and insufficiency can progress rapidly
 - g. A cardiomyopathy may be seen with or without extremity weakness
 - h. Rarely there may be cramps, myalgias, exercise intolerance and myoglobinuria

Neuropathology

1. Muscle biopsy:
 - a. Vacuoles filled with glycogen in subsarcolemmal and intermyofibrillar regions of muscle fibers are seen. The vacuoles stain with PAS and are digested by diastase and do not stain with acid phosphatase
 - b. Free glycogen and some Wiltens liposomes are seen
 - c. Abnormal glycogen can accumulate in the skin and peripheral nerves
 - d. Muscle tissue demonstrates loss of debrancher enzyme activity

Laboratory Evaluation

1. Serum CK is elevated two to twenty times normal
2. EMG:
 - a. An irritative myopathy with myopathic MUAPs similar to the findings seen in acid maltase deficiency
3. Exercise testing reveals a normal rise of serum ammonia but no increase in lactate levels
4. Pulmonary function studies are positive in those with respiratory muscle involvement with decreased forced vital capacity
5. EKG demonstrates conduction defects and arrhythmias
6. Echocardiography
 - a. Hypertrophic obstructive cardiomyopathy

GSDIV (Branching Enzyme Deficiency)*General Characteristics*

1. GSDIV is caused by deletions or nonsense mutations in the glycogen branching enzyme gene (GBE1) that maps to chromosome 3q12
2. Enzyme deficiency causes the deposition of amylopectin – like polysaccharide that has fewer branching points and longer outer chains than normal glycogen
3. There are two infantile forms and an adult form known as adult polyglucosan disease

Clinical Manifestations

1. Fetal akinesia is characterized by:
 - a. Arthrogryposis
 - b. Pulmonary hypoplasia
 - c. Craniofacial dysmorphism
 - d. Intrauterine retarded growth
 - e. Abnormal amniotic fluid volume
 - f. Perinatal death
2. The classic most common type:
 - a. Presents in infancy
 - b. Progressive hepatic dysfunction with hepatosplenomegaly
 - c. Failure to thrive
 - d. Muscular weakness, hypotonia, atrophy and depressed muscle stretch reflexes
 - e. Patients die of liver failure by 5 years of age
 - f. A benign hepatic form has been described
 - g. There is a primary manifestation of muscle weakness, atrophy and cardiomyopathy with either proximal or distal muscle involvement
 - h. A deficit in RBCK1, a ubiquitin ligase, has been described in cardiomyopathy polyglucosan disease
3. Adult form:
 - a. Presentation in adulthood
 - b. Progressive upper and lower motor neuron signs
 - c. Sensory neuropathy
 - d. Neurogenic bladder
 - e. Dementia occurs in approximately 50% of patients
 - f. Cerebellar ataxia
 - g. Rarely polyglucosan neuropathy occurs in children
 - h. A report of two adults with fluctuating signs

Neuropathology

1. Deposition of finely granular and filamentous polysaccharide polyglucosan bodies in the CNS, in axons and Schwann cells, the skin, liver, cardiac and skeletal muscle
2. Polyglucosan bodies are PAS-positive and diastase resistant (not glycogen) which resembles amylopectin
3. Amylopectin-like material can be seen in motor neurons of the brainstem and spinal cord as well as systemically

Laboratory Evaluation

1. Serum CK is normal or only minimally elevated
2. EMG:
 - a. Myopathic pattern
 - b. Hyperactive pattern with increased insertional activity, positive sharp waves and fibrillation potentials
 - c. Similar pattern to that seen in GSDII and III
 - d. In patients with polyglucosan neuropathy EMG reveals:
 - i. An axonal sensorimotor neuropathy with superimposed polyradiculopathy
3. EKG:
 - a. Conduction alterations that may lead to complete AV block
4. Echocardiography
 - a. Dilated cardiomyopathy
5. The enzyme deficiency can be demonstrated in muscle, fibroblasts and leukocytes:
 - a. In patients with primary neuromuscular involvement, the deficiency of GBE may only be seen in muscle and can be normal in adult polyglucosan disease

Type V Glycogenosis (McArdle's Disease)
(Myophosphorylase Deficiency)

General Characteristics

1. Myophosphorylase deficiency is an autosomal recessive disorder caused by mutations in the PYGM gene that maps to chromosome 11q13 and encodes myophosphorylase
2. Myophosphorylase catalyzes the first step of glycogen catabolism by utilizing glucose-1-phosphate from glycogen storage deposits
3. It lyses α -1,4 glucosyl residues from the outer branches of glycogen and generates glucose-1-phosphate
4. It has been recently shown that lack of the generation of ATP may not be the cause of the disease, which is caused by a series of biochemical events that include:
 - a. An increase of adenosine diphosphate
 - b. An intracellular pH that is not low enough in response to exercise
 - c. Low inorganic phosphate levels
 - d. A higher intracellular calcium level that normally occurs in ischemic exercised muscle

- e. It has been postulated that the increase in ADP may inhibit dissociation of the actin-myosin from bridges, which would increase contraction
- f. McArdle's disease patients also demonstrate:
 - i. Decreased concentration of muscle sodium-potassium pump ATP
 - ii. Higher serum potassium concentration with exercise
 - iii. Increased heart rate greater than controls with exercise
 - iv. Increased extracellular potassium partially depolarizes the muscle membrane which inactivates sodium channels and decreases membrane excitability
 - v. The mechanisms that reduce sodium-potassium pump activity in skeletal muscles are not known and may not be the mechanism of disease

Clinical Manifestations

1. Usually presents in childhood or in young adults with exercise intolerance
2. Exercise induced pain and cramps during brief high intensity activity and during prolonged low intensity exercise
3. If exercise is continued after pain is noted, electricity silent contractures may occur
4. A subset of patients present with undue fatigue after exercise without cramps or muscle pain
5. Patients may develop a "second wind" phenomenon that is characterized by less pain and the ability to continue the activity at a low level of function. This effect is due to the metabolism of blood-derived recently mobilized glucose
6. Myoglobinuria is usually not evident until the second or third decade
7. Approximately 50% of myoglobinuria attacks occur with vigorous exercise and 1/3 of them cause renal insufficiency
8. Most patients have normal strength although approximately 1/3 may develop proximal weakness after recurrent bouts of rhabdomyolysis
9. Rarely patients present with proximal muscle weakness rather than exercise intolerance. The weakness may be in the arms to a greater degree than the legs and may be asymmetric
10. Rare congenital patients have developed respiratory failure within the first years

Neuropathology

1. Muscle biopsy:
 - a. Glycogen accumulation occurs subsarcolemmally and between myofibrils
 - b. Variation in fiber size
 - c. Scattered necrotic and regenerating fibers
 - d. Reduced or absent myophosphorylase enzyme activity

Laboratory Evaluation

1. Serum CK is elevated
2. The forearm ischemic exercise test:
 - a. Normal rise in serum ammonia and no significant rise in lactic acid
3. EMG:
 - a. Normal

Type III Glycogenosis (PFK Deficiency)*General Characteristics*

1. PFK deficiency is an autosomal recessive disorder mapped to mutations in the PFK gene in chromosome 12q13
2. PFK is a tetrameric enzyme encoded by three autosomal genes; PFK encodes the muscle subunit, PFKL the liver subunit and PFKP the platelet subunit
3. Mature human muscle expresses only the M subunit and only the M4 homotetramer whereas erythrocytes express both the M and L subunits
4. PFK mutations cause a total lack of enzyme activity in muscle but only a partial deficiency in red blood cells
5. PFK catalyze the conversion of fructose 6-phosphate to fructose 1, 6 diphosphate
6. There is ADP accumulation in muscle, but the status of sodium-potassium pumps has not been defined

Clinical Manifestations

1. Clinically patients have exercise intolerance, muscle pain and contractures and relief by rest
2. There is no “second wind phenomena”
3. There is a lower incidence of myoglobinuria than that which occurs with McArdle’s disease
4. There may be jaundice from mild hemolysis
5. Gouty arthritis may occur due to “myogenic hyperuricemia”
6. Variability of the clinical phenotypes include:
 - a. Hemolytic anemia without myopathy
 - b. Later onset adulthood type with fixed proximal weakness or a scapuloperoneal phenotype; the patients may have had only mild exercise intolerance early in the course of their illness but no cramps or myoglobinuria
 - c. An infantile form with severe generalized weakness and cardiomyopathy may occur with contractures, cortical blindness, and corneal opacifications. They do not have hemolytic anemia. Death occurs from cardiorespiratory failure during infancy or childhood

Neuropathology

1. Muscle biopsy:
 - a. There is an abnormal accumulation of glycogen and polysaccharide (the latter most prominent in older patients) that stains for PAS but is diastase resistant
 - b. Non-specific myopathic changes without abnormal glycogen deposits may occur in the infantile form

Laboratory Evaluation

1. CK is usually elevated and there may be a mild anemia and increased reticulocyte count
2. Exercise forearm testing demonstrates a normal rise in ammonia but minimal increase in lactic acid
3. EMG:
 - a. Normal
4. Glucose or fructose infusion increase exercise intolerance because these patients rely on free fatty acids as their energy source. Glucose reduces blood levels of free fatty acids

Type VIII Glycogenosis (Myophosphorylase Kinase)*General Characteristics*

1. Phosphorylase B kinase is a multimeric enzyme composed of four different subunits α , B, R, J
2. PBK deficiency has been associated with several syndromes that include:
 - a. X-linked recessive hepatopathy
 - b. An autosomal liver and muscle disease
 - c. A pure myopathy predominant in men
 - d. An autosomal liver disease with cirrhosis and
 - e. A cardiomyopathy of infancy
3. The pure myopathy has been best described in men and is due to α mutations in the X-linked gene PBKA1

Clinical Manifestations

1. AR PBK deficiency is associated with various clinical manifestations. The alpha-subunit is muscle-specific
2. Presents in infancy and adulthood
3. The most common presentation is exercise intolerance with cramps and myoglobinuria
4. The infantile form can be associated with mild weakness and delay in achieving motor milestones; a fatal cardiomyopathy may occur
5. Approximately 50% of patients develop from a separate mutation (mutations in any of the PBK genes) in the PRKAG2 gene that encodes the gamma 2 subunit of the AMP activated protein kinase (AMPK)

Neuropathology

1. Muscle biopsy:
 - a. Variability in fiber size, some scattered necrotic fibers and minimal sarcolemmal glycogen
 - b. The biopsy may be normal, other than showing a deficit in myophosphorylase b kinase activity
 - c. PBK catalyzes the conversion of inactive myophosphorylase to an active form as well as converting active glycogen synthetase to an inactive form

Laboratory Evaluation

1. The serum CK is normal or minimally elevated
2. The EMG is usually normal
3. The ischemic forearm exercise test usually demonstrates a blunted lactate rise

Type IX Glycogenosis (PGK Deficiency)*General Characteristics*

1. PGK deficiency is caused by mutations in the PGK gene that map to chromosome Xq11
2. The clinical presentation depends on the isolated or combined involvement of three tissues 1. erythrocytes (hemolytic anemia), 2. skeletal muscle, 3. CNS
3. PGK catalyzes the reaction of acetyl phosphate transfer of 1,3 diphosphoglycerate to ADP that forms 3-phosphoglycerate and ATP in the later stage of glycolysis

Clinical Manifestations

1. Commonly present in male children as hemolytic anemia, mental retardation and seizures
2. The myopathy is associated with exercise intolerance, cramps and recurrent myoglobinuria
3. Some patients develop a slowly progressive proximal myopathy
4. Two patients have been reported with juvenile Parkinson's disease

Neuropathology

1. Muscle biopsy
 - a. May demonstrate mild and diffuse PAS-positive material but is usually normal
2. Electron microscopy
 - a. Reveals abnormal glycogen
3. PGK enzyme activity is decreased

Laboratory Evaluation

1. Serum CK levels are two to three times normal
2. Hemolytic anemia may occur with the myopathy
3. Ischemic forearm exercise test demonstrates normal lactate rise
4. EMG
 - a. Usually is normal

Type X Glycogenosis (PGAM Deficiency)*General Characteristics*

1. PGAM deficiency is caused by mutation in the PGAM gene that has been mapped to chromosome 7p13-p12.3. It is an autosomal recessive disease
2. The enzyme is dimeric and composed of a muscle-specific (M) subunit and a brain specific (B) subunit; normal human muscle contains the MM homo-dimer (that accounts for approximately 95% of the total enzyme activity)
3. None of the fourteen patients reported with the muscle defect have been African-American which suggest a founder effect
4. PGAM catalyzes the interconversion of 2- and 3-phosphoglycerate which is deficient in PGAM myopathy

Clinical Manifestations

1. Presents in childhood or early adulthood

2. Exercise intolerance, cramps and recurrent myoglobinuria

Neuropathology

1. Muscle biopsy:
 - a. PAS staining demonstrates increased glycogen
 - b. Association with tubular aggregates in type 2B muscle fibers
 - c. There may be a severe decrease of PGAM muscle activity with minimally elevated glycogen content

Laboratory Evaluation

1. CK in the serum is minimally increased
2. Ischemic forearm exercise test demonstrates an abnormal lactate response
3. EMG:
 - a. Normal

Type XI Glycogenosis (Lactate Dehydrogenase Deficiency)*General Characteristics*

1. The muscle isoform of lactate dehydrogenase is encoded by the LDHA gene that has been mapped to chromosome 11p15
2. The LDH isoenzyme in muscle has 4M subunits
3. LDH deficiency is autosomal recessive
4. The enzyme catalyzes the interconversion of pyruvate to lactate when oxygen is absent or in short supply. If the concentration of lactate is high, the enzyme decreases the rate of conversion of pyruvate to lactate. The enzyme also catalyzes the dehydrogenation of 2-hydroxybutyrate to a lesser degree

Clinical Manifestations

1. Exercise intolerance, muscle cramps and recurrent myoglobinuria
2. Muscle strength is normal
3. Some patients develop a scaly, erythematous rash
4. Uterine abnormalities in early pregnancy, which has not occurred with other glycogenoses
5. Renal insufficiency may be seen from the recurrent myoglobinuria

Neuropathology

1. Muscle biopsy:
 - a. The histology is normal but there is reduced LDH enzyme activity

Laboratory Evaluation

1. Serum CK is moderately elevated
2. The ischemic forearm exercise test demonstrates no rise in lactate but a normal increase in pyruvate
3. The LDH-M isoform may be less than 5% of normal in muscle
4. EMG:
 - a. Normal

Type XII Glycogenosis (Aldolase A Deficiency)*General Characteristics*

1. Homozygous point mutations in the Aldolase A gene that maps to chromosome 16q22-24 have been reported in patients with myopathy
2. Aldolase catalyzes the reaction of fructose 1,6 phosphate to dihydroxyacetone phosphate and glyceraldehyde-3-phosphate

Clinical Manifestations

1. Exercise intolerance and weakness that is temperature dependent and can occur without hemolysis
2. Myoglobinuria was always triggered by a febrile illness in 3 affected siblings
3. Red cell aldolase deficiency is associated with nonspherocytic hemolytic anemia

Neuropathology

1. Muscle biopsy:
 - a. Histologically normal by light microscopy
2. Electron microscopy:
 - a. Accumulation of lipid
3. Reduced aldolase activity in muscle

Laboratory Evaluation

1. Serum CK is elevated

Type XIII Glycogenosis (Triosephosphate Isomerase Deficiency)*General Characteristics*

1. Triosephosphate isomerase deficiency is an autosomal recessive multisystem disorder caused by homozygous or compound heterozygous mutations in the TPI gene that maps to chromosome 12p13.31
2. TPI adjusts the rapid equilibrium between dihydroxyacetone phosphate and glyceraldehyde-3-phosphate produced by aldolase during glycolysis. This reaction is interconnected to the pentose phosphate pathway by triosephosphates

Clinical Manifestations

1. The phenotype is variable
 - a. An infant onset patient who develops generalized hypotonia, cognitive disability and hemolytic anemia
 - b. Two Bulgarian siblings:
 - i. Hemolytic anemia in infancy
 - ii. Muscle weakness and fatigue at 2 years of age
 - iii. One sibling developed a scissoring gait, areflexia, extensor plantar responses, generalized hypotonia, muscle atrophy, ataxia and jerky movement of the upper extremities; the second sibling had an intention tremor and never gained the ability to walk
 - iv. Other children were born with hypotonia, weakness, hemolytic anemia, and loss of reflexes

Neuropathology

1. Increased glycogen accumulation by both light and electron microscopy

Laboratory Evaluation

1. The serum CK may be normal to moderately elevated
2. EMG:
 - a. Some patients had a myopathic pattern
 - b. Anterior horn cell involvement with neurogenic pattern

Type XIV Glycogenosis (β -Enolase Deficiency)*General Characteristics*

1. Muscle β -enolase deficiency is a rare mutation in the β -enolase gene 3 (ENO3) that maps to chromosome 17p13.2
2. The enzyme catalyzes the interconversion of 2-phosphoglycerate and phosphoenolpyruvate

Clinical Manifestations

1. Exercise intolerance
2. Myalgias
3. Recurrent rhabdomyolysis

Neuropathology

1. Muscle biopsy:
 - a. Abnormal sarcoplasmic glycogen accumulation
 - b. 10–15% of muscle β -enolase activity

Laboratory Evaluation

1. Serum CK levels can be normal to mildly elevated
2. EMG:
 - a. Myopathic pattern

Lysosomal Glycogen Storage Myopathies**Danon Disease***General Characteristics*

1. Danon disease is caused by mutations in the LAMP-2 gene that maps to chromosome Xq24
2. It is an X-linked dominant disease that predominately affects cardiac muscle with skeletal muscle and cognitive impairment as variable components

Clinical Manifestations

1. The initial description by Danon described the triad of hypertrophic or dilated cardiomyopathy, myopathy and cognitive impairment
2. Men are more severely affected than women, although female carriers can be symptomatic
3. Patients are normal at birth but develop proximal muscle weakness and cardiomyopathy by early adulthood
4. Approximately 70% of men are cognitively impaired compared to 6% of women
5. Ophthalmologic features may be concomitant with myopathy, pinhead pigmentary retinopathy, and abnormal visual fields. Cones may be affected more than rods

Neuropathology

1. Muscle biopsy:
 - a. Variation in fiber size
 - b. Autophagic vacuoles
 - c. Increased free glycogen is noted between disrupted myofibrils and within membrane sacs and vacuoles
2. Electron Microscopy:
 - a. Some vacuoles are bound by basal lamina
 - b. Absence of liposome-associated membrane protein-2 (LAMP-2)
 - c. There is no membrane deposition of attack complex in muscle fibers

Laboratory Evaluation

1. Serum CK is moderately elevated
2. EMG:
 - a. Irritative features that include increased insertional activity, positive sharp waves, fibrillation potentials, and complex repetitive discharges. Rarely myotonic discharges occur
 - b. Increased recruitment of low amplitude, short duration polyphasic MUAPs
 - c. Normal NCS
3. EKG:
 - a. Wolffe-Parkinson-White is the most frequent arrhythmia. Other arrhythmias include 1. atrioventricular block, 2. bundle branch block, 3. bradycardia, 4. arterial fibrillation
4. Echocardiography:
 - a. Hypertrophic or dilated cardiomyopathy

X-Linked Myopathy with Excessive Autophagy*General Characteristics*

1. X-linked myopathy with excessive autophagy is an autophagic myopathy frequently classified with Pompe-Danon disease due to some shared features seen in muscle biopsy that include an aberrant accumulation of autophagic vacuoles
2. It is caused by mutations of the XMEA gene that map to chromosome Xq28
3. The mutation reduces the activity of lysosomal hydrolases. XMA2 protein regulates the construction of an ATPase that is required to acidify lysosomes. The increased lysosomal pH and failure to degrade cellular debris may induce the increase in autophagic lysosomes

Clinical Manifestations

1. The onset is variable with presentation both during infancy or early adulthood
2. There is slowly progressive proximal weakness and atrophy
3. Respiratory weakness occurs but it is unusual to develop the cardiomyopathy that is characteristic of Danon disease
4. Cognitive function is intact

Neuropathology

1. Muscle biopsy:
 - a. Variation in fiber size
 - b. Many fibers have vacuoles that are not PAS-positive that distinguishes them from acid maltase deficiency and Danon disease
 - c. LAMP-2 is seen in the vacuoles and the cytoplasm
 - i. Calcium and membrane attack complex (C5 b-q) are seen on the sarcolemmas of affected muscle fibers
 - d. Electron microscopy:
 - i. Some vacuoles are bound by basal lamina adjacent to the sarcolemma where they fuse with the cell membrane. This permits discharge of their contents into the extracellular space
2. Reduction folds of basal lamina surround muscle fibers

Laboratory Evaluation

1. The CK is normal or minimally increased
2. EMG:
 - a. Irritative features include increased insertional activity with positive sharp waves, fibrillation potentials, complex repetitive discharges, and myotonic discharges
 - b. Early recruitment of low amplitude, short duration polyphasic MUAPs
3. Normal NCS (nerve conduction studies)

Disorders of Purine Nucleotide Metabolism***Myoadenylate Deaminase (MAD Deficiency)****General Characteristics*

1. Myoadenylate deaminase deficiency is caused by homozygous and heterozygous mutations in the AMPD gene that maps to chromosome 1p13.2. AMPD1 deficiency causes muscle symptomatology while AMPD3 is found in RBCs

Clinical Manifestations

1. The relationship of clinical symptomatology to myoadenylate deaminase MAD deficiency is controversial because:
 - a. In sustained isometric muscle contraction with ischemic oxygen use, resting and post excessive lactate, phosphocreatine levels are normal
 - b. It has been suggested that the mutations associated with MAD deficiency may be polymorphic
2. Patients may develop exertional muscle pain, fatigue and myoglobinuria which occurs in adolescence to middle age
3. Normal neurological examination

Neuropathology

1. Muscle biopsy:
 - a. Histologically normal
 - b. Low myoadenylate deaminase activity in muscle

2. Myoadenylate deaminase (MAD) catalyzes the reaction that removes an ammonia group from adenosine monophosphate that forms inosine monophosphate. The result of converting AMP to inosine monophosphate is an increase in ATP formation
3. The production of ammonia in the initial reaction buffers lactic acid that is formed during exercise
4. Inosine monophosphate stimulates glycolysis by its effect on the enzyme PFK that is important in the formation of fumarate, a substrate in the Krebs cycle
5. AMPD deficiency covers the level of adenosine. Activated AMP protein kinase (AMPK) is controlled by the concentration of intracellular AMP which may act as an energy sensor. AMPD may control some aspects of muscle metabolism by regulating AMPK activity through the muscle cell AMP concentration

Laboratory Evaluation

1. The serum CK level may be normal or minimally increased
2. EMG:
 - a. Normal
3. Forearm exercise test:
 - a. There is a normal rise of serum lactate but no rise of serum ammonia levels

Lipid Metabolic Disorders

Overview

Long chain fatty acids are the major source of energy for skeletal muscle at rest and during sustained exercise or fasting. Fatty acids pass through the mitochondrial membrane to undergo beta-oxidation by binding with carnitine. Carnitine is primarily synthesized in the liver and is actively transported into muscle against a concentration gradient. Fatty acids are activated upon by fatty acyl CoA synthetase that converts them to acyl coenzyme A (CoA) compounds. Acyl CoA is attached to carnitine by carnitine palmityl transferase (CPT1) on the outer mitochondrial membrane. Acyl carnitine translocase transports the complex through the inner mitochondrial membrane. The compound is converted to free fatty acids and carnitine by carnitine palmitoyl transferase 11 (CPT11) within the mitochondrial matrix. Beta-oxidation of long chain fatty acids occurs within the mitochondria.

Beta-oxidation of fatty acids is accomplished by a sequence of four sequential enzymatic reactions:

1. Flavin-dependent, length specific acyl CoA dehydrogenases (that consist of short, medium, long and very long chain compounds that are converted into enoxl-CoA's) that reduce flavin adenine nucleotides (FAD)
2. Length specific enoxl-CoA hydratase catalyzes the reaction to form 3-hydroxy acyl-CoA compounds

3. 3-hydroxy acyl-CoA dehydrogenases catalyze the reaction that forms 3-ketoacyl CoA esters that is due to a second dehydrogenation reaction
4. During the last step, 3-Keto-thiolase catalyzes the reaction that converts 3-Ketoacyl CoA to acetyl-CoA and fatty acyl-CoA that has shortened the Acyl CoA by two carbons. Electrons that were transferred to FADH₂ and NADH are transferred to the respiratory chain of the inner mitochondrial membrane. Electrons from FADH are transferred to coenzyme Q while the electrons from NADH are transferred to complex I of the respiratory chain. The electrons are transported down an energy gradient that generates a proton motive force that is essential in the production of ATP.

Carnitine Transporter Deficiency (Primary Carnitine Deficiency)

General Characteristics

1. Primary carnitine deficiency is caused by homozygous mutations in the SLC22A5 gene that map to chromosome 5q31
2. Carnitine is generated by endogenous synthesis or supplied by the diet
3. Intracellular levels are 20–50 times higher than extracellular concentrations due to an active transport system
4. Carnitine deficiency decreases the transport of long chain fatty acids into the inner mitochondrial matrix

Clinical Manifestations

1. Systemic primary carnitine deficiency is clinically heterogeneous:
 - a. Early childhood type:
 - i. Acute attacks of vomiting
 - ii. Hypoglycemia
 - iii. Altered mental status
2. Patients may worsen during pregnancy or the post-partum

Neuropathology

1. The defect in the high affinity carnitine transporter that is expressed in muscle, heart, kidney, lymphoblasts and fibroblasts results in impaired fatty acid oxidation in these tissues
2. Impaired or absent carrier dependent uptake of carnitine in fibroblast from patients has been demonstrated
3. Muscle biopsy:
 - a. Variability in fiber size
 - b. Abnormal accumulation of subsarcolemmal and intermyofibrillar lipid primarily in type 1 fibers
4. Electron microscopy:
 - a. Increased lipid
5. Muscle carnitine levels are decreased to less than 4% of normal
6. Secondary carnitine deficiency occurs from:
 - a. Respiratory chain defects
 - b. Organic acidurias

- c. Renal wasting
- d. Liver failure
- e. Toxic medications
- f. Malnutrition

Laboratory Evaluation

1. In primary carnitine deficiency there are very low levels of carnitine in muscle (<4%) while in secondary forms there is only a moderate 25–50% reduction
2. Serum CK levels are normal in 50% of patients with the myopathic form of the disease. They may be markedly elevated in primary systemic carnitine deficiency
3. Fasting in patients with carnitine deficiency may be associated with increased CK levels, hypoglycemia, acidosis (without ketone bodies), and increased liver enzymes
4. EMG:
 - a. May have irritative features of positive sharp waves, fibrillation potentials, increased insertional activity, and complex repetitive discharges
 - b. There is early recruitment of low amplitude, short duration polyphasic MUAPs
5. Echocardiography:
 - a. May demonstrate a biventricular or hypertrophic cardiomyopathy

Carnitine Palmitoyl Transferase 2 (CPT2) Deficiency

General Characteristics

1. CPT2 deficiency is autosomal recessive and is caused by mutations in the CPT2 gene that map to chromosome 1p32
2. Mutations impair the transport of acyl carnitine across the inner mitochondrial membrane that reduces ATP production from fatty acids

Clinical Manifestations

1. Onset is usually in the second or third decade with muscle pain and myoglobinuria after intense or prolonged exercise
2. Fasting and infections may precipitate signs and symptoms
3. The neurologic examination is normal between intervals of rhabdomyolysis and myoglobinuria
4. A severe cardiomyopathy occurs during infancy or early childhood

Neuropathology

1. Muscle biopsy:
 - a. Normal histology with light microscopy
 - b. Electron microscopy:
 - i. Increased lipid content

Laboratory Evaluation

1. Serum CK levels are normal at rest but may be elevated with intense exercise or during fasting
2. Normal forearm exercise tests that are a distinguishing feature from glycogen storage diseases

3. Muscle and serum carnitine levels are normal
4. EMG:
 - a. Usually normal but may show a myopathic pattern
5. EKG is normal

Very Long Chain Acyl CoA Dehydrogenase (VLCAD) Deficiency

General Characteristics

1. VLCAD deficiency is caused by mutations in the VLCAD gene that map to chromosome 17p11.2-p13.1

Clinical Manifestations

1. There are 3 clinical types of VLCAD deficiency:
 - a. A severe early-onset form with cardiomyopathy
 - b. Childhood onset intermediate form with hypoketotic hypoglycemia
 - c. Adult onset myopathic form with isolated muscle involvement:
 - i. The isolated muscle form most often demonstrates rhabdomyolysis

Neuropathology

1. There is abnormal accumulation of lipid in muscle biopsies
2. One adult patient was found to have <10% of residual enzyme activity

Laboratory Evaluation

1. Serum CK is increased during episodes of myoglobinuria but may be normal between attacks
2. Consistent with a defect in beta oxidation of long chain fatty acids in which the serum demonstrates:
 - a. An increased plasma concentration of tetradecanoic acid (C14:1) with normal levels of myristic acid (C14:0)
3. There is reduced VLCAD activity in cultured fibroblasts
4. During episodes of hypoketotic hypoglycemia there is dicarboxylic aciduria
5. EMG:
 - a. Myopathic MUAP

Long Chain Acyl Dehydrogenase (LCAD) Deficiency

General Characteristics

1. Long chain acyl dehydrogenase deficiency is due in some patients to mutations in the ACADL gene that maps to chromosome 2q34-q35

Clinical Manifestations

1. The disease most often presents in infancy with:
 - a. Failure to thrive
 - b. Hepatomegaly
 - c. Cardiomegaly
 - d. Encephalopathy similar to Reye's syndrome
2. Adult patients may develop:
 - a. Exercise intolerance
 - b. Rhabdomyolysis and proximal muscle weakness

Neuropathology

1. Muscle biopsy:
 - a. Increased lipid

Laboratory Evaluation

1. Increased serum CK during attacks of rhabdomyolysis
2. Total and free carnitine levels are decreased in the serum and muscle
3. Long-chain acyl carnitine esters are increased
4. Decreased LCAD in cultured fibroblasts

Medium Chain Acyl Dehydrogenase (MCAD) Deficiency*General Characteristics*

1. MCAD deficiency is caused by homozygous or compound heterozygous mutations in the medium-chain acyl-CoA gene (ACADM) that maps to chromosome p31
2. The enzyme acts on fatty acyl-CoA derivatives whose acyl residues contain four to fourteen carbons

Clinical Manifestations

1. Rare cardiac or skeletal muscle involvement
2. Onset is usually in infancy but symptomatology can occur in later life
3. Intolerance to prolonged fasting
4. Recurrent episode of hypoglycemia and coma
5. Sudden death in early childhood
6. Episodes of rhabdomyolysis and acute encephalopathy can occur in infancy and late in life

Neuropathology

1. Muscle biopsy:
 - a. Increased lipid
2. Enzyme activity is <10% in muscle, muscle fibroblasts and the liver
3. Secondary carnitine deficiency occurs

Laboratory Evaluation

1. Genetic evaluation of the ACADM gene
2. Medium-chain acyl-coenzyme A dehydrogenase deficiency is the most common disorder of mitochondrial fatty acid oxidation
3. Elevated serum CK during episodes of rhabdomyolysis
4. EMG:
 - a. Myopathic pattern
5. Increased urinary secretion of dicarboxylic, adipic and sebatic acids

Short Chain Acyl Dehydrogenase (SCAD) Deficiency*General Characteristics*

1. SCAD deficiency is an autosomal recessive disorder of fatty acid beta-oxidation due to mutations in the SCAD gene that maps to chromosome 12q24.31

Clinical Manifestations

1. There are two clinical phenotypes of SCAD deficiency that present:

a. Infantile type:

- i. A generalized disease in infants
- ii. Failure to thrive
- iii. Metabolic acidosis
- iv. Developmental delay
- v. Seizures
- vi. Myopathy

2. There are no episodes of non-ketotic hypoglycemia that distinguishes this disorder from MCAD deficiency and VLCAD deficiency

a. Early to mid-adulthood type:

- i. Progressive proximal weakness
- ii. Myalgias
- iii. Exercise intolerance

b. Variable signs include:

- i. Facial weakness
- ii. Ophthalmoplegia
- iii. Respiratory muscle involvement
- iv. Cardiomyopathy

Neuropathology

1. Increased lipid in muscle
2. Secondary carnitine deficiency
3. Decreased SCAD in muscle
4. Multicore myopathy has been described with SCAD deficiency

Laboratory Evaluation

1. Serum CK is normal or minimally elevated
2. Ethyl malonate and methyl succinate may be excreted in the urine

Mitochondrial Trifunctional Protein (TFP)*General Characteristics*

1. Trifunctional protein is a complex attached to the inner mitochondrial membrane that catalyzes three specific steps in the beta-oxidation of long chain fatty acids:
 - a. It is composed of four alpha- and four beta-subunits which contain three functional domains:
 - i. The four alpha-subunits contain the enoyl-CoA hydratase and 3-hydroxyacyl-CoA dehydrogenase enzymatic activity
 - ii. The four beta-subunits mediate beta-ketothiolase enzymatic activity
 - iii. The alpha-subunits are encoded by the HADHA gene
 - iv. The HADHA and HADHB genes map to chromosome 2p23.3
 - v. Mitochondrial trifunctional protein catalyzes three of the four steps in beta-oxidation of fatty acids
 - vi. Association with the electron transport chain:
 1. Fatty acid beta-oxidation and oxidative phosphorylation are two of the major metabolic pathways in mitochondria

2. The reducing equivalents from fatty acid beta-oxidation enter the mitochondrial respiratory chain through complexes I and III
3. The trifunctional protein channels substrate between the two enzymes

Long Chain HAD Deficiency (Long-Chain 3-Hydroxy Acyl CoA Dehydrogenase Deficiency)

General Characteristics

1. The muscle disorder is autosomal recessive and maps to chromosome 2p23
2. The enzyme catalyzes the third step in beta-oxidation of fatty acids that converts 3-hydroxyacyl-CoA derivatives to 3-ketoacyl-CoA derivatives

Clinical Manifestations

1. This is a clinically heterogeneous disease:
 - a. Infantile type:
 - i. Presents in infancy or early childhood:
 1. Nausea and vomiting
 2. Seizures
 3. Hypoketotic hypoglycemic
 4. Cardiomyopathy
 5. Respiratory failure
 - b. Childhood early adult form:
 - i. Progressive proximal muscle weakness
 - ii. Recurrent episodes of myoglobinuria
 - iii. Subset of patients develops a progressive sensorimotor polyneuropathy
 - iv. Pigmentary retinopathy
 - v. Mothers of affected patients may develop acute fatty liver of pregnancy or the HELLP syndrome (hemolysis, elevated liver enzymes, low platelets)

Neuropathology

1. Muscle biopsy:
 - a. Increased lipid content
2. Sural nerve biopsy (one patient):
 - a. Loss of myelinated fibers and axonal degeneration

Laboratory Evaluation

1. Elevated serum CK and lactate levels
2. Fibroblast culture identifies the reduced long-chain 3-hydroxyacyl CoA-dehydrogenase deficit
3. EMG:
 - a. Myopathic MUAPs
 - b. NCS reveal features of axonal sensory neuropathy

Glutaric Aciduria Type II

General Characteristics

1. The disorder is also known as multiple acyl-coenzyme A dehydrogenase (MADD) deficiency
2. The disease can be caused by mutations in three different genes:

- a. ETFA that maps to chromosome 15q24.2 – q24.3 (glutaric aciduria II A)
- b. ETFB that maps to chromosome 19q13.41 (glutaric aciduria II B)
- c. ETF-QO that maps to chromosome 4q32.1 – qter (glutaric aciduria II C)
- d. The genes are all involved in electron transfer to the mitochondrial respiratory chain
- e. There is no difference in the clinical phenotypes from mutations in the specific genes
- f. These enzyme defects cause the inability to oxidize the reduced forms of VLCAD, LCAD, MCAD and SCAD

Clinical Manifestations of MADD Deficiency

1. Neonatal onset:
 - a. With congenital anomalies (type I)
 - b. A neonatal form without congenital anomalies (type II)
 - c. These forms are characterized by:
 - i. Severe non-ketotic hypoglycemia
 - ii. Metabolic acidosis
 - iii. Hepatomegaly
 - iv. Both types are usually fatal:
 1. Childhood type:
 - a. May present with progressive proximal muscle weakness and atrophy that are associated with:
 - i. Episodic confusion
 - ii. Nausea and vomiting
 - iii. Ataxia and tremor
 - iv. Recurrent episodes of exercise induced Myoglobinuria
 2. Late onset type:
 - a. Symptoms and age at presentation are variable and are associated with:
 - i. Episodic lethargy
 - ii. Vomiting
 - iii. Hypoglycemia
 - iv. Metabolic acidosis
 - v. Hepatomegaly that is often preceded by metabolic stress
 - vi. Muscle involvement includes:
 1. Pain
 2. Weakness
 3. Intermittent and may only be experienced during illness or catabolic stress
 - vii. Cardiomyopathy

Neuropathology

1. Muscle biopsy:
 - a. Increased lipid

Laboratory Evaluation

1. Decreased ETF-QO concentration in cultured fibroblasts

2. Secondary carnitine deficiency occurs in the plasma, liver, and muscle
3. EMG:
 - a. Myopathic MUAPs
 - b. NCS reveal an axonal sensory neuropathy

Neutral Lipid Storage Disease with Myopathy

General Characteristics

1. Neutral lipid storage disease with myopathy (NLSMD) is an autosomal recessive disease and is caused by mutations in two genes:
 - a. Homozygous or compound heterozygous mutation in the PNPLA2 gene that maps to 11p15.3
2. Encodes adipose triglyceride lipase

Clinical Manifestations

1. Adult onset
2. Slowly progressive proximal muscle weakness affecting both upper and lower extremities
3. Distal musculature may be affected
4. Cardiomyopathy occurs in 50% of patients in the late course of the disease
5. Variable features include:
 - a. Diabetes mellitus
 - b. Hepatic steatosis
 - c. Has sensorineural hearing loss
6. Patients have muscle pain, fatigue and atrophy
7. The pattern of muscle involvement may be asymmetric and variable in severity
8. Patients do not have ichthyosis

Neuropathology

1. Increased lipid droplets in muscle are seen on muscle biopsy
2. Triglyceride containing cytoplasmic droplets are noted in leukocytes, bone marrow and muscle
3. Rimmed vacuoles may be seen

Laboratory Evaluation

1. Jordan anomaly:
 - a. The intracytoplasmic lipid storage in leukocytes
2. Biochemical investigations for abnormalities in lipid metabolism are normal

Chanarin-Dorfman Syndrome (CDS)

General Characteristics

1. Chanarin-Dorfman syndrome is caused by mutation of the abhydrolase domain containing 5 (ABHD5) gene that map to chromosome 3p21.33
2. The enzyme is an acyltransferase that is important for the synthesis of phosphatidic acid which is the major intermediate in membrane and storage lipid biosynthesis. It is also a coactivator of adipocyte triglyceride lipase

Clinical Manifestations

1. Chanarin-Dorfman syndrome is a rare form of non-bullous congenital ichthyosis form of erythroderma (NBCIE)
2. Muscle weakness may begin in adulthood and affects proximal muscles
3. Hepatosplenomegaly in infancy
4. Cognitive impairment
5. No cardiomyopathy

Neuropathology

1. Increased lipid droplets
2. MR spectroscopy (2 patients):
 - a. Lipid accumulation in cerebral white matter, cortex, and the basal ganglia

Laboratory Evaluation

1. Muscle biopsy:
 - a. Lipid droplets in muscle
2. Jordan anomaly in leukocytes of the peripheral blood
3. EMG:
 - a. Myopathic pattern

Mitochondrial Myopathies

Overview

Mitochondrial biogenesis occurs with cell division, but is also induced by: oxidative stimuli; an increased energy requirement by the cell; in specific mitochondrial diseases; exercise training; by electrical stimulation; from hormones and during development. Mitochondrial biogenesis is the process by which cells increase their mitochondrial mass. It is a dynamic process. Mitochondria are the major producer of reactive oxygen species as well as the producer of antioxidants. They have a crucial role in apoptosis, detoxification, Ca^{2+} buffering and ATP productions. In general, mutations in the mitochondrial DNA lead to a loss of function in the OXPHOS respiratory chain system with a decrease in ATP production and an increase of reactive oxygen species (ROS) that cause further mtDNA mutations. In mitochondrial diseases, there are compensatory mechanisms that induce mitochondria to increase ATP production.

These mechanisms include:

1. Overexpression of antioxidant enzymes
2. Increased mitochondrial biogenesis
3. Overexpression of respiratory complex subunits
4. A metabolic shift to glycolysis
5. The pathways that have been defined as a compensatory adaptation to energy deficits are PGC-1, sirtuins and AMPK

Mitochondria are pivotal in the conversion of carbohydrates, proteins and lipids into ATP. In the mitochondria:

1. Fatty acids are converted into acetyl-CoA
2. Amino acids are processed to pyruvate

3. Carbohydrates are metabolized to pyruvate in the cytoplasm and are then transported into the mitochondria where pyruvate is converted into Acetyl-CoA to enter the Krebs's cycle

The electrons generated are transferred to the respiratory chain complexes (I–V) that generate ATP. One classification of mitochondrial disease is based on specific metabolic defects:

1. In transport of substrate
2. Substrate utilization
3. Krebs cycle
4. Oxidation phosphorylation coupling
5. Respiratory chain dysfunction

Mitochondrial DNA and Proteins

General Characteristics

1. The mitochondrial genome is a 16.5 KB circular double-stranded DNA
2. It contains no introns
3. There is a single promoter site
4. Transcription is polycistronic which transcribes mitochondrial gene or two large RNAs which are cleaved into:
 - a. 13 messenger RNAs
 - b. 2 ribosomal RNAs
 - c. 22 transfer RNAs
5. The 13 mRNAs are translated into the subunits of the respiratory chain complexes:
 - a. A mutation in a transfer RNA may compromise the translation of the 13 mitochondrial mRNAs
6. Approximately 95% of mitochondrial proteins are encoded by the nuclear genome, translated in the cytoplasm, and transported into the mitochondrion
7. The mitochondrial contribution to the respiratory chain:
 - a. Complex I (NADH-CoQ reductase):
 - i. 7% of 41 subunits are encoded by mtDNA
 - b. Complex II (succinate dehydrogenase CoQ reductase):
 - i. All four subunits are encoded by nuclear genes
 - c. Complex III (CoQH₂-cytochrome C reductase):
 - i. 1 of 11 polypeptides is encoded by mtDNA
 - d. Complex IV (cytochrome C oxidase):
 - i. 3 of 13 subunits are encoded by mtDNA
 - e. Complex V (ATPase synthase):
 - i. 2 of its 4 subunits are encoded by mtDNA

Genetics of Mitochondrial Diseases

1. During fertilization, all mitochondria are derived maternally
2. All cells contain hundreds of mitochondria and each mitochondrion contains several copies of mtDNA
3. Mutations that involve mitochondria are more likely to manifest clinically than nuclear genes because they have no introns and a minimal DNA repair system
4. During germ cell meiosis and somatic cell mitosis, mitochondrial DNA mutations are randomly distributed

Hereditary Patterns of Mitochondrial Distribution

1. Normal homoplasmy:
 - a. Few or no mutant genome
2. Heteroplasmy:
 - a. A mixture of mutant and normal (wild-type) mitochondrial DNA
3. Mutant homoplasmy:
 - a. Predominantly contain mutant genome
4. The phenotype is determined by the relative proportion of mutant and wild-type mitochondria within each cell. The threshold for normal cell function is determined by the number of mutated mitochondria. If a specific threshold is exceeded patients manifest clinically
5. During meiosis and mitosis, there may be a shift in the proportion of mutant mitochondria in daughter cells that can alter genotype (mitotic/meiotic segregation)
6. Mutated mitochondria can utilize both normal mitochondrial encoded mRNA and tRNA from adjacent mitochondria that are known as complementation. Thus, mitochondria with DNA deletions may be able to translate some mtDNA-encoded protein
7. Energy requirements determine the susceptibility of a specific tissue to mitochondrial deficits. The CNS, heart, and exercising skeletal muscle have high requirements and thus a small decrease in ATP generation is symptomatic
8. Primary mtDNA mutations are only inherited from the mother:
 - i. Mitochondrial segregation and heteroplasmy determine the degree of phenotypic expression
 - ii. Women and men are equally affected
9. Mutations in nuclear genes that encode 95% of mitochondrial proteins are inherited in an autosomal dominant pattern (some types of progressive external ophthalmoplegia), autosomal recessive (MNGIE) and an X-linked pattern (Leigh's syndrome)
10. Inheritance may be sporadic in Kearns-Sayre syndrome
11. There may be nuclear gene control over the mitochondrial genome which results in:
 - a. A role in syndrome that have depletions or multiple mtDNA deletions
 - b. In these instances, there may be an autosomal recessive dominant inheritance pattern
12. There is significant genetic heterogeneity within clinical syndromes (point mutations, multiple DNA deletions) and specific mutations may manifest with heterogeneous phenotypes
13. Clinical phenotype variability occurs within families with identical mtDNA mutations

General Laboratory Evaluation

1. Serum CK, lactic acid, and pyruvate concentrations can be normal or elevated
2. Lactic acid levels can be elevated in the cerebrospinal fluid

3. mtDNA depletion is associated with renal tubular defects
4. Ergometry demonstrates a low workload correlated with tachycardia and increased oxygen consumption. The degree of exercise intolerance correlates with decreased oxidative phosphorylation demonstrated by the peak capacity for muscle oxygen extraction and the mitochondrial mutation load
5. The forearm exercise test demonstrates increased and prolonged lactate generation and increased venous oxygen saturation in patients with mitochondrial myopathies with exercise intolerance
6. Nerve conduction studies are normal in mitochondrial myopathy with the exception of NARP (axonal neuropathy) and MNGIE (demyelinating neuropathy)
7. EMG:
 - a. Most often it is normal
 - b. Some myopathies are irritative with increased insertional activity and spontaneous activity
 - c. Small MUAPs with early recruitment in weak muscles
8. EKG:
 - a. Conduction defects
9. MRI:
 - a. Abnormal in patients with mitochondrial encephalomyopathy
 - b. Muscle MRI may resemble that seen with dystrophic disorders
10. Magnetic Resonance Spectroscopy (MRS):
 - a. Decreased creatine phosphate with increased inorganic phosphates with exercise
 - b. Delay in replenishment of phosphocreatine concentration after exercise
11. Mutational analysis

Neuropathology

1. Muscle biopsy:
 - a. Utilizing the modified Gomori trichrome stain:
 - i. Ragged red fibers are present which react with NADH and SDH
 - ii. Lipid droplet accumulation may also occur in these fibers
 - iii. Disorders without mutations mtRNA may not demonstrate ragged red fibers and may have normal NADH and SDH staining:
 1. COX stain which reacts with a subunit encoded by mtDNA may be sensitive in these instances (reveals reduced COX staining) in both ragged red fibers and normal appearing fibers
 - iv. Variable COX staining with intense SDH staining occurs with mtDNA mutations. COX staining variability is a reflection of heteroplasmy while increased SDH staining (all subunits are encoded by nuclear DNA) reflect a compensatory increase of mitochondria
 - v. Electron microscopy:
 1. Abnormalities include:
 - i. Increased numbers of normal mitochondria
 - ii. Enlarged mitochondria with abnormal cristae
 - iii. ParacrySTALLINE inclusions (increased dimeric mitochondrial creatine kinase)

Myoclonic Epilepsy and Ragged Red Fibers (MERRF)

General Characteristics

1. Approximately 80% of MERRF patients have a point mutation in nucleotide 8344 of the mitochondrial genome:
 - a. The mutation causes an A to C transition in the transfer RNA gene (MTTK)
2. There is great genetic heterogeneity in MERRF with mutations in:
 - a. Other different mutations in the tRNA gene (8350; 8366)
 - b. Mutations in MTTL1 (most commonly seen in MELAS)
 - c. Other tRNA mutations that occur with MERRF include:
 - i. tRNA Leu (MTTH)
 - ii. tRNA Phe (MTTF)
 - iii. tRNA Ser (MTTS1)
 - iv. A MERRF phenotype occurs with POLG (multiple mitochondrial DNA deletions) and ND5 (MTND5) gene mutations

Clinical Manifestations

1. The age of onset of disease severity and the specifics of the phenotype are highly variable due to the percentage of mitochondria that segregate into various tissues
2. Onset in childhood or adulthood
3. Myoclonic and generalized tonic-clonic seizures
4. Cognitive impairment
5. Ataxia
6. Sensorineural hearing loss
7. Optic atrophy
8. Muscle weakness and atrophy:
 - a. Generalized
 - b. Predilection for proximal extremity muscles
9. Sensorimotor polyneuropathy
10. Pes cavus
11. The myoclonus may be present at rest but is stimulus sensitive
12. There is no ptosis, ophthalmoparesis, or pigmentary retinopathy, which are distinguishing points from KSS or PEO
13. Cardiomyopathy with conduction block and CHF are frequent
14. Respiratory muscle weakness
15. A subset of patients has multiple symmetric lipomatosis

Neuropathology

1. Muscle biopsy:

- a. Ragged red fibers
- b. COX-negative fibers with increased SDH staining
- 2. CNS neuropathology (brain):
 - a. Neuronal loss and gliosis occurs in:
 - i. Dentate nucleus
 - ii. Globus pallidus
 - iii. Substantia nigra
 - iv. Cerebellar cortex
 - v. Inferior olivary nuclei
 - vi. Optic nerves
- 3. Neuropathology of the spinal cord:
 - a. Demyelination and gliosis of:
 - i. Spinothalamic tract
 - ii. Posterior columns
 - iii. Corticospinal tracts
- 4. Assays of mitochondrial enzyme activity:
 - a. Decreased activity of complex I and IV
 - b. Approximately 90% of mitochondria must be involved to produce clinical symptomatology

Laboratory Evaluation

- 1. Serum CK levels are normal or minimally elevated or occur with serum lactate elevation
- 2. EEG:
 - a. Generalized background slowing with spike-and-wave complexes
- 3. MRI:
 - a. Cortical and cerebellar atrophy
- 4. EMG:
 - a. May be normal
 - b. Low amplitude, early recruitment of MUAPs in weak muscles
 - c. NCS:
 - i. Reduced sensory nerve action potentials from superimposed axonopathy in a subset of patients

Mitochondrial Myopathy with Lactic Acidosis and Strokes (MELAS)

General Characteristics

- 1. MELAS is maternally inherited in a non-Mendelian fashion
 - a. Approximately 70% of patients carry an mtDNA mutation at nucleotide 3243 that causes an A to G substitution in the (MTTL1) gene that encodes tRNA^{Leu}
 - b. Genetic heterogeneity includes:
 - i. Mutation sites at 3252, 3260, 3271, 3291 in the tRNA^{Leu} gene
 - ii. Genes mutations also occur in:
 - 1. tRNA^{val}(MTTU)
 - 2. tRNA^{lys}(MTTK)
 - 3. tRNA^{phe}(MTTF)
 - 4. tRNA^{ser}(MTTS1)
- 5. Dehydrogenase ubiquinone oxidoreductase Subunits of complex I-NDI (inTND1)

- 6. ND4 (nTND4)
- 7. ND5 (nTND5)
- 8. Cytochrome b of complex III (MTCYB)

Clinical Manifestations

- 1. Onset occurs in the first year of life in less than 10% of patients
- 2. Approximately 60–80% manifest by 15 years of age although there can be a late adult onset
- 3. Recurrent stroke-like episodes
 - a. Nausea and vomiting
 - b. Hemiparesis
 - c. Hemianopia
 - d. Cortical blindness
 - e. Patients may develop cognitive impairment
 - f. Proximal muscle weakness with myalgias and easy fatigability with exercise
 - g. Short stature as occurs with many mitochondrial diseases
 - h. Variable signs and symptoms:
 - i. Myoclonic seizures
 - ii. Ataxia
 - iii. Overlap of symptomatology with MERRF
 - iv. 100% of patients may develop ptosis, ophthalmoparesis, pigmentary retinopathy and cardiomyopathy

Neuropathology

- 1. Muscle biopsy:
 - a. Similar to the usual mitochondrial myopathy
 - i. Ragged red fibers with variable COX staining which may be more prominent than with MERRF
 - ii. COX-negative fibers stain with SDH
 - iii. Increased mitochondria are seen in the muscular walls of small blood vessels
 - iv. Mitochondrial enzyme analysis demonstrates decreased activity of complexes I, III, IV and V
 - v. Mitochondrial dysfunction activates mitochondria-to-nucleus signaling pathways:
 - 1. The mutant mt-tRNA causes oxidative stress in muscles and cybrid cells from patients
 - 2. Mutant MELAS patients lack the taurine containing modification normally present at the wobble uridine (U34) of wild type mt-tRNA^{leu} which may be a cause of MELAS
 - 3. MELAS cybrids have a decrease in several mt-tRNA modification enzymes that are not under transcriptional regulation. Oxidative stress mediates an NFkB-dependent induction of microRNA-9/qd which affects the U34 modification state of wild type tRNAs and may be important in the MELAS phenotype
 - 4. MELAS patients have demonstrated that disease severity and mutation load are inversely correlated with interictal cerebral vascular resistance (CVR) and are directly correlated with frontal CBF

Laboratory Evaluation

1. Serum CK may be normal or elevated while lactate levels are usually increased in the serum and the CSF
2. EMG:
 - a. Early recruitment of myopathic MUAPs
 - b. NCS are normal
 - c. EEG:
 - i. May have epileptic features
 - d. MRI:
 - i. Cortical atrophy
 - ii. High T2 signal and FLAIR abnormalities in the cerebral cortex, basal ganglia, and thalamus
 1. Most often the ADC of the lesions is increased but may be decreased
 2. The pattern of the lesions does not correspond to a vascular territory
 - iii. Magnetic resonance spectroscopy (MRS)
 1. During acute cortical lesions demonstrates:
 - a. Increased lactate levels
 - b. Reduced concentration of N-acetyl aspartyl compounds (neurons), and myoinositol
 - c. MRS of muscle:
 - i. Decreased phosphocreatine
 - ii. Increased inorganic phosphate and free adenosine 5-diphosphate
 - iii. Low phosphorylation potential

Kearns-Sayre Syndrome (KSS)*General Characteristics*

1. Most patients with KSS demonstrate large mtDNA deletions, approximately 43% of patients have a H19KB deletion
2. Muscle tissue is a better source for mutation analysis than peripheral leukocytes
3. Large deletions affect several tRNA genes that impair translation of multiple mtDNA encoded proteins
4. Single deletions rarely occur sporadically

Clinical Manifestations

1. Onset is most often before 20 years of age
2. Short stature
3. Proximal muscle weakness and exercise intolerance
4. Endocrinopathies:
 - a. Diabetes mellitus
 - b. Hypothyroidism
 - c. Hypoparathyroidism
5. Sensorineural hearing loss
6. Cognitive impairment
7. Ataxia
8. Depressed ventilatory drive
9. Pigmentary retinopathy
10. Sensitivity to sedatives
11. 50% of patients develop cardiac conduction defects:
 - a. Bradycardia related conduction defects
 - b. Complete atrioventricular block
12. Cataracts

Neuropathology

1. Muscle biopsy:
 - a. Ragged red fibers most of which lack COX staining
 - b. There is a correlation of the number of ragged red fibers with the number of mitochondria with large deletions
 - c. CNS evaluation reveals spongy degeneration of white matter

Laboratory Evaluation

1. Elevated serum lactate and pyruvate with normal CK levels
2. Elevated CSF protein and lactate
3. EMG:
 - a. Low amplitude small polyphasic MUAP in weak muscles
 - b. Normal insertional activity
 - c. NCS are usually normal but some patients demonstrate low amplitudes consistent with an axonal sensory or sensory motor neuropathy
4. EKG:
 - a. Bradyarrhythmias to complete atrioventricular block
5. Cardiac magnetic resonance imaging:
 - a. Monomorphic ventricular tachycardia and myocardial scarring (demonstrated in one patient)
 - b. May demonstrate presymptomatic disease

Progressive External Ophthalmoplegia*General Characteristics*

1. Most patients with PEO have single large mtDNA deletions (60–70%) that is also seen with Kearns-Sayre syndrome and Pearson syndrome. These are sporadic mutations
2. Point mutations in specific tRNA genes have been described
3. Autosomal dominant PEO is genetically heterogeneous and is associated with multiple DNA deletions
4. The three autosomal dominant genes described for PEO are:
 - a. PEOA1
 - i. Due to mutations in the polymerase gamma gene (POLG) that maps to chromosome 15q25
 - b. PEOA2
 - i. Caused by mutations in the ANT1 gene that maps to chromosome 10q24
 - ii. Encodes adenine nucleotide translocator
 - c. PEOA3
 - i. Caused by mutations in the twinkle gene (100RF2) that maps to chromosome 1q24
 - d. There may be a fourth locus that maps to chromosome 3q14.1-21.4
5. ANT1 functions to transport adenosine triphosphate across the inner mitochondrial membrane
6. Twinkle and polymerase gamma are essential for mitochondrial DNA replication

7. Autosomal recessive progressive external ophthalmoplegia (PEOB)
 - a. Maps to chromosome 15q26.1
 - b. Is caused by homozygous or compound heterozygous mutations in the nuclear encoded DNA polymerase-gamma gene
 - c. Recessive mutations in the POLG also cause SANDO (sensory ataxic neuropathy, dysarthria, and ophthalmoplegia)
 - d. Mutations in POLG also cause Alpers syndrome (psychomotor retardations, intractable epilepsy, and limb failure) in infants and young children
 - e. A case of genetic inheritance has been described

Clinical Manifestations

1. Adult onset of extraocular muscle weakness and ptosis
2. Ptosis
3. Symmetry of EOM limitation
4. Exodeviation
5. No pigmentary retinopathy, cardiac conduction defect or endocrinopathy
6. Patients with sporadic single large mtDNA deletions may demonstrate:
 - a. Proximal muscle weakness
 - b. Cataracts
 - c. Hearing loss
 - d. Ataxia
 - e. Parkinsonism
 - f. Mitral valve prolapse
 - g. GI dysmotility
7. There may be facial and neck muscle weakness

Neuropathology

1. Muscle biopsy:
 - a. Minimal variability in fiber size
 - b. Ragged red fibers without COX

Laboratory Evaluation

1. Serum CK, lactate and CSF are mildly variable, elevated or normal
2. CSF protein may be mildly elevated
3. EMG:
 - a. Myopathic MUAP in weak muscles

Autosomal Recessive Cardiomyopathy and Ophthalmoplegia (ARCO)

General Characteristics

1. Multiple mtDNA deletions often occur from mutations in enzymes that are involved in mtDNA maintenance. POLG1 and POLG2 genes encode polymerase gamma that are essential for mtDNA maintenance and map to chromosome 15q26.1

Clinical Manifestations

1. Onset in childhood

2. Progressive external ophthalmoplegia
3. Facial weakness
4. Proximal muscle weakness
5. Severe cardiomyopathy (dilated)
 - a. Distinguishes the entity from AD and maternally inherited PEO
6. Decreased or absent muscle stretch reflexes

Neuropathology

1. Muscle biopsy:
 - a. Ragged red fibers that are positive for SDH and have no COX staining
 - b. Decreased activity of respiratory chain enzymes whose subunits are encoded by mtDNA
 - c. SDH and citrate synthetase have normal activity

Laboratory Evaluation

1. Serum CK is minimally elevated
2. Serum lactate is normal at rest but is prominently increased with exercise
3. EKG:
 - a. Cardiac conduction defects
4. Echocardiography
 - a. Dilated cardiomyopathy with low ejection fraction
5. EMG:
 - a. Myopathic MUAPs
 - b. NCS are normal

Mitochondrial DNA Depletion Syndrome

General Characteristics

1. Approximately 50% of patients have sporadic mutations as the cause of the disorder. It is inherited in an autosomal recessive fashion
2. There is a correlation with the quantity of mtDNA and the severity of the syndrome. A 99% reduction causes the fatal infantile form, while the more benign myopathy has 36–88% of normal mtDNA
3. Nuclear genes regulate the mitochondrial genome and cause mitochondrial DNA depletion. Specific genes that have been identified include:
 - a. Thymidine kinase 2 (TK2) gene
 - i. Has been mapped to chromosome 16G21
 - ii. Is a mitochondrial deoxyribonucleoside kinase that phosphorylates thymidine, deoxycytidine, deoxyuridine as well as antiviral and anticancer nucleosides or analogues
 1. Deoxyguanosine kinase gene (DGK)
 - a. Maps to chromosome 2P13.1
 2. Succinate – COA ligase gene (SUCLA2)
 - a. Otherwise known as the cause of mitochondrial depletion syndrome 5 is autosomal recessive and maps to chromosome 13q14.2
 - b. The mutations are homozygous or compound heterozygous in the beta-subunit of the succinate COA ligase gene

4. TK2 and DGK:
 - a. Are essential for mitochondrial deoxynucleotide metabolism
5. MPU17 Gene
 - a. Maps to chromosome 2p24
 - b. Encodes an inner membrane protein of unknown function

Clinical Manifestations

1. The mitochondrial depletion syndrome is an autosomal recessive disorder that has a decreased mtDNA copy number in affected tissues
2. The hepatocerebral form, in which there is mitochondrial depletion in liver and brain, is associated with mutations in the POLG, PEO1 (Twinkle) DGK and MPU17 genes
3. Other genes associated with mitochondrial depletion syndromes include: 1. TYMP, 2. SUCA1, 3. OPA1, and RRM2B
4. Onset is usually in infancy or early childhood
5. There is a wide clinical spectrum of severity
6. Infant severe fatal form:
 - a. Generalized hypotonia and weakness
 - b. Infants may appear normal the first years of life
 - c. Proximal muscle involvement
 - d. Ptosis and ophthalmoplegia
 - e. A subset in infants has polyneuropathy
 - f. Absent or decreased muscle stretch reflexes
 - g. Affected infants have systemic involvement that includes:
 - i. Cardiomyopathy
 - ii. De Toni-Fanconi-Debré syndrome (renal tubular defect)
 - iii. Seizures
 - iv. Liver failure
7. Muscle weakness is severe, progressive and causes feeding difficulties, respiratory failure and death usually in the first year
8. Benign infantile form:
 - a. Initially resembles the fatal myopathy
 - b. May present shortly after birth or in childhood
 - c. Muscle strength gradually improves although there may be bulbar and respiratory problems initially
 - d. Motor milestones are delayed but are attained and children may be normal by 2–3 years of age
 - e. Some patients succumb within the first two decades of life but others have a normal life expectancy
 - f. These patients do not have the renal tubular defect

Neuropathology

1. The various mutations cause defects in proteins that are directly involved in mtDNA replication or in the availability of deoxyribonucleotide triphosphates for mtDNA synthesis
2. Muscle biopsy:
 - a. COX-negative fibers

- b. No ragged red fibers
- c. Electron microscopy
 - i. Enlarged mitochondria
 - ii. Concentric or whorled cristae
 - iii. Dense bodies
 - iv. Paracrystalline inclusions

Laboratory Evaluation

1. Both serum CK and lactate can be normal or moderately elevated
2. If the renal tubular defect is present:
 - a. Glycosuria, proteinuria, and aminoaciduria occur
3. EMG:
 - a. Increased insertional activity with positive sharp waves and fibrillation potentials
 - b. Motor units may have a myopathic or neuropathic pattern
 - c. NCS may demonstrate characteristics of an axonal or demyelinating neuropathy
4. MRI:
 - a. Cerebral atrophy
 - b. Hypomyelination of subcortical white matter

Focal Mitochondrial Depletion

General Characteristics

1. Autosomal dominant inheritance has been shown in some patients
2. Mitochondrial abnormalities have been determined
3. Similar muscle biopsy abnormalities have been described in patients with selenium deficiency

Clinical Manifestations

1. A father and two siblings that were evaluated demonstrated in the two children:
 - a. Onset of symptoms in the second decade
 - b. Muscle pain with exercise
 - c. Fatigue
 - d. Mild proximal muscle weakness
2. The father demonstrated a high CK
3. Other patients have shown:
 - a. Weakness at birth
 - b. Hypotonia
 - c. Delayed motor milestones
 - d. Cognitive deficits
4. Axial muscle weakness:
 - a. Increased mitochondrial respiratory chain defects were detected in cervical and lumbar paraspinal muscles that increased with age

Neuropathology

1. Muscle biopsy:
 - a. Approximately 1/3 of type II fibers are centrally devoid of mitochondria
 - b. Remaining mitochondria are enlarged but otherwise normal
 - c. Scattered degenerating and regenerating fibers are noted

Laboratory Evaluation

1. Serum lactate levels are normal. CK levels are elevated both at rest and increase moderately with exercise
2. EMG:
 - a. Myopathic MUAPs
 - b. Normal NCS
3. Decreased selenium level has been reported in one patient

Mitochondrial Neurogastrointestinal Encephalomyopathy (MNGIE)*General Characteristics*

1. MNGIE is caused by mutations in the TYMP gene that map to chromosome 22q13.33. It is a rare autosomal recessive disorder
2. The gene encodes thymidine phosphorylase (TP). Loss of the enzyme causes an accumulation of thymidine and deoxyuridine nucleosides that are incorporated by the mitochondrial salvage pathway. Their accumulation causes a deoxynucleotide triphosphate pool imbalance thought to cause mtDNA instability
3. A few patients with MNGIE have been associated with POLG gene and MTTK gene mutations

Clinical Manifestations

1. Onset is prior to age twenty (range is 2.5 to 32 years)
2. Distal greater than proximal weakness
3. Gastrointestinal dysmotility
4. Stocking and glove sensory loss
5. Decreased muscle stretch reflexes
6. Ptosis and extraocular muscle weakness
7. Rare patients have cognitive deficits
8. Pigmentary retinopathy
9. Sensorineural hearing loss
10. Facial weakness
11. Hoarseness and dysarthria

Neuropathology

1. Muscle biopsy:
 - a. Ragged red fibers
 - b. Ragged blue fibers (NADH and SDH histochemical stains)
 - c. COX-negative fibers
 - d. Neurogenic atrophy of distal muscles
2. Sural Nerve biopsy
 - a. Loss of myelinated fibers
 - b. Demyelination with remyelination with rare onion bulbs
 - c. Electron microscopy:
 - i. Abnormal mitochondria
 - ii. Paracrystalline inclusions in both muscle fibers and Schwann cells
 - d. Enzymatic assay of muscle fibers:
 - i. COX and other respiratory enzyme deficits
 - e. Autopsy:

- i. Endoneurial fibrosis and demyelination of peripheral nerves
- ii. White matter abnormalities in the cerebral cortex and cerebellum
- iii. Cranial nerve and spinal roots are demyelinated to a degree
- iv. Loss of neurons and fibrosis of the autonomic ganglia, celiac and myotonic plexuses

Laboratory Evaluation

1. Serum CK levels are normal or slightly elevated
2. Increased lactate, pyruvate and CSF protein is typical
3. EMG:
 - a. Increased insertional activity, positive sharp waves and fibrillation potentials
 - b. Decreased recruitment of MUAPs may be seen in distal muscles
 - c. Proximal muscles reveal small brief duration MUAPs
 - d. NCS:
 - i. Slow motor and sensory nerve induction velocities to the demyelinating range with prolonged F-wave latency
 - ii. Reduced amplitudes of sensory nerve action potentials
 - iii. Rare reduced amplitude of CMAPs
 - e. MRI:
 - i. Abnormalities of cerebral and cerebellar white matter (leukoencephalopathy)
 - f. Gastrointestinal radiology
 - i. Dilatation and dysmotility of the esophagus, stomach and small intestine
 - g. EKG:
 - i. Conduction defects in a subset of patients that are asymptomatic

Leigh Syndrome*General Characteristics*

1. The incidence is 1 in 40,000 live births, two familial mutations have increased incidences. The mitochondrial mutation in an isolated population near Quebec leads to disease occurrence in 1 in 7000 births and a nuclear encoded mutation in the Faroese populations with a homo- or heterozygous frequency of 1:2,500 births
2. Leigh syndrome is an extremely heterogeneous mitochondrial disorder. The syndrome can be caused by more than 35 different genes that are mitochondrial or nuclear. They involve all five respiratory chain complexes. As noted earlier, there are 13 mtDNA-encoded structural proteins of complex I, II, IV and V and approximately 77 structural protein subunits that are nuclear encoded. Coenzyme Q10 and cytochrome C are also nuclear encoded proteins
3. Mutations in any structural components of the respiratory chain, the Krebs cycle and coenzyme Q can also cause phenotypic Leigh syndrome
4. The mutated genome can be inherited by:

- a. Maternally inherited (mtDNA – encoded)
- b. Autosomal recessive pattern from nuclear genes that encode the mitochondrial chain complex subunits, complex assembly proteins, coenzyme Q, or/and mitochondrial tRNA synthetases
- c. X-linked genes involved in PDHA1 and complex I assembly factor NDUFA1 (nuclear encoded)
- d. Most Leigh affected patients have mutations in nuclear DNA. Approximately 25% have mutations in mtDNA
- e. Leigh syndrome nuclear mutations have been mapped to
 - i. Chromosome – 2q35 and 2q37.3
 - ii. Chromosome – 5p15.33, 5q11.2, 5q12.1 and 5q31.3 (Complex I deficiency)
 - iii. Chromosome – 8q22.1 (complex I deficiency)
 - iv. Chromosome – 9q34.2 (COX deficiency)
 - v. Chromosome – 10q24.2 (cytochrome C-oxidase deficiency)
 - vi. Chromosome – 11q13.2, 11q24.2 (complex I deficiency)
 - vii. Chromosome – 12q22, 12p13.32 (complex I deficiency)
 - viii. Chromosome – 17p12 (COX4 deficiency)
 - ix. Chromosome – 19p13.1
 - x. Mutation in complex I genes (mitochondrial)
 1. MTND2, MTND3, MND5, MTND6
 2. Nuclear encoded: NDUFS1, NDUFS3, NDUFS4, NDUFS7, NDUFS8, NDUFA2, NDUFA9, NDUFA10, NDUFA12, NDUFAF6 and C200RF7
 3. Complex assembly factor NDUFAF2
 4. Mutation in the MTFMT gene that is involved in mitochondrial translation occurs with complex I deficiency
 - xi. Mutations occur in flavoprotein subunit A complex II gene
 - xii. Mutation in the BCS12 gene of complex III involved in the assembly of complex III
 - xiii. The complex IV gene mutations include mitochondrial encoded MTCO3 and nuclear encoded COX10, COX15, SCO2, SURF1 that are involved in the assembly of complex IV. Other mutations affecting complex IV occur in TACO1 and PET100 genes
 - xiv. A mutation in the mitochondrial encoded MTATP6 complex V gene has been described
 - xv. Mitochondrial tRNA gene mutations have been found in MTTV, MTTK, and MTTN genes
 - xvi. Mutations in components of the pyruvate dehydrogenase complex cause Leigh syndrome which include:
 1. The DLD gene that encodes dihydrolipoamide dehydrogenase that is a component of the pyruvate dehydrogenase, alpha-lactoglutarate dehydrogenase complex as well as the branch-
ed – chain alpha – keto acid dehydrogenase complex
 - xvii. The Saguenay-Lac Saint Jean form of Leigh syndrome is caused by a mutation in the leucine-rich PPR motif containing protein gene (LRPPRC). It encodes a mRNA-binding protein pivotal in the processing and trafficking of mtDNA encoded transcripts that cause COX deficiency (LSFC)

Clinical Manifestations

1. Onset in infancy or early childhood but can present in adulthood
2. Recurrent vomiting
3. Cognitive deficits
4. Hypotonia
5. Generalized weakness and muscle atrophy
6. Ptosis and ophthalmoplegia
7. Nystagmus
8. Optic atrophy
9. Sensorineural hearing loss
10. Seizures
11. Spasticity
12. Involuntary movements
13. Peripheral neuropathy
14. A progressive and most often fatal disorder

Neuropathology

1. Muscle Biopsy:
 - a. COX deficient fibers
 - b. Usually there are no ragged red fibers
 - c. COX deficiency is noted in muscle spindles and the smooth muscle of intravascular blood vessels
2. CNS and spinal cord:
 - a. Symmetric optic necrosis
 - b. Spongiform degeneration
 - c. Demyelination
 - d. Areas of vascular proliferation (the mammillary bodies may be hemorrhagic and enlarged)
 - e. Areas affected include:
 - i. The brainstem (medulla)
 - ii. Cerebellum (white matter)
 - iii. Thalamus
 - iv. Basal ganglia
 - v. Dentate nucleus
 - vi. Dorsal columns
 - f. Mechanisms of lesion formation:
 - i. ATP depletion
 - ii. Hyperlacticacidemia
 - iii. Reactive oxygen species
 - iv. Excitotoxicity

Laboratory Evaluation

1. Serum lactate and pyruvate are abnormally elevated with exercise but may be normal at rest
2. Defects in respiratory complex proteins may be demonstrated in muscle tissue which are particularly prominent

in COX, complex I and the pyruvate dehydrogenase complex

3. MRI:

- a. Systemic lesions:
 - i. The brainstem
 - ii. Occasional hemorrhagic mammillary bodies
 - iii. Cerebellum
 - iv. Thalamus
 - v. Spinal cord

Mitochondrial Myopathies Associated with Exercise Intolerance and Recurrent Myoglobinuria

General Characteristics

1. This is a very heterogeneous group of disorders that include:
 - a. The multiple mtDNA deletion syndrome
 - b. Point mutations in tRNA genes
 - c. Microdeletions in genes encoding for COX III (MTCO3)
 - d. Mutations in the gene encoding tRNA subunit 4 of NADH dehydrogenase
 - e. Mutations in cytochrome b (MTCYB)
 - f. Mutations in SDH

Clinical Manifestations

1. Onset may be infancy or early adulthood
2. Short stature
3. Decreased muscle bulk but may have normal strength
4. Patients may have slight proximal weakness
5. Recurrent episodes of myoglobinuria are provoked with exercise and alcohol
6. Progressive deafness may occur

Neuropathology

1. Muscle biopsy:
 - a. Scattered ragged red fibers
 - b. COX-negative fibers
 - c. Increased SDH and NADH fibers
 - d. COX histochemistry may be normal in patients with MTCO3, ND4 and MTCYB mutations
2. Electron microscopy:
 - a. Paracrystalline inclusion in mitochondria

Laboratory Evaluation

1. Serum lactate and pyruvate are abnormally elevated with aerobic exercise
2. CK is elevated during attacks associated with myoglobinuria
3. EMG:
 - a. Needle studies and NCS are usually normal

Myotonic Dystrophies

General Characteristics

1. Myotonic dystrophy is an autosomal dominant muscle disorder caused by a heterozygous trinucleotide repeat expansion (CTG) in the 3-prime untranslated region of the dys-

trophic myotonic protein gene DMPK that maps to chromosome 19q13.32

2. This is a toxic RNA gain of function disease
3. The mutant RNAs that contain the expanded DUGG repeats aggregate in discrete inclusions and are retained in the nucleus. The sequestering of splicing factors of the MBN2 family triggers upregulation of the CUGBP family of proteins. This results in the mis-splicing of their target transcripts from various genes that include those that encode:
 - a. The chloride channel
 - b. Insulin receptor
 - c. Cardiac troponin
 - d. Ryanodine receptor
 - e. Sarcoplasmic/endoplasmic reticulum Ca²⁺ ATPase
4. There is abnormal translation of the mis-spliced RNAs into functional proteins which explains the organ specific systemic manifestations of the disease
5. DM1 has an approximate incidence of 13.5 per 100,000 live births and a prevalence of 3–5 per 100,000 of the population

Clinical Manifestations

1. Onset is variable but may be seen in infancy
2. Limb weakness is distal early in the illness but progresses to involve proximal muscles
3. The course is slowly progressive
4. The neck flexors are weak and atrophy is early
5. Severe atrophy and weakness of facial and jaw muscles leads to the dysmorphic “hatchet face” physiognomy
6. There may be involvement of pharyngeal and lingual musculature that cause dysarthria and dysphagia
7. Myotonia is evident in affected muscles which does not appear to be symptomatic in many patients
8. Myotonia decreases with repeat muscle contraction (“warm-up” sign)
9. Delayed relaxation occurs following percussion of affected muscles (percussion myotonia)
10. Decreased muscle stretch reflexes
11. Normal sensation
12. Congenital disease is associated with severe cognitive dysfunction; adults may have mild cognitive deficits
13. Congenital Myotonic Dystrophy
 - a. Much more severe phenotype than is seen with adult DM1
 - b. Affected infants are born to mothers with myotonic dystrophy
 - c. Pregnancy can be associated with polyhydramnios with decreased fetal movement
 - d. Severe weakness and hypotonia at birth
 - e. Arthrogryposis
 - f. Inducible myotonia is not present at birth but is apparent by five years of age
 - g. Ventilatory assistance is required in a subset of infants
 - h. Severe cognitive deficits affect 75% of surviving children

14. Systemic medical complications:

- a. Decreased gastrointestinal mobility which may cause chronic pseudo-obstruction
- b. Alveolar hypoventilation can occur from weakness of both the diaphragm and intercostal muscles
- c. Sleep apnea
- d. Pulmonary hypertension
- e. Cardiac abnormalities
- f. Conduction defects in the EKG are seen in 70% of patients
- g. Sudden death from arrhythmia correlates with age, male gender and duration of disease
- h. Cognitive impairment and neurobehavioral abnormalities occur in a significant portion of patients
- i. Posterior subcapsular ("stellate") cataracts
- j. Frontal balding
- k. Testicular atrophy
- l. Hyperinsulinemia and glucose intolerance

Neuropathology

1. Muscle biopsy:
 - a. Increased central nuclei
 - b. Type I fiber predominance and atrophy
 - c. Hypertrophic type II fibers
 - d. Ring fibers
 - e. Atrophic fibers with pyknotic nuclear clumps (small angulated fibers)
 - f. Sarcoplasmic masses
2. CNS:
 - a. Neurofibrillary degeneration with abnormal tau-expression

Laboratory Evaluation

1. Mildly elevated or normal CK
2. EMG:
 - a. Myotonic discharges
 - b. Positive sharp waves and fibrillation potentials
 - c. Myopathic MUAPs
3. Muscle MRI (T1-weighted sequences)
 - a. High intensity signals in:
 - i. Flexor digitorum profundus
 - ii. Flexor pollicis longus
 - iii. Abductor pollicis longus
 - iv. Extensor pollicis muscles
 - v. Long standing patients show muscle involvement of proximal muscles

Myotonic Dystrophy Type 2 (DM2)*General Characteristics*

1. DM2 is a multisystem autosomal dominant disease caused by heterozygous expansion of a CCTG repeat in intron 1 of the zinc finger protein-9 gene that maps to chromosome 3q21.3
2. Normal alleles contain up to 30 repeats; mutated alleles have from 75–11,000 repeats

3. Myotonic dystrophy-2 and proximal myotonic dystrophy (PROMM) are now classified as DM2
4. The expanded CCTG transcribed mRNA repeats aggregate as focal collections in the nucleus similar to the CTG repeat found in DM1
5. The aggregates of mutated mRNA sequester RNA-binding proteins that cause abnormal splicing of pre-mRNA from target genes, such as those that encode the chloride channel, insulin receptor, tau, and cardiac tropomyosin. The abnormal translation of these RNAs into proteins in the affected tissues cause the disorder

Clinical Manifestations

1. The onset is between 20–60 years of age but may be seen in childhood
2. Usually presentation is intermittent stiffness and pain in thigh muscles which may be asymmetric
3. Myotonia affects facial and extremity muscles but may be variable and is not always evident
4. Myotonia may be precipitated or worsen during pregnancy
5. The "warm up" phenomenon occurs with continual muscle contraction
6. They myotonia is not exacerbated by cold; some patients demonstrate increased myotonia with heat
7. Patients have episodic pain that is burning and lancinating in the thighs, shoulders, upper arms and chest
8. Most patients have slowly progressive proximal and distal muscle weakness which involves:
 - a. The neck flexors
 - b. Elbow extensors
 - c. Thumb and deep finger flexors
 - d. Hip flexors
 - e. Leg extensors
9. The weakness may fluctuate and periods of exacerbation may last from hours to weeks which improves with exercise
10. Approximately 100% of patients develop muscle atrophy of proximal muscles later in life
11. Calf hypertrophy may occur and may be asymmetric
12. Myoglobinuria has been described
13. Anticipation occurs
14. There is no congenital form of the disease
15. Medical complications:
 - a. Myoglobinuria that usually develops prior to age 50 but has been seen in late childhood
 - b. Cardiac manifestations include
 - i. Syncope
 - ii. Symptomatic tachycardia (8%)
 - iii. Conduction defects (20%)
 - iv. Cardiomyopathy (7%)
16. Sleep apnea
17. Cognitive deficits are not prominent (in contrast to DM1) although there is a subset of patients who demonstrate defects in executive function

18. Variable features:
 - a. Stroke-like episodes
 - b. Seizures
 - c. Hypersomnia
 - d. Parkinsonism
19. Frontal baldness occurs in 20–50% of patients
20. Testicular atrophy with testicular insufficiency
21. No gastrointestinal dysmotility
22. Rare late onset deafness (one kinship with atypical DM2)

Neuropathology

1. Muscle biopsy:
 - a. Mild to moderate central nuclei
 - b. Variable fiber size
 - c. Type 2 fiber atrophy with pyknotic nuclear clumps
 - d. In contrast to DM1 minimal or absent sarcoplasmic masses, type 1 fiber atrophy and ringed fibers
2. CNS:
 - a. Neurofibrillary tangles and abnormal tau expression as seen in DM1

Laboratory Evaluation

1. Serum CK may be minimally elevated
2. Low testosterone levels occur in 30% of male patients
3. Insulin resistance occurs in 75% of patients
4. Low IgG is seen in approximately 65% of patients; low IgM in 11%
5. EMG:
 - a. Myotonic discharges which may be seen more prominently in distal rather than proximal muscles
 - b. NCS are normal
6. EKG:
7. MRI (brain):
 - a. White matter abnormalities
8. Single photon emission computed tomography:
 - a. Frontal and parietal-occipital hypoperfusion

Differential Diagnosis of Myotonic Disorders

1. Myotonic dystrophy type 1
2. Myotonic dystrophy type 2
3. Myotonia congenita
4. Paramyotonia congenita
5. Hyperkalemic periodic paralysis
6. Chondrodystrophic myotonia
7. Drug-induced:
 - a. Statins and fibrates
 - b. Cyclosporine
 - c. Chloroquine

Muscle Channelopathies, Non-Dystrophic Myotonias and Periodic Paralysis

Overview

The muscle channelopathies are caused by mutations in muscle ion channels that cause an increase or decrease in mem-

brane excitability which lead to a spectrum of clinical phenotypes. The non-dystrophic myotonias cause delayed relaxation after muscle contraction that causes stiffness and pain. The periodic paralyses are characterized by various degrees of flaccid paralysis. Non-dystrophic myotonic syndromes are heterogeneous and can be separated into those in which gene mutations cause defects in chloride or sodium channel proteins of the sarcolemma membrane.

Mutations in the chloride channel cause myotonia congenita and can have autosomal dominant or recessive inheritance. The sodium channelopathies include:

1. Hyperkalemic periodic paralysis (HyperKPP; potassium sensitive)
2. Paramyotonia congenita (PMC)
3. Potassium aggravated myotonias that include:
 - a. Myotonia fluctuans
 - b. Myotonia permanens
 - c. Acetazolamide-responsive myotonia
4. Familial hypokalemic periodic paralysis type 2 (HypoKPP2)

Hypokalemic periodic paralysis type 1 (HypoKPP1) is not associated with either clinical or electrical myotonia and is caused by mutations in the dihydropyridine receptor, a calcium channel of the endoplasmic reticulum. The mechanism by which hypokalemic periodic paralysis leads to a depolarized but unexcitable sarcolemma membrane, is a novel gating pore current. Thyrotoxic hypokalemic periodic paralysis has recently been shown to be determined by mutations in a gene that encodes an inwardly rectifying potassium channel Kir2.6. Recent work has also shown that 90% of the known mutations that cause hypokalemic periodic paralysis (HypoKPP) are due to loss of positively charged enzyme residues in the S4 segments of either the SCN4A or CACN15 that carries a gating current.

The Andersen-Tawil syndrome is a hereditary periodic paralysis in which some forms are caused by mutations in a potassium channel.

The EMG in association with both the short and long exercise tests is pivotal in distinguishing the muscle channelopathies. The short exercise test requires the patient to isometrically contract a muscle for 10 seconds, which is followed by measurement of the compound muscle action potential amplitude immediately after the exercise, and then at ten second intervals for 50 seconds (five measurements). The test is first done at room temperature and then with cooling of the tested muscle. In a normal subject, the CMAP may increase 6–14% and then return to baseline levels within 10 seconds. If performed after cooling of the tested muscle, the CMAP amplitude decreases approximately 25% but its duration increases 140%. Changes in CMAP amplitude with the short exercise test distinguish the muscle channelopathies by categorizing them into one of five patterns.

Contract a muscle for five minutes (3–4 seconds of rest are allowed every 30–45 seconds). The CMAP amplitudes

are measured every minute during exercise, immediately after its completion and then every minute for five minutes. Measurements are recorded every five minutes for the next 40–45 minutes.

Normally the CMAP amplitudes only decrease after the period of exercise to a slight degree (mean of 6%) while amplitudes return to normal within 30–60 seconds and do not change over the next 45 minutes. Five patterns of change in CMAP amplitudes have been determined with the short exercise test. These are helpful in distinguishing the muscle channelopathies. Patterns I–III are altered in the non-dystrophic myotonias and patterns IV and V, in association with the long exercise test, distinguish the periodic paralyses.

Chloride Channelopathies

Myotonia Congenita

General Characteristics

1. The CLC-1 chloride channel belongs to the CLC channel/transporter family
2. Mutations in the chloride gene (CLCN-1) which maps to chromosome 7q85 is responsible for Thomsen disease (autosomal dominant) and Becker disease (autosomal recessive) form of myotonia congenita
3. The CLCN-1 gene encodes the chloride channel that is primarily expressed in skeletal muscle
4. The CLC-1 channel is a dimer of two homologous subunits, each forming a chloride ion conducting pore that allows CLC-1 to function as a “double barrel” channel
5. Channel opening in CLC-1 is regulated by two distinct gating patterns:
 - a. The slow gate opens and closes the two subunits simultaneously
 - b. The fast gate regulates the function of independent pores
6. The neurilemma of skeletal fibers at rest has a high chloride conductance. This large inhibitory chloride conductance balances the excitatory depolarizing currents. After the action potential is triggered, repolarization starts with sodium channel fast inactivation and is completed by potassium efflux affected by delayed rectifier potassium channels (the cell is more negative by loss of the K^+ ion). Potassium accumulation in the T-system is responsible for the transient after-depolarization following muscle contractions. The high resting chloride conductance prevents propagation of the depolarization along the neurilemmal membrane
7. In myotonic muscle fibers:
 - a. The chloride conductance is reduced by more than 50%
 - b. The potassium accumulation triggers autonomous muscle fiber action potentials that produce prolonged electrical activity exhibited by myotonia after discharges

Clinical Manifestations

1. In Thomsen disease (AD) the onset of disease is during the first few years of life
2. Infants may have difficulty opening their eyes after crying and stiffness of leg muscles may lead to falls
 - a. Stiffness of arm muscles occurs with age
 - b. Muscles of mastication and swallowing may be involved
 - c. Affected muscles often demonstrate the “warm up” phenomenon and have less myotonia with repeated contraction
 - d. Myotonia is exacerbated by cold and pregnancy
 - e. The severity of the myotonia fluctuates and may be variable in severity among affected family members
 - f. There are no systemic features or increased mortality
 - g. Patients with late onset disease may present with proximal weakness and muscle stiffness
 - h. There is an increased risk of malignant hyperthermia with inhalational anesthetics
 - i. Neurological examination:
 - i. Hypertrophy of muscles
 - ii. Muscle strength is usually normal but there may be slight proximal weakness in some patients
 - iii. There is delayed relaxation of contracted muscles (action myotonia)
 - iv. There is percussion myotonia

Becker Autosomal Recessive Myotonia Congenita

Clinical Manifestations

1. Onset is between 4 and 12 years of age
2. The severity of weakness is worse
3. Transient weakness of the distal arm and other musculature can occur after a severe episode of myotonia
4. There is mild proximal weakness of the extremities and neck flexor musculature
5. There are no systemic manifestations

Neuropathology

1. The CLCN1 mutations include small deletions, insertions, frameshifts, stop codons and splice sites
2. CLCN1 exon deletions or duplications from a single recessive mutation can cause recessive myotonia congenita

Laboratory Evaluation

1. Serum CK is normal or only minimally elevated
2. EMG:
 - a. Motor and sensory conduction velocities are normal
 - b. Repetitive nerve stimulation demonstrates a decremental response after a train of stimuli at 10 Hz. In this subset of patients, there may be a significant decrease of CMAP amplitude with higher rates of stimulation
3. The short exercise test:

- a. PEMP (post-exercise myotonic potentials in motor conduction studies) may or may not be present
- b. In the AR form: CMAP amplitudes are decreased after the last trial which does not occur in the AD form. The reduction in amplitudes decreases after the second and third trials
- c. In autosomal recessive MC, there is no change with cold
- d. There is a reduction in amplitudes after the first trial in autosomal recessive MC that improves after several trials
- 4. Long exercise test:
 - a. There is a slight decrease or no change in CMAP amplitudes immediately after exercise or up to 45 minutes
- 5. Needle EMG:
 - a. Myotonic discharges occur at rest and with voluntary muscle contraction
 - b. There is no exacerbation with cold
 - c. Morphology and recruitment of MUAPs is normal
 - d. Weak muscles may demonstrate short duration and small MUAPs
- b. Increased potassium intake
- c. Fasting
- d. Stress
- 8. Weakness is usually mild but can be severe after prolonged vigorous exercise
- 9. Paresthesias and dysesthesias may occur in muscles prior to weakness
- 10. Thigh and calf muscles may be initially affected prior to spread to other muscles
- 11. Weakness can be focal
- 12. Rarely generalized flaccid weakness occurs which is in contrast to hypokalemic periodic paralysis
- 13. Bulbar and respiratory musculature is rarely involved
- 14. The sphincters are not involved
- 15. The duration of weakness is most often less than 1 hour but residual weakness may persist for a few days (unusual)
- 16. The frequency of attacks is highly variable but may occur several times a day
- 17. The occurrence of paretic attacks decreases with age
- 18. Mild exercise after strenuous exercise may prevent weakness (walking after running)
- 19. Pain may occur in affected muscles after an episode of weakness
- 20. Reflexes are usually decreased or lost during attacks; sensation is normal
- 21. Eyelid myotonia may be the only physical sign between attacks although some patients develop slowly progressive mild proximal weakness

Sodium Channelopathies

Hyperkalemic Periodic Paralysis

General Characteristics

- 1. Hyperkalemic periodic paralysis or potassium sensitive periodic paralysis is inherited as an autosomal dominant disease with high penetrance that maps to chromosome 17q23.3
- 2. Allelic disorders that have overlapping phenotypic features are:
 - a. Paramyotonia congenita
 - b. The potassium aggravated myotonias
- 3. The mutations occur in the subunit of the voltage-dependent sodium channel gene (SCN4A)

Clinical Manifestations

- 1. The disease has three manifestations:
 - a. Weakness without myotonia
 - b. Myotonia (clinical) that can be demonstrated by electrodiagnostic testing
 - c. Associated with paramyotonia congenita
- 2. Attacks of weakness are similar in all forms except that paramyotonia is exacerbated by cold
- 3. Clinical myotonia is generally mild and can be elicited in the face and extremities by percussion or activity
- 4. Myotonia improves with repeat muscle contraction except with paramyotonia in which it is exacerbated along with muscle stiffness
- 5. Onset is usually during the first decade
- 6. Attacks often occur in the morning
- 7. Precipitating factors include:
 - a. Rest following exercise

Neuropathology

- 1. Muscle biopsy:
 - a. Vacuoles may be present

Laboratory Evaluation

- 1. Serum CK may be minimally increased
- 2. Between attacks serum potassium concentrations are usually normal
- 3. During attacks:
 - a. Precipitated by potassium concentration is usually 5–6 mEq/L; occasionally attacks occur with normal potassium serum levels
 - b. Sodium levels may be decreased during attacks of weakness
- 4. EKG:
 - a. Increased precordial T wave amplitude
- 5. Secondary causes of hyperkalemia usually have a serum concentration that is greater than 7 mEq/L, have no family history, and demonstrate no clinical electrical myotonia
- 6. EMG:
 - a. Motor and sensory nerve conduction studies are normal between and during attacks of weakness
 - b. CMAP amplitude may be decreased during attacks
 - c. Short exercise test:
 - i. No PEMP

- ii. There is an increase in CMAPs after the first trial with further increases after the second and third trials
- d. Long exercise test:
 - i. There is a transient increase in CMAP amplitude immediately after exercise
 - ii. Gradual decrease in amplitude over the next 40 minutes
 - iii. Ten seconds of exercise during the paretic phase may increment the CMAP amplitudes
- e. Needle EMG:
 - i. Myotonic discharges occur in 50–75% of patients although clinical myotonia may only occur in 20%
 - ii. Affected muscles in patients with myotonia demonstrate between attacks:
 - 1. Increased insertional activity with positive sharp waves and fibrillation potentials
 - 2. Spontaneous myotonic discharges that may be increased by lowering the limb temperature
 - 3. A slight increase in small amplitude, brief duration polyphasic potentials
 - 4. In plegic muscles during attacks MUAPs decrease in amplitude and duration and may disappear

Paramyotonia Congenita (PMC)

General Characteristics

1. PMC is an autosomal dominant disease with high penetrance caused by mutations of the voltage-gated sodium channel alpha-subunit gene SCN4A that maps to chromosome 17q23.3
2. It is an allelic disorder with hyperkalemic periodic paralysis and the potassium-aggravated myotonias

Clinical Manifestations

1. Onset is within the first decade of life
2. Infants may have difficulty opening their eyes after crying due to myotonia of the orbicularis oculi
3. Cold induced muscle weakness can last for hours and may not reverse even when the extremity is warmed
4. Weakness can be induced by a potassium load
5. Patients may complain of muscle pain that is not as severe as that which occurs with DM2/PROMM
6. Paramyotonia of the eyelids is prominent in most patients
7. Exercise exacerbates muscle stiffness and myotonia
8. There is minimal percussion myotonia
9. Proximal and distal weakness may develop with time

Neuropathology

1. PMC is caused by mutations in the SCN4A gene. Patients may or may not demonstrate myotonia
2. Muscle biopsy:
 - a. Mild fiber size variation with a mixture of normal, atrophic, and hypertrophic fibers

- b. In patients with associated periodic paralysis, there may be intracytoplasmic vacuoles
- c. Electron microscopy:
 - i. Myofibrillar disorganization
 - ii. Tubular aggregates

Laboratory Evaluation

1. Serum CK levels are mildly to moderately elevated
2. Serum potassium may be elevated during an attack with paralysis
3. EMG:
 - a. Normal motor and sensory conduction velocities between attacks
 - b. Repetitive stimulation at greater than 5 Hz may induce a decremental CMAP in a subset of patients
4. Short exercise test:
 - a. PEMP are noted
 - b. CMAP amplitudes may be amplified or decrease with the first trial and decrease after the second or third trial
 - c. Amplitude reduction of CMAPs is exacerbated by cold
5. Long exercise test:
 - a. Decrease in CMAP amplitudes during and following exercise that may persist for hours
6. Needle EMG:
 - a. Normal MUAPs
 - b. Patients with associated periodic paralysis, cooling may induce fibrillation potentials and decreased MUAP production
 - c. In flaccid paralyzed muscles myotonic discharges cease and there may be complete electrical silence
 - d. In pure PMC (without periodic paralysis), local cooling exacerbates myotonic discharges in the face of normal recruitment and morphology of MUAPs
7. Single fiber EMG:
 - a. Slight increase in jitter and fiber density

Potassium Aggravated Myotonias

Myotonia Fluctuans

General Characteristics

1. Myotonia fluctuans is caused by mutations in the SCN4A gene that map to chromosome 17q23.3

Clinical Manifestations

1. Onset is usually in early childhood
2. Fluctuating myotonia that is variable in severity
3. Myotonia may be increased following exercise (delayed onset of minutes)
4. Paramyotonia affects the eyelids
5. The “warm-up” phenomenon for the myotonia occurs in the extremities
6. There are no episodes of weakness following cold, an increased potassium load or exercise
7. There is increased myotonia with a potassium load but not cold

8. The fluctuating myotonia distinguishes this entity from PMC, myotonia congenita and the patients with myotonia that have hyperKPP
9. The severity of myotonia has a wide spectrum from minimal stiffness to that which affects extraocular muscles, bulbar musculature, and the extremities
10. Exercise induces myotonia that may be delayed in onset and is not exacerbated by cold

Neuropathology

1. Muscle biopsy:
 - a. Fiber size variation
 - b. Central nuclei
 - c. May be normal
 - d. Electron microscopy:
 - i. Vacuoles may be demonstrated in some fibers

Laboratory Evaluation

1. Serum CK is minimally evaluated
2. Short exercise test:
 - a. Mildly decreased amplitude of CMAP that improves with repetitive activity
 - b. No PEMP
3. Long exercise test:
 - a. No change

Myotonia Permanens

General Characteristics

1. Myotonia permanens is caused by the G1306A mutation of the SCN4A gene that maps to 17q23.3

Clinical Manifestation

1. The myotonia causes constant muscle stiffness
2. Aggravated by a potassium load
3. Is exacerbated by activity
4. Respiratory muscle involvement
5. No episodic weakness nor increase of myotonia with cold

Neuropathology

1. The mutation may cause a positive shift in voltage dependence
2. "Leaky" closed sodium channels

Laboratory Evaluation

1. Normal or slightly elevated CK levels
2. Short exercise test:
 - a. No PEMP
3. Long exercise test:
 - a. No change

Acetazolamide-Responsive Myotonia

General Characteristics

1. Acetazolamide-responsive myotonia is caused by mutations in the SCN4A gene that map to chromosome 17q13.1-13.3

Clinical Manifestations

1. Onset in childhood with painful muscle stiffness that worsens in early adulthood
2. Myotonia is most severe in the face and hands
3. The myotonia is exacerbated by a potassium load, fasting and mildly by exercise
4. Muscle pain may be benefited by high carbohydrate meals
5. Patients demonstrate action and percussion myotonia
6. There is normal strength
7. Paradoxical myotonia occurs in the eyelids

Neuropathology

1. Muscle biopsy:
 - a. Normal in many patients
 - b. Generalized muscle fiber hypertrophy

Laboratory Evaluation

1. Mildly elevated CK level
2. Short exercise test:
 - a. No PEMP
 - b. Mild decrease in CMAP amplitude that improves with repetitive muscle contraction
3. Long exercise test:
 - a. No change

Familial Hypokalemic Periodic Paralysis Type 2

General Characteristics

1. A subset of patients with familial hypokalemic periodic paralysis (hypoKPP) have mutations in the SCN4A gene that maps to chromosome 17q13.1-13.3
2. The mutations are clustered in the second repeat (D2S4). This region is the voltage sensor that decreases sarcolemmal membrane excitability by enhancing inactivation of sodium channels

Clinical Manifestations

1. The age of onset is approximately 16 years
2. The duration of attacks may be shorter, approximately 1 hour
3. HypoKPP2 patients do not develop fixed proximal muscle weakness
4. Acetazolamide may exacerbate weakness
5. Attacks otherwise are similar to those of hypokalemic PP1

Neuropathology

1. Muscle fibers may demonstrate tubular aggregates rather than non-rimmed vacuoles which are seen with Hypokalemic PP Type 1
2. Recent expression studies have demonstrated anomalous hyperpolarization-activated gating pore currents in mutant channels. This gating pore conductance causes a small inward current at the resting membrane potential that contributes to susceptibility to depolarization in the presence of low K^+ concentration during attacks of weakness

Laboratory Evaluation

1. Serum potassium decreases during attacks of paralysis
2. CK may be normal or slightly elevated
3. Short exercise test:
 - a. No PEMPs
 - b. No change
4. Long exercise test:
 - a. Slight increase of CMAP amplitude may occur during and immediately following exercise which after 10–20 minutes decreases. The decay is less than that which occurs with hyperKPP
5. EMG:
 - a. The EMG is normal between attacks
 - b. There are no myotonic discharges
6. EKG:
 - a. May not demonstrate the usual changes expected with very low serum potassium concentrations in some instances

Primary Hypokalemic Periodic Paralysis Type 1 (HypoKPP1)
General Characteristics

1. Most patients with familiar hypokalemic periodic paralysis have mutations in the α -subunit of the skeletal muscle L-type channel gene that maps to chromosome 1q31-32.5
2. The mutations occur in the arginine residues of the voltage-sensing segments of the calcium channel
3. Hypokalemic periodic paralysis may also be caused by mutations in:
 - a. KCNE3 gene
 - b. SCN4A gene
 - c. Mutations that affect the thiazide sensitive sodium chloride cotransporter (Gitelman syndrome)
4. Calcium channel (Cav1.1 structure):
 - a. The Cav1.1 has five subunits ($\alpha 1$, $\alpha 2$, β , δ and μ)
 - b. The $\alpha 1$ -subunit has four domains which contain six transmembrane segments and the dihydropyridine receptor
 - c. The dihydropyridine receptor is a calcium ion channel for the T-tubular but is also a voltage sensor for excitation-contraction coupling
 - d. The remaining subunits of the calcium channel regulate the $\alpha 1$ -subunit
 - e. The S4 segment of the $\alpha 1$ -subunit is the voltage sensor for the channel and the site of most mutations that occur in hypoKPP1
 - f. The voltage-gated Ca^{2+} channels couple membrane depolarization to Ca^{2+} -dependent intracellular physiologic signaling. The mechanism is by mediating Ca^{2+} ion influx or by direct conformational coupling to intracellular Ca^{2+} release channels
- g. Mechanisms:
 - i. Muscle fibers are depolarized and inexcitable during an attack of paralysis. Possible mechanisms include:

1. Loss of function due to defect that causes reduced ionic current density
2. Reduction in ATP-sensitive K current
3. Reduced calcium influx through the T-tubule system may impair excitation-contraction coupling
4. Myotube electrophysiologic recordings that express mutant calcium channels show a decreased calcium current density and a negative shift in the steady state inactivation current
5. The kinetics of the sodium channel are affected by CACN1A mutations
6. Sodium conduction is increased which leads to depolarization of the resting membrane potential from -80 mV to -50 mV which is a partially depolarized state. Thus there would not be sufficient repolarized sodium channels to conduct an action potential

Clinical Manifestations

1. HypoKPP1 is the most frequent periodic paralysis with a prevalence of 1/100,000 of the population
2. Male to female ratio of 3–4:1
3. It is autosomal dominant but with reduced penetrance in women
4. The onset of episodic weakness with paralysis occurs within the first two decades of life
5. Precipitating causes include:
 - a. Intense physical exercise followed by rest, sleep or a high carbohydrate or sodium meal (pizza and ice cream)
 - b. Emotional stress
 - c. Menstruation
 - d. Viral illness
 - e. Beta-agonists, steroids and insulin
6. Most attacks occur in the morning often upon awakening. They may occur at any time during the day
7. The severity of attacks are variable and range from minimal weakness to complete flaccid paralysis
8. There is no myotonia or paramyotonia as opposed to PMC and hyperKPP
9. Most often facial and respiratory muscles and sphincters are spared. Some patients feel as if their bladder is full and that their muscles are swollen
10. Rare instances of respiratory muscle involvement and cardiac arrhythmias have been reported
11. Absent muscle stretch reflexes
12. Severe muscle weakness can last for hours to days. The muscles that are first affected are the last to recover
13. Attacks can occur several times a week to less than once per year. Attacks may start to diminish when the patient reaches 30 and some patients have had a remission in their forties and fifties
14. Fixed proximal muscle weakness occurs more severely in the legs than the arms

15. A prodrome for an oncoming attack is a sensation of heaviness in or pain in the back and swelling in the thighs and calves that spreads to proximal arm muscles. Low grade exercise during the prodrome may ward off or lessen the degree of weakness

Neuropathology

1. Muscle biopsy:
 - a. Intracellular vacuoles (often in the center of muscle fibers), dilatation of the sarcoplasmic reticulum, and tubular aggregates
 - b. Vacuoles are more common in the hyperkalemic periodic paralysis 1, while tubular aggregates are seen with hypokalemic periodic paralysis 2
 - c. Fiber size variability, split fibers, both hypertrophic and atrophic fibers are seen. Rarely necrotic and degenerating fibers occur

Laboratory Evaluation

1. The serum potassium levels are below 3.0 mEq/L and rarely fall below 2 mEq/L
2. The EKG usually demonstrates:
 - a. Bradycardia
 - b. Flattened T-waves
 - c. Prolonged PR and QT intervals
 - d. The EKG may not reflect the degree of hypokalemia
3. CK is mildly to moderately elevated between paralytic attacks and rises during attacks
4. EMG:
 - a. Motor and sensory nerve conduction velocities are normal between attacks of weakness
 - b. During a paralytic attack:
 - i. CMAP amplitudes are decreased
 - ii. Repetitive stimulation may prevent the decrease of CMAP to a degree (simulating the prevention of attacks by exercise in the prodromal period)
 - c. Short exercise test:
 - i. No PEMP
 - ii. No change
 - d. Long exercise test:
 - i. A slight increase in CMAP amplitude occurs during and immediately after exercise that is followed by a delayed decrease in CMAP after 10–20 minutes

Secondary Hypokalemic Periodic Paralysis

General Characteristics

1. Secondary hypoKPP may occur with severe potassium loss from either kidney or gastrointestinal disease, an acid base disturbance that causes a shift of K^+ into cells or may be stimulated by drugs or endogenous hormones

Clinical Manifestations

1. Attacks of generalized weakness without extraocular, respiratory or bulbar involvement

2. Residual weakness may last for days (usually proximal musculature)
3. May be associated with cardiac arrhythmias
4. Renal tubular acidosis may be associated with seizures due to calcium loss
5. Emesis gravidarum with prolonged vomiting (may also be associated with Wernicke disease)
6. Bartter's and Gitelman disease may be associated

Neuropathology

1. Necrotizing myopathy

Laboratory Evaluation

1. Dependent on the underlying condition

Thyrotoxic Periodic Paralysis

General Characteristics

1. Recent evidence demonstrates that the loss of function mutations of skeletal muscle-specific inward rectifying K^+ (Kir) channels (Kir2.6) cause thyrotoxic periodic paralysis
2. The reduced outward K^+ efflux from skeletal muscle due to potassium channel mutations or inhibition of the channels by adrenalin or insulin leads to paradoxical depolarization. This inactivates Na^+ channels, which in turn causes unexcitability of the muscle and paralysis

Clinical Manifestations

1. The disease is most seen in Asian patients, primarily in males
2. The paralysis only occurs with associated hyperthyroidism
3. Attacks can occur at any time but are most frequently seen in the morning (attacks occur at night)
4. Flaccid, areflexic paralysis that may be generalized or can affect the legs primarily
5. During attacks the serum K^+ is depleted. A full recovery usually occurs with replenishment of potassium. The disease responds to treatment of the hyperthyroidism
6. Patients have the clinical signs of variable degrees of hyperthyroidism
7. Attacks may be prolonged without treatment (1–2 days)
8. Attacks may be precipitated after carbohydrate meals and post-exercise rest as well as with alcohol

Neuropathology

1. Skeletal muscle is the largest single pool of total body K^+ and plays a major role in K^+ homeostasis
2. Na^+-K^+ ATPase and inward rectifying K (Kir) and delayed rectifying K^+ channels are the major mechanism for the influx and efflux of K^+ across the muscle membrane
3. Thyroid hormone also stimulates the Na^+-K^+ ATPase pump by acting on the thyroid hormone responsive elements that upregulate the transcription of the gene coding Na^+-K^+ ATPase and enhance its membrane insertion through non-genomic mechanisms

4. Thyroid hormone also enhances the stimulation of the pump by β_2 -adrenergic agonists by amplifying intracellular cAMP activity
5. Hyperinsulinism also occurs in acute attacks of thyrotoxic periodic paralysis. It may induce intracellular K^+ shifts by stimulating Na^+-K^+ pump activity or enhancing the pump's membrane insertion
6. Present evidence supports the mutations in the gene encoding Kv2.6 as the major cause of thyrotoxic periodic paralysis. In familial hypoKPP mutations in the voltage sensor of Nav1.4 and Cav1.1 channels cause an aberrant gating pore current and an imbalance between an inward leak current and an outward current. In thyrotoxic periodic paralysis, the loss of function for the Kv2.6 (decreased K^+ efflux) causes an imbalance between inward leak current and outward K^+ current that causes paradoxical depolarization
 - d. Palpitations
 - e. Syncope
 - f. Cardiac arrest
9. Developmental anomalies include:
 - a. Clinodactyly
 - b. Hypertelorism
 - c. Mandibular hypoplasia
 - d. Syndactyly
 - e. Scoliosis
10. Dysmorphisms
 - a. Low set ears
 - b. Short stature
 - c. Broad nose and forehead
 - d. Cleft and high arched palate
 - e. Vaginal atresia
 - f. Bradydactyly
 - g. Cardiac valve lesions
 - h. Hypoplastic kidneys
 - i. Cognitive deficits

Laboratory Evaluation

1. Most patients have a significant decrease in serum K^+ concentration but there are examples of thyroid periodic paralysis (TPP) with normal and even increased potassium levels
2. EMG:
 - a. Similar to familial hypoKPP

Andersen-Tawil Syndrome (ATS)

General Characteristics

1. Two-thirds of patients with the ATS syndrome have heterozygous mutations in the KCNJ2 gene that maps to chromosome 17q24. There is marked intrafamilial variability and incomplete penetrance of this autosomal dominant disease
2. The gene encodes an inwardly rectifying potassium channel (Kv2.1) that is expressed in heart, skeletal muscle and the brain
3. The disease is characterized by periodic paralysis, cardiac arrhythmias, and skeletal dysmorphisms

Clinical Manifestations

1. Approximately 60% of patients manifest the entire triad
2. De novo inheritance occurs although this is primarily an autosomal dominantly inherited disease
3. Onset is during the first or second decade of life
4. The attacks consist of episodic weakness that can be spontaneous or are triggered by rest after exercise
5. The attacks vary from hours to days in duration. They may occur only once in a lifetime to daily
6. Proximal weakness of extremities may occur over time
7. There is no myotonia or paramyotonia
8. Cardiac manifestations include:
 - a. Bidirectional ventricular tachycardia
 - b. Polymorphic ventricular tachycardia
 - c. Torsades de Pointes

Neuropathology

1. Muscle biopsy:
 - a. Tubular aggregates
2. The Kv2.1 mutation causes alterations of muscle membrane depolarization and repolarization by failing to stabilize resting membrane potential
3. Sustained depolarization is accompanied by Na^+ channel activation with loss of action potential induction
4. In the heart muscle, it causes delayed after-depolarization in the terminal phase of repolarization

Laboratory Evaluation

1. Serum CK is usually normal but may be minimally elevated
2. Potassium levels are often decreased during attacks but may be normal or even elevated
3. EKG:
 - a. Prolonged QT interval occurs in 80% of patients
 - b. Ventricular tachyarrhythmias
4. EMG:
 - a. Motor and sensory nerve conduction velocities are normal

KCNE3 Channelopathy

General Characteristics

1. Mutations in the KCNE3 gene that maps to chromosome 11q13.4-q14 may cause attacks of episodic weakness
2. A missense mutation in the KCNE3 potassium channel gene is associated with susceptibility to thyrotoxic hypokalemic periodic paralysis
3. The subthreshold voltage-gated potassium channel of skeletal muscle contains MinK-related peptide 2 (MiRP2) and the pore-forming subunit Kv3

Clinical Manifestations

1. Age at onset: early childhood
2. Attacks occur during sleep and last for approximately 12 hours
3. One patient suffered weakness of the lower extremities that lasted for hours to days; precipitated by strenuous exercise that was followed by rest or prolonged sitting
4. Attacks in 1 patient occurred during wakefulness
5. G-to-A transition in the KCNE3 gene has been identified in a Danish family with the Brugada syndrome
6. Possible association with the long QT syndrome

Neuropathology

1. KCNE3 protein forms a complex with the pore-forming unit Kv3.4. The resulting potassium channel has increased conductance, faster inactivation recovery, and slower cumulative inactivation. The channels are active at -40 mV and are important in maintaining the muscle membrane potential

Laboratory Evaluation

1. Patients have low potassium levels during attacks
2. EKG:
 - a. Possible association with the long QT syndrome

Additional Calcium Channelopathies***Malignant Hyperthermia****General Characteristics*

1. Malignant hyperthermia is usually triggered by exposure to volatile anesthetics or succinylcholine
2. Susceptibility is usually inherited in an autosomal dominant pattern
3. The most frequent gene involved encodes the ryanodine receptor (RYR1) that maps to chromosome 19q13.1. Mutations in this gene also cause central core disease
4. Only a small number of patients with malignant hyperthermia (MH) carry this gene mutation
5. Malignant hyperthermia syndrome 2 [MHS2] maps to chromosome 17q11.2-24 and is allelic to 1. hyperKPP, 2. PMC, and 3. PAM
6. MHS3 has been mapped to chromosome 7q24-7q22
7. MHS4 maps to chromosome 3q13.1
8. MHS5 is caused by mutations in the dihydropteridine receptor gene that maps to chromosome 1q31 which is allelic to HyKPP
9. MHS6 maps to chromosome 5P
10. Patients with dystrophinopathies are susceptible to MH

Clinical Manifestations

1. The incidence of MH in patients that have been exposed to inhalation anesthetics varies from .5–.0005%
2. Approximately 50% of patients had previous anesthesia without incident

3. Attacks usually begin during surgery but they have been documented post-operatively
4. During an attack:
 - a. The earliest sign often includes masseter muscle contracture after the administration of succinylcholine
 - b. Increased minute ventilation
 - c. Unexplained tachycardia
 - d. Severe muscle rigidity
 - e. Elevation of body temperature is most often a late sign but may be seen early in severely affected patients

Neuropathology

1. Muscle biopsy:
 - a. Variation in fiber size
 - b. Increased central nuclei
 - c. Moth eaten fibers
 - d. Necrotic fibers following an attack
2. Release of excess calcium into the cytoplasm

Laboratory Evaluation

1. Respiratory acidosis (end-tidal CO_2 above 55 mm Hg and arterial pCO_2 above 60 mm Hg)
2. Metabolic acidosis (base excess lower than -8 ; $\text{pH} < 7.25$)
3. CK $> 20,000$ units
4. Myoglobin in the urine or serum
5. Potassium above $8 \mu\text{eq/L}$
6. Temperature increase ($T > 39.9^\circ\text{C}$)
7. EMG:
 - a. Normal between attacks
 - b. NCS are normal between attacks
8. Susceptibility test:
 - a. "Caffeine halothane contracture test" that requires a muscle biopsy

Brody Disease*General Characteristics*

1. Brody disease is caused by mutations in the ATP2A1 gene that maps to chromosome 16p12.2-12. It is inherited in an autosomal recessive pattern
2. Brody syndrome has the same phenotype but no mutations in the ATP2A1 gene
3. The ATP2A1 gene encodes the fast-twitch skeletal muscle sarcoplasmic reticulum Ca^{2+} ATPase (SERCA1) in type 2 muscle
4. The mutations result in a decreased rate of ATP-dependent calcium transport across the channel
5. During a normal muscle contraction/relaxation cycle, Ca^{2+} is released from the lateral cisterns of the sarcoplasmic reticulum. It then binds to troponin (in the cytoplasm) of the thin filament that initiates actin and myosin interaction which causes muscle contraction. Calcium is pumped back into the sarcoplasmic reticulum which initiates relaxation. In Brody disease the calcium-ATPase that is located in the sarcoplasmic reticulum is deficient which results in decreased rate of removal of Ca^{2+} from the sarcoplasm

Clinical Manifestations

1. Onset is most often in childhood
2. Patients demonstrate impaired muscle relaxation after muscle contraction which is manifest by cramps and stiffness
3. The muscle contractions may be painful
4. A subset of patients have the problem in the orbicularis oculi which causes difficulty in reopening the eye after forced closure
5. The stiffness worsens with activity
6. There is no percussion myotonia
7. A subset of patients may have mild proximal weakness
8. Patients with Brody syndrome:
 - a. Have more severe myalgias in exercised muscle

Neuropathology

1. Muscle biopsy:
 - a. Type 2 fiber atrophy
 - b. Increased central nuclei in muscle fibers
 - c. Decreased calcium ATPase in type 2 muscle fibers
2. Electron microscopy:
 - a. Rare swollen mitochondria with crystalline inclusions
3. Skeletal muscle fibers are extremely sensitive to caffeine

Laboratory Evaluation

1. Serum CK is normal or only minimally elevated
2. Potassium concentration is normal
3. Exercise forearm test:
 - a. A normal rise in lactate and ammonia
4. EMG:
 - a. Needle EMG demonstrates electrical silence in muscles that demonstrate impaired relaxation
 - b. NCS and EMG are otherwise normal

Schwartz-Jampel Syndrome (Chondrodystrophic Myotonia)*General Characteristics*

1. Schwartz-Jampel syndrome (SJS) is an autosomal recessive disease due to mutations in the HSPG2 gene that maps to chromosome 1p34-36.1
2. It encodes perlecan which is the major heparan sulfate proteoglycan of basement membrane
3. Truncating mutations cause instability of HSPG2 mRNA from nonsense mRNA-mediated decay
4. Missense mutations involve the cysteine residues, which causes intracellular retention of perlecan

Clinical Manifestations

1. Onset is at birth
2. Affected children have dysmorphic features that include:
 - a. Micrognathia
 - b. Narrowed palpebral fissures
 - c. Low set ears
3. As the disease progresses there is:

- a. Kyphoscoliosis
 - b. Short stature
 - c. Bowing of the diaphysis in long bone
 - d. Irregular epiphyses
 - e. Pectus carinatum
4. Infants may demonstrate bulbar weakness as manifested by a decreased suck reflex and weak high-pitched cry
 5. Myotonia of the face may be prominent as it is in myotonia congenita
 6. Developmental milestones are delayed
 7. Movement is slow due to stiffness from the myotonia and muscles may be mildly hypertrophic

Neuropathology

1. Muscle biopsy:
 - a. Variation in fiber size
 - b. Mixture of hypertrophic and atrophic fibers
 - c. Scattered degenerating and regenerating fibers
 - d. Replacement of muscle fibers with fat and connective tissue occurs with time

Laboratory Evaluation

1. Serum CK levels are normal or minimally increased
2. EMG:
 - a. Complex repetitive discharges, myokymic discharges, myotonic and pseudomyotonic discharges can be seen
 - b. Motor and sensory conduction velocities are normal

Inflammatory Myopathies*Overview*

The major categories of idiopathic inflammatory myopathies include:

1. Dermatomyositis (DM)
2. Overlap myositis (OM)
3. Polymyositis
4. Necrotizing myositis (immune-mediated)
5. Inclusion body myositis
6. A large array of autoantibodies that are associated with well-defined clinicopathological disorders includes:
 - a. Antisynthetase
 - b. AntiSRP
 - c. 200/100(HMGCR)
 - d. CADM-140(MDA5)
 - e. SAE-p155
 - f. MJ(NXP-2)
 - g. PMS1

Specific entities may cause inflammatory changes in muscle and include human immunodeficiency virus and human T-cell lymphotropic virus. Drugs that include statins, tumor necrosis factor inhibitors, and proton pump inhibitors can also mimic idiopathic inflammatory myopathies. Muscle mimics include muscular dystrophies and some metabolic myopathies.

The idiopathic inflammatory myopathies are rare and have an annual incidence of 1 in 100,000 of the population. They are primarily diseases of adults with the exception of juvenile dermatomyositis. They are more frequent in women than men, as are many autoimmune processes.

Dermatomyositis

General Characteristics

1. Adult onset with the exception of the juvenile form
2. Women are affected more than men
3. Often diagnosed before the other inflammatory myopathies because of the characteristic rash
4. May have systemic manifestations

Clinical Manifestations

1. The onset can be at any age including infancy but is most often in childhood
2. The course may be insidious over months to subacute over weeks
3. The pattern of weakness is usually symmetric with proximal muscles of the legs > than proximal muscles of the arms; neck flexors are weaker than neck extensors
4. Bulbar and oropharyngeal involvement occurs in 20–30% of patients that causes difficulty chewing and swallowing and rarely dysphasia
5. Children most often have an insidious onset of muscle weakness and pain often preceded by fatigue, a low grade fever and a rash
6. Reflexes are often maintained in accordance with the degree of weakness of the affected muscle. Rarely they can be increased during periods of exacerbation (particularly the patellar reflexes)
7. The rash:
 - a. Often precedes or accompanies muscle weakness. It can develop years after the onset of the weakness
 - b. In dermatopathic DM, patients develop the rash without muscle weakness with isolated myositis
 - c. A heliotrope rash is a purplish discoloration of the eyelids and adjacent subcutaneous tissue that is often associated with periorbital edema (most common in the juvenile form)
 - d. Generalized or limb edema is rare
 - e. Gottron's papules are erythematous lichenoid papular scaly eruptions on the extensor surface of the hands and fingers. The papules may occur on the volar aspect of the extremities ("inverse Gottron's papules")
 - f. The macular erythematous rash may be most prominent in the face, neck and anterior chest ("V-sign") or the upper back ("the shawl sign"). Gotton's sign refers to its distribution over the extensor surfaces of the elbows, knuckles, knees or toes. It is often most evident over the knuckles. In SLE involvement in the hands is between the interphalangeal joints. The rash may be prominent over the hip ("holster sign")

- g. Nail beds may demonstrate dilated capillary loops with periungual hyperemia. In SLE, there may be a distal nail bed capillary flush
- h. Nail fold capillary density is decreased in juvenile dermatomyositis (JDM)
- i. Subcutaneous calcinosis may occur in up to 30% of JDM patients but is uncommon in adults
- j. Thickened and cracked skin occurs in the dorsal and ventral surfaces of the hand in patients with anti-synthetase syndrome (arthritis, Raynaud's phenomenon, interstitial lung disease)
- k. Patients may have severe pruritus

Associated Medical Complications

1. Cardiac:
 - a. Less than 10% of patients develop cardiac symptomatology which includes:
 - i. Arrhythmias
 - ii. Wall motion abnormalities
 - iii. Low ejection fraction
 - iv. Pericarditis and myocarditis
 - v. Congestive heart failure
2. Pulmonary:
 - a. Interstitial lung disease occurs in 10–20% of patients
 - b. Bronchiolitis with pneumonia (rare)
 - c. The manifestation of interstitial lung diseases are primarily a dry non-productive cough and dyspnea:
 - i. Insidious onset
 - ii. May precede the rash or muscle weakness
 - iii. X-ray demonstrates a reticulonodular pattern that is most prominent at the lung base or a ground glass pattern with severe disease
 - iv. Pulmonary function test demonstrate a restrictive pattern with decreased forced vital capacity and diffusion pattern
 - v. Anti-Jo-1 antibodies (against t-histidyl transfer RNA synthetase) occur in approximately 50% of ILD patients with inflammatory myopathies
3. Gastrointestinal system:
 - a. Vasculopathy of the gastrointestinal tract is much more common in JDM than in adults and causes mucosal ulceration, perforation and severe hemorrhage
 - b. Involvement of both striated muscles (oropharynx) and smooth muscles cause esophageal, aspiration and delayed gastric emptying
4. Joints:
 - a. Involves both large and small joints with pain and arthritis
 - b. Contractions can occur across major joints (flexion)
 - c. Toe walking form flexion contracture across the ankles occur in children
5. Vasculopathy:
 - a. Vasculopathy may involve the skin, muscles and gastrointestinal tract
 - b. Massive GI hemorrhage may occur in JDM

- c. Muscle infarction causes myoglobinuria and if severe renal tubular necrosis
- 6. Association with malignancy:
 - a. The association with malignancy is approximately 10% (range 6 to 45%)
 - b. There is no malignancy association with JDM; the association in adults is in patients > 40 years of age
 - c. The risk of malignancy is equal between men and women
 - d. Malignancies are usually diagnosed within 2 years of the onset of the myositis
 - e. There is no correlation of malignancy with clinical symptomatology

Neuropathology

- 1. Muscle biopsy:
 - a. The pathognomonic finding is perifascicular atrophy; this may be a late finding and is seen in <50% of biopsies
 - b. Perifascicles contain degenerating and regenerating necrotic fibers
 - c. Scattered necrotic fibers
 - d. Wedge shaped microinfarcts
 - e. Inflammatory cell infiltrates which is composed of macrophages, B-cells, and CD4⁺ lymphocytes which is seen in both perimysial and perivascular areas. The CD4⁺ cells are primarily phasmocytoid, dendritic cells (PDC) and T-helper cells
 - f. Little invasion of non-necrotic muscle fibers which is in contrast to PM and IBM
 - g. Muscle fibers express MHC-1 antigen, STAT 1 and interferon -alpha/beta-inducible protein myxovirus resistance (MxA) in the sarcolemmal membrane early in the pathologic process
 - h. The microangiopathy of DM is seen by the decreased number of capillaries per area of muscle with compensatory dilation of unaffected vessels
 - i. An early initial histochemical feature is the deposition of the complement membrane attack complex perivascularly which may occur prior to perifascicular atrophy
 - j. Deposition of C3 and C9 complement components, IgM and less frequently IgG are also deposited around the walls of intramuscular blood vessels
 - k. MxA is also expressed on capillaries
- 2. Electron microscopy:
 - a. Endothelial hyperplasia of microvacuoles and tubule reticular cytoplasmic inclusions
- 3. Pathogenesis:
 - a. There are competing hypotheses:
 - i. Humorally/complement mediated microangiopathy demonstrated by the presence of MAC complexes
 - b. Increased expression of genes induced by Type I interferons which supports the initiation of the disease from a viral infection that triggers an autoimmune response
 - c. Dysregulated interferon X/B production that is damaging to small blood vessels

Laboratory Evaluation

- 1. Necrosis of muscle fibers causes increased serum levels of:
 - a. CK which is the most sensitive and specific marker of muscle damage and is seen in 90% of patients
 - b. Aldolase, lactate dehydrogenase, aspartate aminotransferase (AST) and alanine aminotransferase (ALT)
 - c. Serum CK may not correlate with the severity of weakness particularly in children and patients with an insidious cause
 - d. LDH, ALT and AST may correlate with the weakness
 - e. Erythrocyte sedimentation is usually slightly elevated and is not a reliable marker of disease activity
 - f. Anti-nuclear antibodies are seen in 30–60% of patients but are more common in overlap syndromes
 - g. Myositis specific antibodies are seen in some patients and include:
 - i. Antibodies against tRNA synthetases (8 described) and the antisignal recognition particles
 - ii. Antibodies against Mi-2 and Mas antigens
 - iii. The most common anti-synthetase antibody is the Jo-1 which is associated with myopathy and interstitial lung diseases
 - iv. The other anti-synthetase antibodies are seen in approximately 25% of patients
 - v. Mi-2 antibody:
 - 1. Associated with dsA nuclear protein and is seen in 15–20% of DM patients
 - 2. Associated with:
 - a. Acute onset
 - b. Severe rash
 - c. Good response to therapy and good prognosis
- 2. EMG:
 - a. Increased insertional activity that manifests as spontaneous firing, positive sharp waves, fibrillation potentials, pseudomyotonic or complex repetitive discharges
 - b. MUAPs are of brief duration, small amplitude and show polyphasic
 - c. Early recruitment of MUAP at normal frequencies. Recruitment may be decreased if there is marked loss of muscle tissue
 - d. Decreased insertional activity occurs in chronic disease from fibrosis
 - e. In long standing disease fiber splitting and regeneration cause long deviation high amplitude polyphasic MUAPs

Polymyositis (PM)

General Characteristics

- 1. PM is caused by an HLA-restricted cell-mediated cytotoxic immune response against muscle fibers
- 2. MHC-1 antigens are expressed in the surface of non-invaded intact myocytes. A rare plasmic reticular pattern of internal MHC-1 reactivity is seen. The autoantigens expressed by MHC-1 may be endogenous muscle peptides

3. The endomysial CD8+ cytotoxic cells are antigen specific and lyse myocytes through the perforin pathway
4. Myeloid dendritic cells surround non-necrotic fibers and act as antigens presenting cells
5. Microarray studies demonstrate increased immunoglobulin gene expression. The immunoglobulin is secreted by endomysial plasma cells
6. The type 1 interferon signature is overexpressed and is correlated with disease severity
7. There is no correlation between other cytokine levels that include IL-1Q, IL-13, IL-1B or TNF-alpha and disease severity
8. A viral infection could trigger an autoimmune response by molecular mimicry or by loss of self-tolerance
9. Cytotoxic T-cell muscle destruction occurs through the perforin pathway. Granzymes (serine proteases) are released by cytoplasmic granules within cytotoxic T-cells that are packaged with perforin. The cytotoxic granules are released by exocytosis, the granules are released into an immune synapse with the target cell (muscle fiber) and finally the sarcoplasm. Pore formation occurs in the sarcolemma that also contributes to muscle fiber destruction by osmolysis

Clinical Manifestations

1. Onset is usually over the age of 20 years. Extremely rare to occur in childhood
2. More prevalent in women
3. Symmetrical proximal arm and leg weakness that is slowly progressive over weeks or months
4. Some distal muscle involvement but not to the degree that occurs in proximal muscles
5. A significant number of patients have muscle pain
6. Neck flexor muscle weakness
7. Dysphagia occurs in approximately 1/3 of patients; there may be mild facial weakness in a small subset of patients
8. In patients with an acute quadriparetic presentation weakness of jaw opening occurs which is rare in Guillain-Barré syndrome
9. Extraocular muscles are not affected
10. Muscle stretch reflexes are usually preserved but depressed in accordance with the degree of weakness

Medical Complications

1. Myositis with congestive heart failure has been reported in approximately 1/3 of patients. It is probably more common when investigated with modern technology
2. Anti-signal recognition particles (SRP) are associated with cardiac myositis; this finding is controversial as histopathology appears more compatible with necrotizing myopathy. Other studies have demonstrated a microvasculopathy on muscle biopsy more supportive of a diagnosis of DM
3. Interstitial lung disease occurs in approximately 10% of patients at least 50% of whom have anti-Jo-1 antibodies

ies; however, muscle biopsy may be more compatible with DM

4. At the time of diagnosis, approximately 45% of patients have oligo arthritis
5. The risk of malignancy is unclear but appears to be lower than with DM but higher than expected in the general population

Neuropathology

1. Muscle biopsy:
 - a. Variation in fiber size
 - b. Scattered necrotic and regenerating fibers
 - c. An inflammatory cell infiltrate
 - d. Invasion of non-necrotic muscle fibers by T-cells
 - e. Perivascular, perimysial and endomysial inflammatory cells are seen in PM but may also occur in IBM, DM and some dystrophies
 - f. In PM, the endomysial inflammatory cells are activated CD8+ cells that are cytotoxic, alpha and beta T-cells
 - g. Rarely reported are patients that demonstrate CD4+, gamma and delta T-cell infiltration
 - h. Myeloid dendritic cells in the endomysium that surround non-necrotic fibers and present antigen to cytotoxic T-cells
 - i. Plasma cells are seen in the endomysium and expression of immunoglobulin genes are noted with gene assay
 - j. There is an oligoclonal pattern of gene arrangement in plasma cells
 - k. There is no deposition of complement, MAC or immunoglobulins on the microvasculature

Laboratory Evaluation

1. The CK is greatly elevated (>5x normal) in most cases. It is never normal in acute cases which is different from DM and IBM
2. The CK does not correlate with the degree of weakness
3. Erythrocyte sedimentation rate (ESR) is most often normal
4. Positive ANA occurs in 16–40% of patients
5. The relationship of muscle-specific antibodies to PM is not settled
6. EMG:
 - a. Increased insertional activity is demonstrated by positive sharp waves, fibrillation potentials and complex repetitive discharges
 - b. Short-duration, small amplitude and polyphasic MUAPs

Differential Diagnosis of Polymyositis

1. Inclusion body myositis
2. Dermatomyositis (without dermatitis)
3. Necrotizing myopathy
4. Inflammatory myopathy associated with infections:
 - a. HIV
 - b. HTLV-1

- c. Hepatitis B & C
- 5. Muscular dystrophies:
 - a. FSH
 - b. Congenital myopathy
 - c. Dysferlinopathies
 - d. Limb-girdle dystrophies
 - e. Myotonic dystrophy type 2
 - f. Amyloid myopathy (light chain or familial)
 - g. Metabolic myopathy with rhabdomyolysis
 - h. Endocrine myopathy:
 - i. Hypothyroidism
 - ii. Hyperparathyroidism
 - iii. Diabetic muscle infarction
 - iv. Acromegaly
 - i. Drug-induced myopathies:
 - i. Cholesterol lowering drugs
 - ii. Cyclosporine
 - iii. Amiodarone
 - iv. Colchicine
 - v. D-penicillamine
 - j. Juvenile or adult onset spinal muscular atrophy (including) Kennedy's disease
 - k. Polymyalgia rheumatism

Serum CK Elevation in PM

While it is normal in fibromyalgia and polymyalgia rheumatism and can be normal in IBM. MRI abnormalities are seen in muscular dystrophies, rhabdomyolysis, toxic reactions to medications (statins) and diabetic vasculopathy. The pattern of muscle involvement (anterior less than posterior by compartment), extent and replacement of muscle by fat and connective tissue in the absence of edema on MRI differentiate PM from a dystrophic process. Diffuse myotonic discharges are seen in myotonic dystrophy (DM type 2). Muscle biopsy reveals specific diagnostic features that suggest IBM, other myopathies, and include rimmed vacuoles, eosinophilic inclusions, ragged red fibers, cytochrome oxidase negative fibers, and cycloid deposits. Muscle biopsy is important to rule out dystrophy, metabolic myopathy, (acid maltase deficiency, lipid droplets) or necrotizing myopathy.

Overlap Syndrome

DM and PM are often associated with other connective tissue disorders that include:

1. Scleroderma
2. Mixed connective tissue disease (MCTD)
3. Sjögren's syndrome
4. Systemic lupus erythematosus (SLE)
5. Rheumatoid arthritis

In general, muscle biopsy in patients with overlap syndromes are similar to DM or non-perimyopathic disorders where CD8⁺ cells invade non-necrotic muscle fibers. These diseases may be more responsive to immunotherapy than DM or PM.

Scleroderma

General Characteristics

1. 5–17% of scleroderma patients have muscle involvement which occurs in:
 - a. Progressive systemic sclerosis
 - b. CREST (calcinosis, Raynaud's phenomena, esophageal dysmotility, sclerodactyly, and telangiectasia)

Clinical Manifestations

1. Proximal muscle weakness

Neuropathology

1. Muscle biopsy
 - a. Mild variability in fiber sizes
 - b. Type 2 fiber atrophy
 - c. Perimysial fibrosis
2. It is a complex systemic autoimmune disease that targets the vasculature, connective tissue-producing cells (fibroblasts/myofibroblasts) and components of the innate and adaptive immune system. The clinical and pathologic manifestations are caused by:
 - a. Production of autoantibodies and cell-mediated immunity
 - b. Microvascular endothelial cell/small vessel fibroproliferative vasculopathy
 - c. Dysfunction of fibroblast production of collagen and matrix components of the skin and internal organs

Laboratory Evaluation

1. Normal serum CK unless there is myositis in which case it may be moderately elevated
2. EMG:
 - a. Is usually normal although it may demonstrate imitative feature during myositis
3. CREST is associated with anti-centromere antibodies while progressive systemic sclerosis has anti-Scl-70 antibodies
4. Patients with scleroderma myositis may also have anti-PM-Scl antibodies

Sjögren's Syndrome

General Characteristics

1. Characterized by the sicca complex that includes:
 - a. Xerophthalmia (dry eyes)
 - b. Dry mouth and dryness of other mucous membranes
 - c. Complicated by both peripheral and CNS involvement
 - d. More common in women than men

Clinical Manifestations

1. Sicca complex
2. PNS features:
 - a. Length dependent axonal sensorimotor neuropathy; patients may have the neuropathy without signs of the sicca complex

- b. Distal predominant weakness
- c. Pure small fiber neuropathy
- d. Autonomic neuropathy that involves the cardiovascular system
- e. Cranial neuropathy often involving the fifth cranial nerve
- 3. CNS complications:
 - a. Transverse myelitis
 - b. Posterior columns may be predominantly involved
 - c. Most often presents in middle age
 - d. Loss of muscle stretch reflexes

Neuropathology

- 1. Pathogenesis of the peripheral neuropathy and sensory neuronopathy/ganglionopathy is most likely autoimmune
- 2. Necrotizing vasculitis may be a cause of the neuropathy particularly in patients with asymmetric, multiple mononeuropathy patterns of involvement
- 3. Nerve biopsy:
 - a. Axonal degeneration and some degree of secondary segmental demyelination
 - b. Rarely perivascular inflammation of perineurial or endoneurial blood vessels is seen
 - c. Loss of large myelinated fibers and perivascular lymphocytes; CD8+ cells are seen in the endomysial and perineurial vessels

Laboratory Evaluation

- 1. Approximately 90% of patients have positive ANA, SS-A/Ro and SS-B/La antibodies
- 2. The CSF is usually normal
- 3. Schirmer's test is positive in those patients with keratoconjunctivitis
- 4. Autoimmune destruction of salivary glands (biopsy)
- 5. EMG:
 - a. Absent or reduced SNAPs particularly in patients with sensory neuropathy/ganglionopathy
 - b. Normal or minimally slowed motor and sensory NCVs

Systemic Lupus Erythematosus

General Characteristics

- 1. Central nervous system manifestations that include seizures, psychosis and stroke are the most common neurological complications of systemic SLE

Clinical Manifestations

- 1. Myositis occurs in SLE but weakness is often exacerbated by disuse atrophy and pain as well as immunosuppressive medication (steroids)

Neuropathology

- 1. SLE is a prototype type II hypersensitivity reaction in which local deposition of anti-nuclear antibodies in complex with released chromatin activate the complement system that induces severe inflammation

Laboratory Evaluation

- 1. The great majority of patients demonstrate ANA titers against DNA and ribonuclear proteins (RNPs)
- 2. Anti-RNP antibodies are demonstrated in approximately 50% of patients (SS-A and SS-B); anti-SM antibodies are specific for SLE while RNP antibodies occur with Sjögren's disease and anti-V1 RNP is seen with mixed connective tissue disease
- 3. There is upregulation of type I interferon inducible genes that is also seen in the muscle biopsies of DM patients
- 4. MxA is highly expressed in the blood of SLE patients as in the muscle of dermatomyositis patients
- 5. Electron microscopy:
 - a. Tubular reticular inclusion bodies are seen in endothelial cells in SLE and DM

Rheumatoid Arthritis (RA)

General Characteristics

- 1. Most often weakness in RA occurs from type II atrophy, disuse and medications
- 2. A myositis may be seen

Clinical Manifestations

- 1. The clinical picture is dominated by severe joint pain and destruction
- 2. Steroids as well as disuse cause type 2 fiber atrophy that is associated with proximal muscle weakness
- 3. Disruption of the transverse collateral ligament may be associated with odontoid compression of the medulla and quadriplegia. It is usually manifest with paresthesias and dysesthesias of the of the upper extremities prior to spinal cord compression and weakness
- 4. Severe joint involvement in the hand (ulnar deviation and joint destruction) is associated with intrinsic hand muscle atrophy

Neuropathology

- 1. Muscle biopsy:
 - a. Type 2 fiber atrophy
- 2. Post-translational modifications of proteins is a major mechanism of pathology in RA B-cell responses to citrullinated antigens that include vimentin, fibrinogen and α -enolase

Mixed Connective Tissue Disease

General Characteristics

- 1. Mixed connective tissue disease is defined by patients who have components of scleroderma, rheumatoid arthritis, SLE and muscle inflammation
- 2. Two or more systemic autoimmune diseases need to be present

Clinical Manifestations

- 1. Most common signs and symptoms reported from different cohorts:

- a. Polyarthritis
- b. Raynaud's phenomena
- c. Puffy fingers
- d. Lung involvement
- e. Esophageal involvement

Pulmonary arterial hypertension and interstitial lung disease accrue over the long course of the disease. Myositis occurs in a subset of patients.

Neuropathology

1. Muscle biopsy:
 - a. DM is more common than PM
2. The antigen recognized by the distinct autoantibody originally termed ribonuclear sensitive extractable nuclear antigen (RNAase sensitive ENA) is a V1 ribonucleic protein (RNP complex)
3. Antibody may be detected prior to the onset of the disease
4. The specificity of these antibodies is most closely related to a 70 KD epitope on V1RNP molecules. The epitope is characterized as containing the RNA-binding domain on the peptide component of the V1RNP cell dependent B-cell maturation complex
5. The 70KD anti-V1RNP antibody response is associated with CD4/Th1 T-cells that express HLA-DR4 or Dr2-phenotype which share a common set of amino acids in the beta chain. These amino acids form a pocket for antigen binding

Laboratory Evaluation

1. EMG:
 - a. Axonal sensorimotor polyneuropathy
 - b. RNP complex antibodies in the serum

Inclusion Body Myositis

General Characteristics

1. The pathogenesis of IBM is not entirely clear. There is evidence that it is a primary inflammatory myopathy due to its clinically restricted inflammatory cell infiltrate of cytotoxic T-cells
2. It is the most common inflammatory myopathy of older patients

Clinical Manifestations

1. Onset is most often after the age of 50 years
2. It presents with insidious slowly progressive proximal and distal weakness
3. Males are more commonly affected than females
4. The pattern of weakness:
 - a. Early weakness of the quadriceps, wrists and finger flexors and the ankle dorsiflexors
 - b. This pattern of weakness is seen in approximately 2/3 of patients
 - c. The deep finger flexors such as the flexor pollicis longus are most often severely affected

- d. Muscle weakness in IBM is often asymmetric
- e. Atrophy of the forearm flexor compartment with sparing of intrinsic hand muscles
- f. Esophageal and pharyngeal muscle weakness causes dysphagia in approximately 40% of patients
- g. Mild facial weakness occurs in approximately 1/3 of patients
- h. There is neck flexor weakness
- i. A subset of patients has a generalized sensory neuropathy
- j. Reflexes are maintained in parallel with muscle strength. The patellar reflexes may be lost early

Associated Medical Complications

1. IBM patients do not have associated lung disease, myocarditis or increased risk of malignancy
2. IBM patients (15%) may have another autoimmune disease that includes SLE, Sjögren's syndrome, scleroderma, sarcoidosis, thrombocytopenia or immunoglobulin deficiency

Neuropathology

1. Muscle biopsy:
 - a. Rimmed vacuoles with granular material
 - b. Endomysial inflammation
 - c. Grouped atrophy
 - d. Eosinophilic cytoplasmic inclusions
 - e. Amyloid deposition in vacuolated muscle fibers and within muscle nuclei
 - f. Ragged red fibers and COX-negative fibers
 - g. Abnormal myonuclei
 - h. Electron microscopy:
 - i. 15–21 nm cytoplasmic and intranuclear tubulofilaments are seen in vacuolated muscle fibers
 - ii. Vacuolated fibers may also contain 6–10 nm amyloid-like fibrils
 - iii. The endomysial infiltrate contains macrophages and CD8⁺ cytotoxic suppressor T-lymphocytes
 - iv. Myeloid dendritic cells surround non-necrotic muscle fibers. MHC class I antigens are expressed in both necrotic and non-necrotic muscle fibers
 - v. T-cell receptors demonstrate an oligoclonal pattern of gene rearrangement. Some patients have been demonstrated to show a persistent clonal restriction of T-cell receptors that support the mechanism of pathology as an antigen driven immune response against muscle
 - vi. The cytotoxic T-cells in IBM release perforin granules that cause pores in the muscle membrane that result in osmolysis

Laboratory Evaluation

1. CK levels are normal or only minimally increased
2. Muscle-specific antigens are not found but approximately 20% of patients have positive ANAs

3. HLADR3 phenotype is increased in IBM
4. EMG:
 - a. Increased spontaneous and insertional activity
 - b. Early recruitment of low amplitude polyphasic MUAPs
 - c. In approximately 1/3 of patients there may be large polyphasic MUAPs (which have been described in PM, DM and muscular dystrophy) and are thought to represent chronicity of disease rather than reinnervation in a neurogenic process
 - d. NCS are slow, axonal sensory neuropathy

Differential Diagnosis of Inclusion Body Myositis

The most common misdiagnosis is PM. The diagnosis of IBM clinically is supported by slowly progressive asymmetric weakness of the quadriceps and wrist, finger flexor with atrophy in patients older than 50 years of age.

In early stages the disease has been misdiagnosed as ALS. A major distinction is intrinsic hard muscle weakness (particularly the first dorsal interosseous in ALS) whereas in IBM the atrophy and weakness is in the forearm flexor musculature.

In hereditary IBM:

1. Onset is in early adult life
2. There is preferential involvement of the tibial anterior muscle in those patients with the autosomal recessive form of the disease
3. Shoulder and hip girdle musculature is affected
4. Valosin gene mutation (AD), causes IBM with Paget's disease and frontal temporal dementia

Pathologic Differential Diagnosis

1. Rimmed vacuoles, amyloid deposition, and tubular or filamentous inclusions are seen in hereditary forms of IBM but can also be encountered in:
 - a. Limb-girdle muscular dystrophy type IA (myotilin)
 - b. LGMD2J (titinopathy)
 - c. Oculopharyngeal dystrophy
 - d. Welander distal myopathy
 - e. Myofibrillar myopathy

Necrotizing Myopathy

General Characteristics

1. Probably 20% of inflammatory myopathy is due to necrotizing myopathy
2. Several forms have been distinguished neuropathologically that includes:
 - a. "Pipestem" capillaries
 - b. Malignancy associated form with connective tissue staining for alkaline phosphatase
 - c. SRP associated

Clinical Manifestations

1. Onset of proximal weakness which may be acute or insidious

2. Underlying diseases include:
 - a. Scleroderma
 - b. Mixed connective tissue disease
 - c. Paraneoplastic necrotizing myopathy from cancers of the gastrointestinal tract or adenocarcinoma both small and large cell types of the lung
 - d. May occur with statin use
3. Patients may improve with immunotherapy
4. Proximal muscle weakness
5. May be accompanied by myalgias
6. If associated with statins, weakness may continue after the statins have been withdrawn

Neuropathology

1. Muscle biopsy:
 - a. The hallmark of autoimmune necrotizing myopathy is:
 - i. Scattered necrotic myofibers with myophagocytosis
 - ii. Absence or paucity of T-lymphocyte inflammation
 - iii. Microvascular deposition of complement MAC (support for a hemorally mediated microangiopathy)
 - iv. Minimal perivascular inflammation
 - v. No endothelial tubuloreticular inclusions by electron microscopy
 - b. Specific subtypes of necrotizing myopathy:
 - i. "Pipestem" capillaries
 1. Thick-walled and enlarged capillaries of normal number
 - ii. Malignancy associated with necrotizing myopathy (NM)
 1. Alkaline phosphatase muscle connective tissue proclivity
 - iii. SRP-associated NM
 1. Bimodal distribution of fiber sizes, increased endomysial and decreased endomysial capillaries, the remaining being enlarged and thickened
 2. Marked fibrosis ensues with MAC deposited in endomysial capillaries
 3. There is no perifascicular atrophy
 - c. Statin-induced autoimmunity
 - i. Statins block 3-hydroxy 3-methylglutaryl coenzyme A reductase protein that is thought to be the antigen in statin induced autoimmune myopathy. The process may be driven by the levels of HMGCR expression in regenerating muscle fibers

Laboratory Evaluation

1. Serum CK level is markedly increased
2. ANA antibodies may be detected
3. Anti-HMGCR are highly sensitive for autoimmune NM
4. EMG:
 - a. Increased insertional and spontaneous activity
 - b. Myopathic MUAPs that show early recruitment

- c. Newer antibodies associated with necrotizing myopathy and severe DM include:
 - i. Encompass enzymatic proteins that are involved in gene transcription or post-translational modification and include:
 - 1. TIF-V
 - 2. NXP-2
 - 3. MDA5
 - 4. SAE
 - 5. MNGCR

Rarer Inflammatory Myopathies

Eosinophilic Myopathies

General Characteristics

1. Eosinophilic myopathy may occur as a part of the hyper-eosinophilic syndrome whose diagnostic criteria are:
 - a. Eosinophilic of at least 1500 eosinophilic/mm³ for 6 months
 - b. No other cause of eosinophilia
 - c. Organ system involvement from eosinophilic infiltration
 - d. The subclassification of eosinophilic myopathy includes:
 - i. Focaleosinophilic myositis
 - ii. Eosinophilic polymyositis
 - iii. Eosinophilic perimyositis

Clinical Manifestations

1. Focal eosinophilic myositis and polymyositis:
 - a. Focal or generalized muscle weakness
 - b. Often with myalgias
 - c. Skin abnormalities
2. Perimyositis with eosinophilia
 - a. Myalgias without significant weakness
3. Hypereosinophilic syndrome:
 - a. Muscle weakness
 - b. Encephalopathy
 - c. Cranial nerve involvement
 - d. Mitochondrial involvement that includes:
 - i. Pericarditis
 - ii. CHF
 - iii. Arrhythmia
 - iv. Conduction block
 - e. Pulmonary involvement
 - i. Pleuritis
 - ii. Asthma
 - f. Renal involvement
 - g. Gastrointestinal involvement
 - h. Skin changes:
 - i. Petechiae rash
 - ii. Nail bed splinter hemorrhages
 - iii. Raynaud's phenomena
 - iv. Livedo reticularis

Neuropathology

1. Muscle biopsy:
 - a. Focal eosinophilic myositis and eosinophilic myositis:
 - i. Endomysial inflammatory cell infiltrate most often containing eosinophils
 - ii. Inflammatory cells surround muscle fibers
 - iii. Nodular granules
 - b. Eosinophilic perimyositis
 - i. An inflammatory cell infiltrate (may not be invariant) is restricted to the fascia and superficial perimysium
 - c. Oligoclonal expansion of T-cells within muscle in eosinophilic polymyositis
 - d. Interleukin-5 and 3 are secreted by T-lymphocytes that grow and differentiate eosinophils. Eosinophils release a toxic major basic protein that targets cell membranes

Laboratory Evaluation

1. CK levels are usually increased in eosinophilic polymyositis and focal disease; may be normal in eosinophilic perimyositis
2. Hypereosinophilia usually greater than 1500 cells/mm³
3. Hypergammaglobulinemia
4. Anemia
5. Increased rheumatoid factor
6. ESR is elevated in approximately 50% of patients
7. Negative ANA
8. EKG:
 - a. Cardiac arrhythmia
9. Chest X-ray
 - a. Pulmonary infiltrates
10. EMG:
 - a. Increased insertional activity as manifested by positive sharp waves, fibrillation potentials
 - b. Early recruitment of low amplitude polyphasic MUAP
 - c. Nerve conduction velocities may be decreased due to superimposed neuropathy

Differential Diagnosis of Eosinophilic Myopathy

1. Parasitic infection
2. Churg-Strauss syndrome
3. T-cell lymphoma
4. Aplastic anemia
5. Toxic oil syndrome
6. L-tryptophan
7. Idiopathic
8. HES and variants
9. LGMD2A

Diffuse Fasciitis with Eosinophilia

General Characteristics

1. A rare scleroderma-like disease most likely due to an autoimmune process, clinically and histologically it is similar to L-tryptophan induced muscle disease and rapeseed oil intoxications. A few patients describe its onset after intense physical exercise

Clinical Manifestations

1. Men are affected 2:1 > than women
2. Most commonly it affects patients between 30–60 years of age; children can be affected
3. The onset is with myalgias, low-grade fever, muscle weakness (possibly due to pain), and arthralgias
4. Contracture of the hands, elbows, and knees and rarely in the hips and shoulders
5. Involvement of the extremities and trunk with a morphea-like skin lesion (painful peau d'orange-like lesions)
6. Visceral organs are usually not involved which distinguishes it from HES and eosinophilic PM
7. Possible association with hematologic diseases that include:
 - a. Aplastic anemia
 - b. Idiopathic thrombocytopenia
 - c. Leukemia
 - d. Lymphoma

Neuropathology

1. Fascial and skin biopsy:
 - a. The fascia is thickened and is infiltrated with lymphocytes, macrophages plasma cells and eosinophils
 - b. Some patients demonstrate the deposition of immunoglobulin and C3 in the fascia
 - c. The inflammatory infiltrate may infiltrate adjacent subcutaneous tissue, the perimysium and endomysium in association with scattered necrotic atrophy
 - d. Interstitial myositis has been reported in over 50% of patients but most often does not cause clinically significant weakness

Laboratory Evaluation

1. Approximately two thirds of patients have peripheral eosinophilia over 7%
2. Elevated ESR and hypergamma globulinemia occur in approximately one third of patients
3. Positive ANA occurs in one quarter of patients
4. CK is normal
5. EMG:
 - a. Superficial muscle may demonstrate membrane instability and myopathic MUAPs
6. MRI of muscle:
 - a. In 80% of patients in the acute phase there is increased T2 signal within the fascia and gadolinium enhancement
 - b. The fascia is thickened

Granulomatous Myositis*General Characteristics*

1. Granulomatous or giant cell myositis is most often seen with myasthenia gravis or thymoma (benign or malignant)

Clinical Manifestations

1. Proximal muscle weakness

2. If associated with myasthenia gravis there are bulbar features and extraocular muscle involvement
3. Associated with granulomatous myocarditis

Neuropathology

1. Granulomatous inflammation with multinucleated giant cells
2. Cell mediated immunities supported by histologic inflammation and giant cell formation. The association with MG is evidence for a component of humorally mediated immunity in the pathologic process

Laboratory Evaluation

1. Elevated serum CK
2. Patients with associated MG demonstrate acetylcholine receptor antibodies
3. EMG:
 - a. Myopathic MUAPs
 - b. Increased insertional activity
 - c. If MG is causal there may be a decremental response
 - d. Chest CT to R/O thymoma
 - e. EKG: 1. Conduction block and arrhythmias in patients with myocardial involvement
 - f. Echocardiography: 1. Low ejection fraction and 2. Ventricular wall motion abnormalities in those with Myocarditis

Sarcoid Myopathy*General Characteristics*

1. Granulomas are frequently encountered in muscle biopsies of patients with sarcoid that are asymptomatic
2. More prevalent in black than Caucasian patients; rarely affects children
3. Most patients with sarcoid are diagnosed from pulmonary manifestations. Erythema nodosum and ankle lesions may be early signs

Clinical Manifestations

1. Proximal weakness is predominant but distal weakness occurs
2. Focal myalgias and atrophy occur in a subset of patients as well as a generalized chronic myopathy that may involve the trunk
 - a. May present similarly to DM and IBM
 - b. May have an associated peripheral neuropathy
 - c. Systemic complications:
 - i. Myocardial involvement with cardiomyopathy and conduction defects
 - ii. Pulmonary involvement with diffuse nodular or interstitial forms
 - iii. Skin and joint involvement
 - iv. Visceral infiltration

Neuropathology

1. Muscle biopsy:

- a. Non-caseating granulomas that contain epithelial cells, lymphocytes and giant cells around blood vessels in the perimysium and endomysium
- b. Epithelioid granulomas have CD4 positive lymphocyte infiltration, the sarcolemma membrane stains with HLA-ABC, HLA-DR and intercellular adhesion molecules-1 antibodies which supports active antigen presentation

Laboratory Evaluation

1. Serum CK is normal or only minimally elevated
2. Elevated serum angiotensin-converting enzyme levels are frequently seen
3. Skin antigen energy
4. Chest x-ray:
 - a. Hilar lymphadenopathy
 - b. Interstitial pattern
5. EMG:
 - a. Normal (some patients)
 - b. Usually a myopathic pattern or mixed myopathic pattern may be seen in chronic patients and in those with a superimposed neuropathy
6. MRI (one patient with acute sarcoidmyositis):
 - a. Multiple bilateral, nodular and spindle-shaped lesions in the gastrocnemius and soleus muscles

Behçet's Disease

General Characteristics

1. Behçet's disease is a systemic vasculitis with the clinical triad of oral and genital ulcers and ocular lesions

Clinical Manifestations

1. Onset may occur in childhood or adult life
2. Patients may develop generalized myalgias with or without weakness
3. Medical associations:
 - a. Ocular lesions:
 - i. Iritis
 - ii. Uveitis
 - b. Colitis
 - c. Thrombophlebitis
 - d. Erythema nodosum
 - e. Meningoencephalitis
 - f. Oral and genital ulcers
 - g. Myocarditis
 - h. The calves are predominant with lower extremity muscle involvement

Neuropathology

1. Muscle biopsy:
 - a. CD4+ and CD8+ lymphocytes and neutrophils that invade non-neurotic muscle fibers
 - b. Expression of MHC-1 antigen on muscle fibers similar to what is seen in PM
 - c. Complement factor C3 and immunoglobulins on blood vessel walls similar to DM support its role as a systemic vasculitis

Laboratory Evaluation

1. Serum CK is normal or minimally elevated
2. Elevated ESR and C-reactive protein
3. HLA-beta5 positivity is documented in approximately 50%

Focal Myositis

General Characteristics

1. Is a rare benign inflammatory pseudotumor of muscle

Clinical Manifestations

1. Onset in adults but occasionally affects children
2. It usually presents as a localized painful swelling within the soft tissue of an extremity, that is painless and insidiously enlarges over weeks
3. The leg is the most common site of involvement but it has been described in the upper extremities, sternocleidomastoid muscle, head and abdomen
4. Rarely, it may progress to polymyositis
5. Lesions may resolve spontaneously and respond to steroids
6. It may be recurrent (rare)
7. The mass is moveable and unattached to the overlying skin
8. Unusual sites of involvement include the tongue, eyelid and esophagus
9. Focal myositis has been reported with chronic S1 radiculopathy

Neuropathology

1. Muscle biopsy:
 - a. Immunohistochemical studies reveal increased macrophage and CD4+ and CD8+ T-lymphocytes that invade the endomysium
 - b. Neurosis and phagocytosis of muscle fibers
 - c. Variability of fiber size, central nuclei, split fibers with endomysial fibrosis
 - d. The macrophage and T-cell lesions may be replaced by B-cell and dendritic plasmacytosis if there is marked inflammation

Laboratory Evaluation

1. Serum CK and ESR are often normal or minimally elevated
2. MRI and CT of muscle:
 - a. Diffuse swelling of the involved muscle with edema

Differential Diagnosis

1. Thrombophlebitis
2. Myositis ossificans
3. Proliferative myositis
4. Infections
5. Eosinophilic fasciitis
6. Localized nodular myositis
7. Amyloidosis
8. Neurogenic hypertrophy

9. Pseudohypertrophy
10. Dystrophies
11. Rhabdomyoma
12. Intramuscular lipoma
13. Fibromatosis
14. Malignancies
 - a. Rhabdomyosarcoma
 - b. Leiomyosarcoma
 - c. Liposarcoma
 - d. Lymphoma

Viral Infections

Human Immunodeficiency Virus

General Characteristics

1. Patients with HIV may develop an inflammatory myopathy that is more common in adults than children
2. It can develop in the early stages of HIV and in those with prolonged seroconversion but is most common in patients with AIDS

Clinical Manifestations

1. A subacute or chronic progressive symmetrical proximal muscle weakness associated with myalgia
2. There often is associated HIV-related neuropathy with sensory loss of both large and small fiber modalities
3. Rhabdomyolysis may occur with HIV infection alone or with antiretroviral therapy and/or statin use
4. Patient may have a clinical picture that resembles DM
5. Concomitant medical associations include:
 - a. Rash
 - b. Arthritis
 - c. Myocarditis
 - d. Secondary infections

Neuropathology

1. Muscle biopsy:
 - a. Perimysial and endomysial inflammation that is composed of macrophages and CD8+ cytotoxic T-cells which invade non-necrotic muscle fibers
 - b. Perivascular inflammation occurs without necrotizing vasculitis
 - c. Rarely ragged red fibers, nemaline rods and cytoplasmic bodies and rimmed vacuoles are seen
2. Electron microscopy:
 - a. The virus is only seen in inflammatory cells
3. The present hypotheses is that the HIV virus triggers a T-cell mediated and MHC-1 restricted immune response to muscle antigens

Laboratory Evaluation

1. CK elevation
2. EMG:

- a. Increased muscle membrane irritability with positive sharp waves fibrillation potentials and complex repetitive discharges
- b. Low amplitude MUAPs

Human T-Cell Leukemia Virus Type I

General Characteristics

1. Most often HTLV-1 causes spastic paraparesis and adult T-cell leukemia
2. A myositis can occur in patients without leukemia or spastic paraparesis

Clinical Manifestations

1. Subacute onset of proximal myopathy with myalgias
2. In patients with tropical spastic paraparesis HTLV-1 myositis causes proximal upper extremity and neck flexor weakness

Neuropathology

1. Muscle biopsy:
 - a. Similar to HIV myositis and PM
 - b. Rimmed vacuoles similar to IBM occur
2. Electron microscopy:
 - a. HTLV-1 can be demonstrated in inflammatory cells but not in muscle fibers
 - b. Evidence supports a T-cell mediated and MHC-1 restricted process similar to that of HIV
 - c. HIV/HTLV-1-coinfected patients have greater production of Th-1 cytokines

Laboratory Evaluation

1. The serum CK is increased
2. EMG:
 - a. Myopathic features
 - b. In patients with TSP there may be an altered pattern of recruitment that is seen with upper motor neuron disease

Influenza Virus

General Characteristics

1. Influenza A, B and C cause upper respiratory infections and concomitant myalgias with fever and the sickness response; posited to be caused by release of proinflammatory cytokines
2. Children and adults may develop a myositis that has a different clinical course

Clinical Manifestations

1. Children:
 - a. Severe pain, swelling and tenderness of the calves as the infection resolves
 - b. Children may toe walk or crawl rather than walk due to the severe pain
 - c. Signs and symptoms usually last <1 week
 - d. Myoglobinuria may occur

2. Adults:
 - a. The myositis is usually more severe in adults
 - b. Proximal muscle weakness occurs in approximately 50% of patients
 - c. Myoglobinuria with renal involvement is more common in adults than in children
 - d. There is generalized muscle pain

Neuropathology

1. Muscle biopsy (children):
 - a. Interstitial mononuclear and polynuclear inflammatory cells
 - b. Scattered necrotic and regenerating fibers
2. Electron microscopy:
 - a. No viral particles in muscle tissue
3. Muscle biopsy in adults:
 - a. Scattered necrotic and regenerating fibers with minimal infiltration of mononuclear cells
 - b. Electron microscopy:
 - i. Viral particles within membrane-bound vacuoles adjacent to the sarcolemma have rarely been seen
 - ii. Intranuclear inclusions have been demonstrated in fibers that had no viral particles. The inclusions consisted of 7–9 nm parallel filaments

Laboratory Evaluation

1. Serum CK is elevated in patients with myositis
2. EMG:
 - a. Characteristics of an active necrotizing myopathy

Rarer Viral Myositides

1. Coxsackie virus
2. Mumps
3. Measles
4. Adenovirus
5. Herpes simplex
6. Cytomegalovirus
7. Hepatitis B and C
8. Epstein-Barr
9. Respiratory syncytial
10. Echovirus
11. Arbovirus

Bacterial Infection of Muscle

Pyomyositis

General Characteristics

1. Pyomyositis is a pyogenic infection of skeletal muscle most often seen in tropical countries
2. The incidence is increasing in developed countries from HIV infection and intravenous drug abuse

Clinical Manifestations

1. Onset is with muscle pain, tenderness and fever

2. The most common sites of infection are the quadriceps, glutei and deltoid musculature
3. Rarely the paraspinal muscles are infected which causes severe back pain
4. Spread into the epidural space has been reported with spinal cord involvement

Neuropathology

1. Muscle biopsy:
 - a. Abscess with necrotic tissue that contains polymorphonuclear cells, lymphocytes and rarely eosinophils
2. The most common organisms are:
 - a. Staphylococcus aureus
 - b. Streptococcus
 - c. Escherichia coli
 - d. Yersinia enterocolitica
 - e. Legionella
3. The pyomyositis may arise as an extension from an adjacent infection or by hematogenous spread

Laboratory Evaluation

1. Serum CK may be normal or markedly increased
2. An elevated ESR and C-reactive protein as well as leukocytosis is usually seen
3. MRI:
 - a. Helpful in localizing the extent of the infection

Lyme's Disease

General Characteristics

1. Lyme's disease is most often associated with peripheral and CNS manifestation although myalgia is common

Clinical Manifestations

1. Patients with myositis present with focal or generalized weakness with myalgias
2. Associated medial complications include:
 - a. The migratory rash
 - b. Arthritis (knee is the most common joint)
 - c. Myocarditis
3. Rhabdomyolysis may occur with severe myositis

Neuropathology

1. Muscle biopsy:
 - a. Focal nodular infiltrates
 - b. Perimysial inflammation
 - c. Scattered necrotic muscle fibers
 - d. Lymphocytic and plasma cell infiltrates have been described adjacent to small endomysial blood vessels
 - e. Infiltrates are composed of CD4+ T-lymphocytes and macrophages with a minor contribution from CD8+ T-lymphocytes and B-cells

Laboratory Evaluation

1. CK levels are normal or minimally elevated

2. Intrathecal IgG antibodies to *Borrelia burgdorferi*
3. PCR of CSF is not very sensitive
4. In patients with early disease the serum may be negative while the CSF has a positive antibody response
5. EMG:
 - a. Myopathic pattern
 - b. May have concomitant polyradiculoneuropathy

Fungal Myositis

General Characteristics

1. Fungal muscle infections are almost always encountered in a setting of severe immunosuppression or hematologic malignancy
2. *Candida* is the most common organism and most infections are seen with its systemic spread
3. Invasive *Candida* infections are seen with:
 - a. Immunocompromised states
 - b. Hematopoietic stem cell transplantation
 - c. Solid organ transplantation
 - d. Chemotherapy within the past three months
 - e. Severe neutropenia
 - f. Surgery within the past 30 days
 - g. Acute renal failure
 - h. Liver failure
 - i. Increased baseline creatine

Clinical Manifestations

1. Diffuse myalgias, tenderness and weakness of involved muscles

Neuropathology

1. Muscle biopsy:
 - a. Infiltration of the muscle by hyphae and yeast forms
 - b. Inflammation and hemorrhagic necrosis
2. The cytokine IL-10 gene rs1800896GG genotype polymorphism may be important as this genotype was associated with a higher risk of invasive *Candida* infections

Laboratory Evaluation

1. Setting of neutropenia and severe immunosuppression, liver and renal failure
2. (1 to 3)-B-D-glucan (BDG) and *Candida albicans* germ tube antibody (CAGTA) tests are being evaluated

Parasitic Infections

Trichinosis

General Characteristics

1. Trichinosis is caused by *Trichinella spiralis* and is the most common parasitic disease of muscle worldwide
2. Its incidence has declined in the USA as awareness of the illness has increased and pigs are less likely to be fed raw garbage
3. Most infections arise from the ingestion of inadequately cooked pork

Clinical Manifestations

1. Approximately two to twelve days after ingestion there is
 - a. Hematogenous spread of larvae to muscle
2. The muscles infected include: 1. the diaphragm, 2. extraocular muscles, 3. tongue, 4. masseter, 5. laryngeal, 6. intercostal, 7. trunk and 8. extremities
3. There is generalized muscle pain and weakness
4. Fever, abdominal pain and gastrointestinal symptoms
5. Periorbital edema and ptosis are prominent
6. Subconjunctival hemorrhage
7. Erythematous or petechial rash may be seen
8. Weakness and myalgias are most severe in the third week of the infection but can be prolonged
9. Rarely there is myocarditis and meningoencephalitis

Neuropathology

1. Muscle biopsy:
 - a. In the early stages of infection there is muscle infiltration by eosinophils and polymorphonuclear leukocytes
 - b. In the chronic stages the inflammatory profile shifts to mononuclear cells
2. The parasite induces long-lasting molecular cross talk with the host by means of muscle larvae excretory secretory products (ESL1). These molecules modulate parasite-specific immune responses. This immunomodulatory network encompasses Th2 and Treg-type responses
3. In chronic stages there is focal calcification of cysts, fibrosis and granuloma formation

Laboratory Evaluation

1. Eosinophilic leukocytosis
2. Increased serum CK
3. Serum antibodies against *Trichinella spiralis* can be detected 3–4 weeks after the infestation

Cysticercosis

General Characteristics

1. Cysticercosis is usually caused by the ingestion of undercooked meat, primarily pork that contains the larva form of *Taenia solium*
2. The tongue and calves are frequently involved
3. Muscle involvement is frequently overshadowed by seizures, encephalopathy, and focal neurologic deficits

Neuropathology

1. Muscle biopsy:
 - a. Larvae may be surrounded by eosinophils, plasma cells, macrophages, lymphocytes and occasional giant cells within a fibrotic capsule
 - b. Chronic lesions calcify

Laboratory Evaluation

1. Serum CK is elevated
2. Increased serum eosinophil counts

Toxoplasmosis

General Characteristics

1. Toxoplasmosis is caused by the protozoa *Toxoplasma gondii* and is a life-threatening infection in immunocompromised patients
2. Cerebral toxoplasmosis is extremely common in HIV immune-compromised patients as well as patients undergoing solid organ transplantation and hematopoietic stem cell transplantation. It can occur in immunocompetent patients

Clinical Manifestations

1. Myositis can occur in isolation or may be associated with systemic disease
2. Onset is with fever, myalgias and weakness

Neuropathology

1. Muscle biopsy:
 - a. Lymphocytes, macrophages and some giant cells invade the endomysium and perimysium
 - b. Cysts that contain the bradyzoite stage are more common in muscle than the free tachyzoite form
2. The mode of infection is by ingestion of oocysts from contaminated food or cysts that contain bradyzoites from undercooked food. The organisms mature to tachyzoites which spread through the bloodstream and lymphatics

Laboratory Evaluation

1. Serum CK levels are increased
2. EMG:
 - a. An inflammatory myopathic pattern
3. Definitive diagnosis relies on parasite DNA detection by PCR:
 - a. Serologic tests include:
 - i. Sabin-Feldman dye
 - ii. Complement fixation
 - iii. Indirect hemagglutination
 - iv. Indirect fluorescent antibody test

Differential Diagnosis of Myositis Autoantibodies

Overview

1. The well tested clinically relevant autoantibodies are separated into two groups based on their diagnostic accuracy in determining a specific myositis phenotype:
 - a. The myositis-specific antibodies (MSA) include:
 - i. Their diagnostic specificity for autoimmune myositis is greater than 90%
 - ii. They target cytoplasmic or nuclear ribonucleoproteins that are involved in gene transcription, protein synthesis, translocation and innate antiviral immune responses

- iii. They are associated with distinct disease phenotypes
- b. Myositis-associated antibodies (MAA):
 - i. May be present in 50% of myositis patients
 - ii. Are not disease-specific
 - iii. Primarily found in myositis overlap symptoms

Myositis-Specific Antibodies (MSA)

Anti-ARS Antibodies

1. ARS are cytoplasmic enzymes that catalyze the reaction that synthesizes the antibodies. Eight t-RNA synthetases have been identified as immunologic targets and include:
 - a. Histidyl (Jo-1)
 - b. Threonyl (PL-7)
 - c. Alanine (PL-12)
 - d. Glycyl (EJ)
 - e. Isoleucyl (PL-12)
 - f. Asparaginyl (KS)
 - g. Tyrosyl (Ha)
 - h. Phenylalanyl (Zo)
2. Anti-Jo-1:
 - a. Is found in 20–30% of patients with PM and 60–70% of myositis patients with interstitial lung disease
 - b. Anti PL-7, PL-12 occur in <5% of PM and DM patients
 - c. Anti-KS, OJ, EJ, Zo and Ha in less than 2% of PM or DM
 - d. Anti-ARS antibodies are associated with myositis and:
 - i. Interstitial lung disease (ILD)
 - ii. Raynaud's phenomenon
 - iii. Thick and cracked hand skin

Anti-SRP Antibody

1. SRP is a cytoplasmic multimeric ribonucleoprotein that is a complex of six polypeptides with one 7SL RNA
2. It is involved in secretory protein recognition and translocation across the rough endoplasmic reticulum
3. Anti-SRP antibodies are specific for idiopathic inflammatory myopathies
4. They are found in 4–8% of PM patients
5. They are associated with the anti-SRP syndrome:
 - a. Necrotizing myopathy
 - b. Myofiber necrosis and regeneration with little inflammation
 - c. Rapidly progressive weakness with poor response to treatment

Anti-TiF1-V Antibody

1. The antibody is found in 20–30% of adult and juvenile DM patients
2. It is directed against nuclear transcription factors that belong to the Transcriptional intermediary factor (TiF-1) family

3. The antibody is associated with severe skin lesions in both adult and juvenile DM
4. It is also associated with paraneoplastic DM in adult patients (>50 years of age)

Anti-NXP-2 Antibody

1. The autoantibody is detected against a nuclear protein (nuclear protein 2; NXP2)
2. These antibodies have been detected in approximately 25% of juvenile or adult DM patients but rarely in PM
3. In adolescent onset DM:
 - a. Severe cutaneous lesions that include calcinosis
 - b. Muscle contractures
 - c. An association with cancer has been documented in male adults
 - d. If both anti-TiF-1-V and anti-NXP-2 antibody testing is done for cancer-associated DM, the yield is approximately 50%

Anti-MDA5 Antibody

1. IFN-induced melanoma differentiated-associated proteins 5 (MDA5):
 - a. Is seen in 20–30% of Asian patients with DM
 - b. Clinical Manifestations include:
 - i. Amyopathic DM
 - ii. Rapidly progressive interstitial lung disease
 - c. MDA5 regulates the innate antiviral immune response against cytoplasmic viral RNA
 - d. Anti-MDA5 may also be seen in Caucasian patients with idiopathic inflammatory myopathy with ILD

Anti-SAE Antibody

1. Anti-small ubiquitin-like modifier activating enzyme (SAE) antibodies are found in 8% of adult DM patients
2. Clinical manifestation include:
 - a. Severe skin disease
 - b. Dysphagia
 - c. Systemic features
3. Related to a specific HLA haplotype
4. Antibodies are directed against SUMO-1 activating enzyme heterodimer which is a small nuclear protein that resembles ubiquitin
5. The enzyme effects sumoylation which is a post-translation enzymatic aggregation of protein

Anti-HMGCR Antibody

1. The autoantibody has been detected in 3–8% of adult idiopathic inflammatory myopathies (IIM)
2. The antibody is directed against 3-hydroxy-5-methylglutaryl-Coenzyme A reductase (HMGCR); an important component of cholesterol synthesis inhibited by statins
3. A putative marker of a necrotizing myopathy most often but not invariably induced by statins exposure
4. Associated Clinical Manifestations include:
 - a. Similar to other IIM

- b. Proximal muscle weakness
- c. Elevated CK levels
- d. Myopathic EMG pattern
- e. Response to immunosuppressive therapy
- f. Myofiber necrosis and degeneration with inflammatory cells

The Major Myositis Associated Antibodies

1. Include anti-Ro/SSA, anti-PM/Scl, anti-Ku and anti-U1RNP antibodies
2. They are found when PM/DM phenotype is seen with another connective tissue disease as a component of an overlap syndrome
3. These antibodies may also be detected in the absence of another Connective tissue disease (CTD)
4. The overlap of PM/DM and systemic sclerosis (PDM/SSc) accounts for 44% of scleroderma overlap syndrome

Anti-Ro/SSA

1. The antibody is directed against the Ro52 subunit and is the most common MAA in myositis
2. Anti-Ro/SSA and anti-LA/SSA are most often detected in PDM/Sjögren's syndrome patients
3. Anti-Ro/SSA is detected in approximately 30% of myositis patients in conjunction with ARS and other MAA antibodies
4. In anti-Jo-1 positive patients, the anti-Ro52 antibody association has been detected in patients with:
 - a. Severe ILD (interstitial lung disease)
 - b. Myositis
 - c. Joint involvement
 - d. Cancer risk

Anti-PM/Scl and Anti-Ku Antibodies

1. Are primarily markers of PDM/SSc, although they are found in PM, DM and systemic sclerosis without overlap
2. In patients with overlap PDM/SSc these antibodies are encountered in approximately 60% of patients
3. In addition to myositis in PM/Scl-positive PDM/SSc patients other clinical features include:
 - a. Raynaud's phenomenon
 - b. ILD
 - c. Arthritis
 - d. Thickened hand skin
4. Anti-PM/Scl and anti-Ku positive PDM/SSc are most often detected in the limited form of cutaneous scleroderma. These patients demonstrated less digital ulcer, more myositis, ILD and arthritis compared to anti-centromere antibody positive limited SSc
5. The HLA haplotype DGA1*0501, DQB1*02 and DRB1*0301 occur with anti-PM/Scl antibody that is associated with PDM/SSc

Anti-U1RNP

1. Anti-U1RNP are more common in patients with systemic lupus

2. Associated Clinical Manifestations in the overlap syndrome include:
 - a. Erosive arthritis
 - b. Alopecia
 - c. ILD
 - d. Oral ulcers
 - e. Renal disease is rare
 - f. DM is more common than PM

Summary of Myositis-Specific Antibodies (MSA)

Evidence Supports the Hypothesis

1. Myositis autoantigens are able to induce and maintain a B-cell antigen specific immune response in muscle
2. There is aberrant expression of Jo-1, Mi-2, HMGCR in the regenerating fibers of PM and DM
3. Classic and novel myositis antigens are over expressed in other organs:
 - a. Jo-1-lungs
 - b. M1-2-epidermal basal lamina
 - c. TiF-1-V (gamma) and NXP-2 in adenocarcinoma
4. Myositis antigens in target tissues act as proinflammatory and immunostimulants
5. Most myositis autoantigens are associated with nucleic acids which suggest that they stimulate IFN type 1 secretion pathways that increase antigen concentration and the extent of the immune response

Myopathies of Systemic Disease

Thyrototoxic Myopathy

General Characteristics

1. Thyroid hormone is a major determinant of the composition of muscle fibers
2. MicroRNA 133a1 targets the gene associated with thyroid hormone in muscle. It regulates slow-to-fast twitch muscle fiber type conversion by targeting TEA antigen domain family member
3. 1 (TEAD1) which is a major regulator of slow muscle gene expression
4. TH negatively regulates the transcription of myosin heavy chain 1 indirectly via miR-133a/TEAD
5. It is proposed that TH inhibits the slow muscle phenotype through an epigenetic mechanism involving microRNA-133a1
6. The exact molecular mechanism of thyroid hormone on muscle in deficit or excess is not known

Clinical Manifestations

1. Most hyperthyroidism has its onset in the 5th decade
2. The myopathy severity may not correlate with the degree of thyrotoxicosis
3. The onset of myopathy is often after the other manifestations of hyperthyroidism are manifest

4. Thyrotoxicosis is more common in females while the myopathy is more frequently seen in males
5. Approximately 60–80% of patients with hyperthyroidism have proximal myopathy by exam. It is a rare chief complaint
6. Proximal muscle weakness and atrophy. It may preferentially affect the shoulder girdle and rhomboid muscles
 - a. Distal weakness may predominate in 20% of patients
 - b. Bulbar and intercostal muscles may be affected:
 - i. Thyroid ophthalmopathy and proptosis (Collier's sign) occurs with Grave's disease
7. Rhabdomyolysis can occur with severe thyrotoxicosis
8. Muscle stretch reflexes are increased; rarely fasciculation and myokymia are seen:
 - a. The tongue is very active and may demonstrate apparent fibrillation
9. There may be associated MG (myasthenia gravis). Thyrotoxicosis myopathy does not fluctuate, has more atrophy than what is seen in MG, and does not respond to anticholinesterase therapy
10. Association with hypokalemic periodic paralysis:
 - a. Sporadic occurrence, but appears to be most common in Asian patients
 - b. More common in males
 - c. Attacks are similar to those of familial hypokalemic periodic paralysis but occur later in life
 - d. Most often, the serum potassium concentration is low during attacks but may be normal
 - e. Treatment of the thyrotoxicosis stops the attacks

Neuropathology

1. Muscle biopsy:
 - a. May be normal
 - b. Rare patients demonstrate:
 - i. Variability of fiber size
 - ii. Central nuclei
 - iii. Type 1 and 2 fiber atrophy
 - iv. Rare necrotic fibers
2. Electron microscopy (in some patients demonstrate):
 - a. Z-band streaming
 - b. Swelling of T-tubules
 - c. Elongated mitochondria
 - d. Decreased mitochondria
 - e. Subsarcolemmal glycogen
3. EM in patients with periodic paralysis:
 - a. Vacuoles (centrally placed in myofibers)
 - b. Sarcolemmal blebs filled with glycogen
 - c. Dilated terminal cisternae of the sarcoplasmic reticulum
4. Thyroid hormone causes increased potassium reflux from muscle; there may be an increased number of Na/K ATPase pumps in the muscle membrane that causes this reflux

Laboratory Evaluation

1. CK concentration is usually normal

2. TSH level is decreased in the face of increased thyroxine (T₄) and T₃ elevation
3. EMG:
 - a. It is usually normal
 - b. Rarely repetitive and complex discharge may be seen
 - c. NCS are normal

Hypothyroid Myopathy

General Characteristics

1. Approximately one-third of patients with hypothyroidism develop muscle symptomatology
2. Hypothyroidism is associated with reduced oxidative metabolic capacity and is associated with fiber type switching from fast- to slow-twitch as well as insulin resistance

Clinical Manifestations

1. The Kocher-Debre-Semelaig syndrome may be seen in congenital hypothyroidism which is characterized by:
 - a. Generalized muscular hypertrophy
 - b. Predominant calf hypertrophy
2. Adult hypothyroid patients:
 - a. Proximal extremity muscle weakness
 - b. Myalgias, cramps and fatigue
 - c. A subset of patients may develop generalized muscle hypertrophy (Hoffman syndrome)
 - d. Rarely the respiratory muscle may be involved
 - e. Rhabdomyolysis can occur in severe patients
 - f. Delayed deep tendon reflex relation
 - g. Myoedema (painless and electrically silent mounding of muscle) can be elicited with percussion
 - h. There may be associated myasthenia gravis

Neuropathology

1. Muscle biopsy:
 - a. Variability of fiber size
 - b. Atrophy of type 2 fibers; rarely type 1 fibers are affected
 - c. Hypertrophic muscle fibers
 - d. Rare necrotic fibers
 - e. Central nuclei
 - f. Ring fibers
 - g. Increased glycogen
2. Electron Microscopy:
 - a. Mitochondrial swelling and inclusions
 - b. Myofibrillar disorganization; central core-like material
 - c. Autophagic vacuoles
 - d. Increased lipid and glycogen accumulation
 - e. Dilated sarcoplasmic reticulum
 - f. T-tubule proliferation

Muscle Biopsy in Hashimoto Disease

1. Moderate to severe muscle fiber atrophy
2. Autophagosomes

3. Capillary alterations
4. Fiber type 2 predominance
5. Infiltration of muscle cells by mast cells and macrophages
6. Immunoglobulin deposition occurs in 80% of patients

Laboratory Evaluation

1. The serum CK is markedly elevated (10–100x normal)
2. Low serum concentrations of T₃ and T₄ with elevated TSH levels
3. EMG:
 - a. Short duration, low amplitude polyphasic MUAPs in affected muscle
 - b. Normal motor and sensory conduction velocities unless there is a concomitant neuropathy

Hyperparathyroidism and Osteomalacia

General Characteristics

1. Muscle weakness occurs in > 70% of patients with osteomalacia and approximately 2%–10% in those with hyperparathyroidism
2. Primary hyperparathyroidism is most often caused by parathyroid edema or hyperplasia or pituitary edema
3. Secondary hyperparathyroidism is most often encountered in the setting of chronic renal failure which causes the reduction of 1, 25-dihydroxy-vitamin D conversion. In turn, there is decreased intestinal absorption of calcium and decreased renal phosphate clearance, which induces secondary hyperparathyroidism and osteomalacia
4. There are hereditary forms of both primary hyperparathyroidism and vitamin D deficiency leading to osteomalacia
5. Parathyroid hormone:
 - a. Increases muscle proteolysis
 - b. Decreases muscle energy production, transfer and utilization
 - c. Decreases the sensitivity of contractile myofibrillar proteins to calcium
6. Vitamin D:
 - a. Increases muscle adenosine triphosphatase concentration, which accelerates amino acid protein incorporation into muscle
 - b. Enhances calcium uptakes by the sarcoplasmic reticulum and mitochondria

Clinical Manifestations of PTH and Osteomalacia

1. Symmetric proximal muscle weakness that is more severe in the lower extremities
2. Concomitant microfractures of bone with pain
3. Neck extensor weakness may cause the “dropped head” syndrome
4. Unusual signs and symptoms (controversial):
 - a. Hoarseness
 - b. Dysphagia
 - c. Spasticity
 - d. Respiratory muscle involvement

5. Increased muscle stretch reflexes with no Babinski sign
6. Approximately 50% of patients have severe cramps and paresthesia
7. A significant number of patients have a stocking-and-glove pattern of large or small fiber sensation and decreased muscle stretch reflexes that support the diagnosis of peripheral neuropathy
8. Psychiatric and behavioral manifestations from the hypercalcemia
 - a. In secondary hyperparathyroidism:
 - i. Proximal muscle weakness occurs in a setting of renal failure
 - ii. Muscle neurosis and myoglobinuria occur and may be due to arterial calcification in some patients

Neuropathology

1. Muscle biopsy:
 - a. No specific myopathy
 - b. Type 2 fiber atrophy; rarely Type 1 atrophy
2. The calcium-sensory receptor (CaR) modulates renal calcium reabsorption and parathyroid hormone PTH secretion; it is involved in the secondary hyperparathyroidism of chronic kidney disease. Pathophysiologic PH (acidification) that occurs in chronic kidney disease (CKD) inhibits CaR activity

Laboratory Evaluation

1. Serum CK concentration is most often normal in primary and secondary hyperparathyroidism as well as osteomalacia
2. In primary hyperparathyroidism:
 - a. Calcium serum concentrations are elevated and phosphate concentrations are low
 - b. Urinary calcium excretion is low and excretion of phosphate is high
 - c. Elevated excretions of cyclic adenosine monophosphate with hypercalcemia
 - d. Serum PTH levels and 1,25-dihydroxy-vitamin D levels are elevated in PTH
 - e. There are low levels of 1,25-dihydroxy-vitamin D levels (and therefore decreased calcium intestinal absorption) in secondary hyperparathyroidism due to renal failure
3. In osteomalacia:
 - a. Low serum calcium concentration
 - b. Serum phosphate concentration is low
 - c. Low serum 25 OH vitamin levels are low
 - d. Urinary excretion of calcium is low except with renal tubular acidosis and when phosphate excretion is elevated
 - e. Serum alkaline phosphatase is elevated in osteomalacia
4. Bone X-ray with primary hyperparathyroidism:
 - a. Salt-and-pepper lesions in the skull
 - b. Bone erosion and resorption of the phalanges (radial side of the index finger) and acromial portion of the clavicle

- c. Brown tumors and cysts
- d. Diffuse demineralization
- e. Pathological fractures of the long bones
5. DEXA X-ray absorptiometry (DEXA) scan and the trabecular bone (gray-level) textural analyses of DEXA images demonstrates an indirect index of trabecular microarchitecture
6. Loss of trabeculae, thinned bone cortices and abnormal trabecular microstructures are demonstrated

Hypoparathyroidism

General Characteristics

1. Hypoparathyroidism occurs in a wide spectrum of diseases that include:
 - a. Surgical complications
 - b. Osteomalacia
 - c. Hypo- or hypomagnesemia
 - d. X-RT
 - e. Drugs
 - f. Sepsis
 - g. Infiltrative diseases
 - h. Hereditary and developmental diseases

Clinical Manifestations

1. A few patients have been described with proximal muscle weakness
2. Painless myoglobinuria without weakness may occur (rare)

Neuropathology

1. Muscle biopsy:
 - a. Variability of fiber size
 - b. Central nuclei
 - c. Decreased glycogen phosphorylase activity

Laboratory Evaluation

1. The serum CK is normal or minimally elevated
2. Low serum PTH with high serum phosphate levels
3. EMG:
 - a. Needle EMG reveals normal insertional activity but doublets or triplets or multiple MUAPs
 - b. MUAP morphology and recruitment are normal
 - c. Normal motor and sensory nerve conduction studies

Hyperadrenalism

General Characteristics

1. Approximately 60% of patients with Cushing's disease have muscle weakness
2. The zona fasciculata of the adrenal gland produces and secretes glucocorticoids. Adrenal tumor or hyperplasia of the adrenal gland often cause excess secretion of glucocorticoids and proximal myopathy
3. Rarely the zona glomerulosa, which is the source of mineralocorticoids such as aldosterone cause a proximal myopathy by means of a hypokalemic mechanism
4. Anabolic steroids from the zona reticularis increase muscle mass and strength

Steroid Myopathy

General Characteristics

1. Steroid myopathy, most often from exogenous use for immunosuppression, and rarely from adrenal or pituitary tumors, are the most common endocrine-induced myopathy
2. The fluorinated glucocorticoids such as dexamethasone, triamcinolone and beta-methasone are more destructive to muscle than other glucocorticoid preparations

Clinical Manifestations

1. Approximately 50–80% of endogenous or iatrogenic induced Cushing's disease develop proximal myopathy
2. Distal extremity, ocular, bulbar and facial muscles are not affected
3. Women have a higher risk of developing steroid myopathy than men
4. Alternate day dosing may decrease the risk of developing a myopathy
5. Proximal weakness occurs after several weeks of high dose therapy (>30 mg of prednisone) but is usually noted with chronic usage
6. Acute quadriplegia may occur with high dose intravenous usage with or without neuromuscular blocking agents in critically ill patients or those treated for asthma

Neuropathology

1. Muscle biopsy:
 - a. Atrophy of Type 2B fibers
 - b. Less atrophy and increased lipid deposition in Type I fibers
2. The catabolic effects of glucocorticoids on muscle proteolysis may be due to activation of the major cellular proteolytic systems:
 - a. Ubiquitin proteasome
 - b. The lysosomal system (cathepsin)
 - c. Calcium dependent system (calpain)
3. The microfibrillar proteins are primarily affected. Actin and myosin are dissociated by calpain and then are acted upon by the ubiquitin proteasomal system
4. The mechanisms of glucocorticoid inhibition of protein synthesis include:
 - a. Inhibition of amino acid transport into muscle
 - b. Inhibition of insulin, insulin-like growth factor and leucine in the phosphorylation of 4E-BP1 and S6K1. These transcriptional factors control the initiation of mRNA translation
 - c. Possible role of glucocorticoids in inhibiting myogenesis by down-regulation of myogenin, a transcription factor that is essential for satellite cell differentiation into muscle cells
 - d. Glucocorticoid muscle atrophy may be caused by:
 - i. Decreasing the production of IgF-1, which increases protein synthesis and myogenesis

- ii. Stimulating the production of myostatin which down-regulates the proliferation and differentiation of satellite and protein synthesis
- e. Glucocorticoids may have a deleterious effect on mitochondria as well as producing hypokalemia
 - f. Endogenous Cushing's syndrome
 - i. Elevated levels of ACTH decrease the quantal content of the endplate potential, which impairs neuromuscular transmission

Laboratory Evaluation

1. Serum CK is not affected
2. Serum potassium and phosphate may be low and sodium slightly elevated
3. EMG:
 - a. EMG and NCS are normal

Adrenal Insufficiency

General Characteristics

1. Adrenal insufficiency is the deficient production or action of glucocorticoids, mineralocorticoids and adrenal androgens
2. It is classified as: 1. primary (the adrenal cortex is affected), 2. secondary from anterior pituitary gland dysfunction and 3. tertiary from disorders of the hypothalamus

Clinical Manifestations

1. The primary features include:
 - a. Anorexia
 - b. Abdominal pain
 - c. Weight loss
 - d. Orthostatic hypotension
 - e. Hyperpigmentation of the skin with primary adrenocortical failure
2. In secondary or tertiary adrenal insufficiency, clinical features result from glucocorticoid deficiency
3. Subjective muscle weakness
4. Overwhelming fatigue
5. Objective weakness (proximal muscles) may be the result of hyperkalemia or other associated endocrinopathies

Neuropathology

1. Muscle biopsy
 - a. Normal

Laboratory Evaluation

1. Serum CK concentration is normal
2. EMG is normal

Acromegaly

General Characteristics

1. Growth hormone producing adenomas in 10–15% of all pituitary adenomas. The two most common types are densely and sparsely granulated
2. The muscle weakness is correlated with the length of the illness rather than the level of growth hormone

Clinical Manifestations

1. Patients develop slowly progressive proximal arm and leg weakness with slight muscle hypertrophy
2. Associated neurologic complications that cause weakness include:
 - a. Entrapment neuropathies (particularly carpal tunnel syndrome)
 - b. Bony overgrowth of face and joints and spinal exit foramina with concomitant nerve root and spinal cord compression
 - c. Severe arthropathy with pain that causes disuse atrophy

Neuropathology

1. Muscle biopsy:
 - a. Variation of muscle fiber size
 - b. Hypertrophy and atrophy of all fiber types
 - c. Scattered necrotic fibers
 - d. Hypertrophy of satellite cells
 - e. Electron microscopy:
 - i. Myofibrillar loss
 - ii. Abnormal glycogen accumulation
 - f. Effects of increased growth hormone:
 - i. Increased protein synthesis of muscle fibers that causes hypertrophy
 - ii. Decreased respiratory quotient of muscles
 - iii. Switch from carbohydrate to lipid metabolism
 - iv. Decreased myofibrillar ATPase activity

Laboratory Evaluation

1. Serum CK is normal or minimally increased
2. EMG:
 - a. Myopathic pattern with short duration and low amplitude MUAPs of affected proximal muscles
 - b. NCS are normal or demonstrate compression entrapment neuropathies, the most common of which are at the carpal cubital tunnels

Panhypopituitarism*General Characteristics*

1. Mutations in genes encoding both signaling molecules and transcription factors have been described in hypopituitarism that occur with and without specific syndromic features which include:
 - a. Dominant and recessive mutation in HESX1 are associated with septo-optic dysplasia
 - b. Duplications and polyalanine expansions within the SOX3 transcription factor are associated with infundibular hypoplasia, hypopituitarism and cognitive deficiency
 - c. Mutations in the transcription factor SOX2 cause hypopituitarism, cognitive deficits, and, esophageal atresia
 - d. Mutations within the LIM domain of the LHX3 gene are recessive and cause GH, TSH, LH and FSH deficiencies but spare the corticotrophs. These patients manifest a short, stiff neck with restricted lateral rotation

- e. Mutations of the LHX4 gene are dominantly inherited and cause GH, TSH, and ACTH deficiencies. They are associated with a hypoplastic anterior pituitary, deficits in the posterior pituitary and alterations of the cerebellar tonsils
- f. PROP1 and POV1F are recessive mutations within pituitary-specific transcription factors. Mutations of Pit1 or POP1 cause deficiencies of GH, prolactin and TSH; variable LH and FSH deficiencies. This mutation may be associated with an enlarged sella turcica that simulates an intrasellar tumor. The mutation may also be associated with ACTH deficiency
- g. POOF1 mutations may cause a hypoplastic anterior pituitary that is associated with GH, and prolactin deficiencies
- h. Acquired pan-hypopituitarism more frequently occurs from intrasellar compression and destruction from enlarged chromophobe adenomas, X-RT therapy for gliomas post-surgery and rarely hemorrhage (apoplexy, lymphocytic hypophysitis and Sheehan syndrome)

Clinical Manifestations

1. Generalized muscle weakness and severe fatigue
2. Patients may have the muscle manifestations of secondary hypothyroidism and glucocorticoid deficiency
3. Prepubertal pan-hypopituitarism is associated with dwarfism and deficient sexual and muscle development. These patients may have an alabaster white complexion due to lack of MSH

Neuropathology

1. Thyroid and cortical steroid deficiencies as well as decreased GH, thyroid and sexual hormones all determine aspects of muscle pathology

Laboratory Evaluation

1. Dependent on the spectrum of hormonal deficiencies incurred

Diabetic Muscle Infarction (Diabetes Myoneurosis)*General Characteristics*

1. Diabetic myoneurosis is an unusual and underdiagnosed complication of poorly controlled diabetes
2. The setting is in patients with retinopathy, nephropathy and neuropathy

Clinical Manifestations

1. The usual presentation is acute pain and swelling in the thigh. The calf may be affected rarely
2. The mean age of patients is 44.5 years (range 20 to 67 years); the length of time patients had diabetes was 19 years (range 5 to 33 years)

3. A tender mass may be palpated in the vastus lateralis, biceps femoris, thigh adductors and the gastrocnemius muscle
4. Nephropathy is the most common diabetic complication and is seen in approximately 75% of patients

Neuropathology

1. Muscle biopsy:
 - a. Muscle infarction with areas of necrosis, edema, hemorrhages and inflammatory infiltrate. Chronically, the infarcted areas are replaced by connective and adipose tissue
 - b. There is thickening of the basement membrane, hyperplasia of the media, fibrin occlusion of the lumen and calcification of small and medium-sized muscle blood vessels
 - c. Suggested mechanisms for diabetic myonecrosis include:
 - i. Reperfusion of ischemic tissue associated with endothelial dysfunction
 - ii. Hypercoagulability
 - iii. Inflammatory vasculopathy

Laboratory Evaluation

1. The serum CK concentration is usually normal
2. EMG:
 - a. Muscle membrane instability with positive sharp waves and fibrillation potentials
 - b. Small polyphasic MUAPs with early recruitment
3. MRI:
 - a. T2-weighted signal abnormalities in the infarcted tissue

Myopathies Associated with Electrolyte Abnormalities (Hypokalemia)

General Characteristics

1. Hypokalemia with muscle weakness is similar to familial hypokalemic periodic paralysis both clinically and electrodiagnostically

Clinical Manifestations

1. Most often patients present with symmetric proximal weakness, although there may be asymmetry and distal involvement
2. Weakness is often associated with cramps, myalgia and a feeling of swelling in the affected muscles
3. Reflexes are absent (deep tendon) and there are no myotatic reflexes (muscle contractions from percussion)
4. Rarely there is rhabdomyolysis with myoglobinuria and renal involvement
5. Cardiac arrhythmia

Neuropathology

1. Muscle biopsy:
 - a. Vacuoles in myofibers
 - b. Scattered necrotic fibers
2. The muscle membrane may not be excitable in the face of decreased extracellular K^+ concentration

Laboratory Evaluation

1. The serum potassium level is less than 2.5 mEq/L before the muscle is affected
2. Serum CK concentrations are elevated
3. EMG:
 - a. Positive sharp waves and fibrillation potentials
 - b. Small amplitude and brief durations of MUAPs with early recruitment
 - c. NCS are normal
4. EKG:
 - a. Brachycardia
 - b. Prolonged PR and QT intervals
 - c. Flattened T-waves
 - d. U waves

Differential Diagnosis of Secondary Hypokalemia

1. Thyrotoxic periodic paralysis
2. Renal tubular acidosis
3. Villous adenoma of the intestine
4. Bartter syndrome
5. Gitelman syndrome
6. Sjögren's syndrome
7. Hyperaldosteronism
8. Diuretics, glucocorticoids, licorice
9. Amphotericin B toxicity
10. Alcoholism
11. Toluene toxicity
12. Barium poisoning

Hyperkalemia

General Characteristics

1. Hyperkalemia causes prolonged depolarization of the sarcolemmal membrane that inactivates sodium channels, which blocks the initiation of an action potential
2. Increased muscle membrane excitability

Clinical Manifestations

1. Generalized muscle weakness
2. Chvostek sign
3. Myotonic lid lag

Neuropathology

1. Muscle biopsy:
 - a. Normal

Laboratory Evaluation

1. In patients with severe weakness the potassium level is usually greater than 7 mg/L (most often in renal failures)
2. Serum CK levels are usually normal
3. EMG:
 - a. Small amplitude MUAPs, with early recruitment
 - b. No myotonic discharges occur with acquired hyperkalemia
 - c. Nerve conduction studies are normal

Differential Diagnosis of Secondary Hyperkalemic Paralysis

1. Addison's disease

2. Hyperaldosteronisms
3. Isolated aldosterone deficiency
4. Increased potassium intake
5. Potassium sparing diuretics (spironolactone and triamterene)
6. Chronic renal failure
7. Rhabdomyolysis

Hypophosphatemia

General Characteristics

1. A wide spectrum of diseases are associated with hypophosphatemic myopathy, the most common of which are hyperalimentation, phosphate-binding antacids, diabetic ketoacidosis and severe diarrhea
2. Usually serum phosphate levels less than .4 M/L are required to produce muscle disease

Clinical Manifestations

1. Generalized muscle weakness
2. Associated:
 - a. Guillain-Barré-like syndrome
 - b. Paresthesias and dysesthesias
 - c. Hypophosphatemia osteomalacia
 - d. Bone and joint pain

Neuropathology

1. Muscle biopsy:
 - a. Not described
2. Abnormalities in muscle density and decreased peak force probably occur if it is associated with hypophosphatemia rickets

Laboratory Evaluations

1. Dependent on the associated disease
2. In hypophosphatemic rickets there may be associated hyperglycemia and increased hydroxyprolinuria
3. In adult hypophosphatemic osteomalacia with myopathy there may be associated low levels of 25 – OHY-Vitamin D3

Differential Diagnosis of Hypophosphatemia

1. Diabetic ketoacidosis
2. Hyperalimentation
3. Primary Sjögren's syndrome
4. Hypophosphatemic rickets
5. Fanconi syndrome (adefovir)
6. Burn patients
7. Severe diarrhea

Rare Myopathies Associated with Systemic Disease

Amyloid Myopathy

General Characteristics

1. Primary systemic myositis usually presents with nephrotic syndromes, cardiomyopathy, hepatomegaly and peripheral

neuropathy. Amyloid myopathy is rare. It does not occur in secondary amyloidosis. It does occur in familial forms

Clinical Manifestations

1. Presents with the serum indices, subacute onset of primarily proximal myopathy. A subset of patients may have distal involvement. (may be related to a concomitant peripheral neuropathy)
2. Hypertrophy of involved muscles
3. Tongue involvement (macroglossia)
4. Muscles of respiration may be involved from myopathy of the diaphragm or phrenic nerve neuropathy
5. Pain, stiffness and indurations of involved muscle occurs

Neuropathology

1. Muscle biopsy:
 - a. Variability of fiber size
 - b. Hypertrophied and atrophied fibers
 - c. Increased central nuclei
 - d. Scattered degenerating and regenerating fibers
 - e. Grouped atrophy (associated denervation)
2. Amyloid deposits surround small arterioles and venules but may also encase muscle fibers
3. In primary amyloidosis the deposits are composed of K light chains, which may be associated with membrane attack complexes
4. APOE may be concomitantly deposited
5. Electron microscopy:
 - a. Deposition of non-branching 10 nm amyloid filaments that surround small blood vessels and muscle fibers

Laboratory Evaluation

1. Elevation of serum CK 2–5 times normal but has been described as markedly elevated with gelsolin familial amyloidosis
2. Primary amyloid (light chain amyloidosis): there is increased monoclonal immunoglobulin in the serum or urine
3. EMG:
 - a. Irritable muscle membrane with positive sharp waves and fibrillation potentials (prominent in paraspinal and proximal arms and legs). There may be complex and repetitive myotonic discharges
 - b. Weak proximal muscles demonstrate low amplitude polyphasic MUAPs, which are recruited early
 - c. Nerve conduction studies are abnormal in those patients with concomitant peripheral neuropathy
4. MRI of muscle:
 - a. Hypointense reticular appearance of subcutaneous fat with minimal muscle signal intensity supports the diagnosis of primary amyloidosis

Polymyalgia Rheumatica (PMR)

General Characteristics

1. PMR is the second most common inflammatory autoimmune rheumatic disease in the United States

2. Annual incidence is 58.7 per 100,000 people over the age of 50
 - a. The mean age at diagnosis is 73 years. Its incidence increases with age; it is more common in Caucasian people of northern latitudes

Clinical Manifestations

1. An insidious onset is usual, but cases of acute onset occur in patients between 70–79 years of age
2. A diffuse muscular non-articular pain occurs in the neck, shoulder or pelvic girdle
3. A low grade fever and fatigue often accompany the muscle pain
4. Strength is normal although most patients complain of weakness
5. Approximately 16% of patients develop concomitant temporal arteritis
6. Stiffness that lasts for a half hour or longer occurs in the morning or after periods of activity which may improve with activity which contrasts with osteoarthritis
7. Constitutional symptoms, in addition to low grade fever, include fatigue, malaise, anorexia, weight loss, are common
8. A subset of PMR patients has swelling of distal joints in the hands and feet due to tenosynovitis that results in seronegative symmetrical synovitis with pitting edema syndrome

Neuropathology

1. Muscle biopsy:
 - a. Usually normal
 - b. Variation in fiber size
 - c. Type 2 fiber atrophy
 - d. Moth eaten fibers
 - e. No inflammatory changes

Laboratory Evaluation

1. Increased ESR, usually over 40 mm/hr; normal in 6–20% of patients
2. Normal serum CK
3. Normal EMG and NCS
4. Ultrasonography and MRI imaging:
 - a. Affects primarily the periarticular structures:
 - i. Subacromial bursitis
 - ii. Subdeltoid bursitis
 - iii. Trochanteric bursitis
 - iv. Glenohumeral and hip joint effusions and synovitis
 - b. Variabilities in temporal arteries can occur in (<8%) in asymptomatic patients (giant cell arteritis)

Toxic Myopathies

Overview

Cholesterol lowering medications that include 3-hydroxy-3-methyl-glutaryl-coenzyme A (3-HMG-CoA) reductase inhibitors, fibric acid derivatives, niacin, and ezetimibe all can

cause a toxic myopathy and are in wide use. There is a wide spectrum of clinical phenomena from asymptomatic increase in serum creatine kinase concentration to a severe necrotizing myopathy with myoglobinuria and renal failure. In general the degree of increased CK in the serum corresponds with the extent of muscle damage and discontinuance of the medication resolves the myopathy. However, in a subset of patients, these drugs can trigger a severe immune-mediated inflammatory or necrotizing myopathy. A mechanistic approach to toxic myopathies includes those caused by 1. necrotizing myopathy, 2. amphiphilic toxicity, 3. antimicrotubular myopathy, 4. mitochondrial dysfunction, 5. inflammation, 6. hypokalemia and 7. critical illness.

HMG-CoA Reductase Inhibitors

General Characteristics

1. Statins inhibit 3-HMG-CoA reductase the rate limiting enzyme for cholesterol synthesis
2. The downstream pathways from this enzyme blockade that are important for muscle metabolism and may be a component of 3-HMG-CoA reductase toxicity include:
 - a. Geranylgeranyl which is pivotal in the biosynthesis of coenzyme Q
 - b. Dolichol, which is a component of glycoprotein synthesis
3. Isopentylamine, which is component of tRNA and regulatory proteins
4. Squalene is the first metabolite in the synthesis of cholesterol and is derived from mevalonate, the first product of HMG-CoA reductase

Clinical Manifestations

1. The major statins include:
 - a. Lovast
 - b. Simvastatin
 - c. Pravastatin
 - d. Atorvastatin
 - e. Fluvastatin
 - f. Cerivastatin
2. All may cause:
 - a. Asymptomatic elevation of CK
 - b. Proximal muscle weakness
 - c. Myalgia
 - d. Myoglobinuria
3. There is a 2–7% incidence of myalgia and a .1–1% incidence of weakness or elevated CK; myoglobinuria occurs in <.5% of patients
4. A recent study of 35% of biopsied patients, 233 of whom fulfilled criteria for inflammatory/immune-mediated myopathy show that this complication of statin is increasing (anti-HMGCR autoantibodies)
5. The risk of toxic myopathy increases with the addition of fibric acid drugs, niacin, erythromycin, cyclosporine and ezetimibe. These combinations also raise the risk of kidney and liver complications. The combination of lovastatin

and cyclosporine causes a severe myopathy in as many as 30% of patients

6. Statin use can cause dermatomyositis
7. Recently it has been demonstrated that progressive proximal weakness, elevated serum CK levels, a necrotizing myopathy or muscle biopsy and autoantibodies to HMGCR is a major cause of immune-mediated myopathy that occurs with statin use

Neuropathology

1. Muscle biopsy:
 - a. Muscle fiber necrosis with phagocytosis
 - b. Lipid-filled vacuoles within myofibers
 - c. Cytochrome oxidase-negative fibers
 - d. No endomysial inflammatory infiltrate involving non-necrotic muscle fibers

Laboratory Evaluation

1. Elevated CK serum concentration that is proportional to the degree of muscle destruction
2. EMG:
 - a. Increased insertional activity with positive sharp waves, fibrillation potentials (statins and cyclosporine)
 - b. Myopathic MUAPs
3. Antibodies to CR HMGCR in patients with statin induced autoimmune myopathy

Differential Diagnosis of Drugs Causing Necrotizing Myopathy

1. Cholesterol lowering agents
2. Cyclosporine
3. Labetalol
4. Propofol
5. Alcohol

Fibric Acid Derivatives

General Characteristics

1. Clofibrate and gemfibrozil are branched-chain fatty acid esters that can cause a myopathy usually within 2 to 3 months of use. The myopathy has been described to start after two years of use

Clinical Manifestations

1. Generalized weakness
2. Myalgias and cramps
3. Myoglobulinuria and rhabdomyalgia are rare complications
4. Patients using both clofibrate gemfibrozil or with concomitant HMG-CoA reductase inhibitors are at increased risk of developing a severe myopathy
5. Chronic kidney disease increases myopathy risk

Neuropathology

1. Muscle biopsy:

- a. Scattered necrotic fibers
- b. Experimental models demonstrate:
 - i. Non-inflammatory necrosis of muscle fibers
 - ii. Small atrophic fibers
2. Putative destabilization of the lipophilic muscle membrane

Niacin

General Characteristics

1. At pharmacologic doses niacin lowers total cholesterol, LDL-C, non-HDL-C, triglycerides, apolipoprotein B and lipoprotein(a). It increases levels of HDL-C and apolipoprotein A

Clinical Manifestations

1. May cause myalgia and cramps
2. Symptoms improve with discontinuance of the drug
3. Rhabdomyolysis has been reported in patients taking concomitant statins

Neuropathology

1. Muscle biopsy:
 - a. Not defined
2. Putative similar mechanism of action as statins (inhibit HMG-CoA reductase)

Laboratory Evaluation

1. Serum CK concentration may be markedly elevated
2. Electrodiagnostic studies have not been reported in detail

Ezetimibe

General Characteristics

1. Ezetimibe is a synthetic 2-azetidininone that inhibits the absorption of sterols (including cholesterol) in the intestine
2. It is primarily used as monotherapy or in combination with statins to reduce low-density lipoprotein cholesterol

Clinical Manifestations

1. Weakness
2. Myalgias
3. Increased serum CK concentration
4. Most complications occur in combination with statin therapy
5. Myopathy usually resolves within a short time after drug withdrawal

Neuropathology

1. A few patients have developed a probable necrotizing myopathy on an autoimmune basis

Laboratory Evaluation

1. Elevated serum CK concentrations in symptomatic patients

Cyclosporine and Tacrolimus*General Characteristics*

1. The immunophilins are the targets of cyclosporine and tacrolimus
2. Immunophilins are endogenous cytosolic peptidyl-prolyl isomerases that interconvert between the cis and the trans/positions. Cyclophilin catalyzes the esterous isomerizations of peptic bonds

Clinical Manifestations

1. Cyclosporine and tacrolimus are utilized primarily as immuno suppressants in transplant patients
2. They may cause the insidious onset of proximal myopathy after months of use
3. Myoglobinuria may be induced particularly with the concomitant use of anticholesterol agents and colchicines
4. Myalgias, weakness and cardiomyopathy (from tacrolimus) improve with withdrawal from the drugs
5. Associated tremor, myoclonus, mental status changes, seizures and movement disorders and posterior reversible encephalopathy may overshadow the myopathy with cyclosporine use

Neuropathology

1. Muscle biopsy:
 - a. Necrosis, vacuoles and type 2 muscle fiber atrophy
 - b. No endomysial inflammatory cell infiltrate of non-necrotic fibers

Laboratory Evaluation

1. Elevated CK serum concentration
2. EMG:
 - a. Increased insertional activity with positive sharp waves, fibrillation potentials and myotonic discharges
 - b. Early recruitment of small amplitude, brief duration MUAPs
 - c. NCS are normal
3. Putative mechanism is destabilization of lipophilic muscle membrane

Labetalol*General Characteristics*

1. Only a few patients have been reported with labetalol induced necrotizing myopathy

Clinical Manifestations

1. Patients may develop an acute or insidious onset of proximal myopathy or myalgia that resolves with medication withdrawal

Neuropathology

1. Muscle biopsy:
 - a. Normal
 - b. Necrotic and regenerating fibers
2. Electron microscopy (one patient):
 - a. Subsarcolemmal vacuoles

Laboratory Evaluation

1. Elevated CK levels in the serum
2. EMG:
 - a. Increased insertional activity
 - b. Myopathic pattern of short duration, small amplitude, polyphasic and early recruiting MUAPs

Propofol*General Characteristics*

1. Propofol is a widely used anesthetic and sedative often used in mechanically ventilated patients and for the treatment of status epilepticus
2. Its use in intensive care settings is due to:
 - a. Rapid onset of action with short half-life
 - b. Decreased cerebral oxygen consumption
 - c. Reduction of intracranial pressure
 - d. It is not associated with malignant hyperthermia

Clinical Manifestations

1. Propofol-related infusion syndrome:
 - a. Cardiac failure and arrhythmias (bradyarrhythmias, ventricular fibrillation)
 - b. Metabolic acidosis
 - c. Rhabdomyolysis
 - d. Acute kidney injury
 - e. Hyperlipidemia
 - f. Hepatomegaly
2. In one large study the reported incidence of propofol-related infusion syndrome was 1.1% (<1000 patients in the trial). There is reported 80% mortality with this complication
3. Acute quadriplegic myopathy has been reported with propofol use and high-dose intravenous corticosteroids

Neuropathology

1. Muscle biopsy:
 - a. Necrosis of skeletal and cardiac muscle
 - b. In patients with acute quadriplegic myopathy there may be necrosis and loss of thick filaments
2. Propofol alters the function of the mitochondrial respiratory chain that decreases adenosine triphosphate. Soya bean is added to propofol to increase its solubility that increases its triglyceride load. There is impaired fatty acid oxidation with an accumulation of toxic fatty acid intermediates in addition to cellular hypoxia and inability of the liver to metabolize lactate exacerbates acidosis. The impairment of lipid metabolites in both cardiac and skeletal muscle in addition to decreased ATP synthesis is the putative mechanism for myocytolysis. Other triggering mechanisms include excess exogenous and endogenous catecholamines and steroids administered to critically ill patients

Laboratory Evaluation

1. Markedly elevated serum CK levels

2. Hyperlipidemia
3. Usually severe metabolic acidosis
4. Rhabdomyolysis with myoglobinuria
5. EKG:
 - a. Brachyarrhythmias and ventricular fibrillation
 - b. ST-segment elevation in right precordial leads

Amphiphilic Drug Myopathies (Drug-Induced Autophagic Lysosomal Myopathy)

General Characteristics

1. Chloroquine is a quinolone derivative that is used in the treatment of malaria and autoimmune diseases that include: 1. SLE, 2. sarcoid, 3. connective tissue diseases
2. It is amphiphilic, with separate hydrophobic and hydrophilic domains that enable it to interact with the anionic phospholipids of cell membranes

Clinical Manifestations

1. A subset of patients develops a slowly progressive, painless, proximal myopathy with atrophy
2. The lower extremities are more severely affected than the arms
3. The usual dose that is required for the myopathy is 500 mg/day for one year
4. There is often an associated neuropathy with sensory loss and decreased muscle stretch reflexes
5. A cardiomyopathy and retinopathy may also be associated

Neuropathology

1. Cardiac and skeletal muscle fibers demonstrate autophagic vesicles that preferentially affect type I fibers
2. The vacuoles are of lysosomal origin
3. Electron microscopy:
 - a. Vacuoles are filled with concentric lamellar myeloid material and curvilinear bodies
 - b. Autophagic vacuoles are also noted in peripheral nerves and Schwann cells
4. Chloroquine interacts with lipid membranes to form drug-lipid complexes that are not digested by liposomal enzymes, which causes the formation of autophagic vacuoles

Laboratory Evaluation

1. Serum CK levels are elevated
2. EMG:
 - a. Increased insertional activity with positive sharp waves, fibrillation potentials and myotonic discharges
 - b. Small amplitude, short duration polyphasic MUAPs in weak proximal muscles
 - c. If there is a concomitant neuropathy:
 - i. Motor or sensory nerve conduction velocities are minimally reduced
 - ii. Slight reduction of amplitudes on NCS

- iii. Neurogenic MUAPs with decreased recruitment is seen on distal muscles
3. Hydroxychloroquine
 - a. The myopathy is not as severe as with chloroquine, with fewer vacuoles on routine biopsy
 - b. Electron microscopy:
 - i. Demonstrates myeloid and curvilinear bodies in vacuoles

Amiodarone

General Characteristics

1. Amiodarone is a widely used antiarrhythmic agent for the treatment of both ventricular and supraventricular tachyarrhythmias
2. Its most widely recognized complications affect the eyes, lungs, liver, heart, skin and thyroid
3. The prevalence of amiodarone-induced neurotoxicity has been cited as 27.5–74% with prolonged use: These include:
 - a. Tremor
 - b. Ataxia
 - c. Peripheral neuropathy
 - d. Encephalopathy
 - e. Parkinsonism

Clinical Manifestations

1. Severe proximal and distal weakness with distal sensory loss and reduced or absent muscle stretch reflexes
2. The legs are more severely affected than the arms
3. Renal failure predisposes to toxicity
4. Concomitant use of simvastatin and amiodarone may cause rhabdomyolysis
5. Muscle strength may improve with drug withdrawal

Neuropathology

1. Muscle biopsy:
 - a. Scattered muscle fibers that contain autophagic vacuoles
 - b. Distal muscles demonstrate neurogenic atrophy
2. Electron microscopy:
 - a. Myofibrillar disorganization and autophagic vacuoles that contain myeloid debris which is also seen on nerve biopsies. They are lipid membrane inclusions that may persist for 2 years following drug withdrawal
3. Putative pathogenesis is similar to that of chloroquine

Laboratory Evaluation

1. Serum CK levels are moderately increased
2. EMG:
 - i. Increased insertional activity in both proximal and distal muscles with positive sharp waves and fibrillation potentials
 - ii. Proximal muscles demonstrate polyphasic, short duration small amplitude, early recruiting of MUAPs

- iii. Distal muscles often demonstrate a neuropathic pattern with large-amplitude, long-duration polyphasic MUAPs, with decreased recruitment

Antimicrotubular Myopathies

Colchicine

General Characteristics

1. Colchicine is weakly amphiphilic, but its effects are primarily mediated by its binding with tubulin and disruption of its polymerization that form microtubules

Clinical Manifestations

1. The neuromyopathy usually develops with prolonged use, but occasionally after I.V. administered acutely
2. Risk factors are age greater than 50 years and duration of use
3. Onset is most often with proximal muscle weakness over several months
4. Clinical myotonia has been described in a subset of patients
5. Distal sensory loss with decreased or loss of muscle stretch reflexes from a concomitant peripheral neuropathy
6. Signs and symptoms resolve in 4–6 months after the drug is discontinued
7. Toxicity increases with the use of statins

Neuropathology

1. Muscle biopsy:
 - a. Acid phosphatase-positive autophagic vacuoles that contain membranous debris
2. Immunohistochemistry:
 - a. Microtubule-associated protein light chain 3 (LC3) that binds p62/SQSTM1 which is an adapter protein selectively degraded by autophagy is positive (positive in all autophagic vacuolar myopathies)
 - b. Colchicine destabilizes the microtubule system by impairing autophagosome-lysosome fusion

Laboratory Evaluation

1. Markedly elevated CK serum levels; elevated alanine amino-transferase (ALT) and aspartate aminotransferase (AST)
2. EMG:
 - a. Increased insertional activity associated with positive sharp waves, fibrillation potentials and complex repetitive discharges
 - b. Myopathic MUAP in proximal muscles that can be marked in distal muscles from the concomitant peripheral neuropathy
 - c. Myotonic discharges
 - d. Nerve conduction studies:
 - i. Reduced amplitude
 - ii. Slightly prolonged latencies
 - iii. Slow conduction velocities of motor and sensory nerves in both upper and lower extremities

Vincristine

General Characteristics

1. Vincristine is utilized in various chemotherapeutic protocols for non-Hodgkin's and Hodgkin's lymphoma, acute lymphoblastic leukemia, and neuroblastoma
2. Major adverse off-target effects are severe peripheral neuropathy, hyponatremia, hair loss, and constipation
3. It inhibits mitosis by binding to tubulin which inhibits the separation of chromosomes during metaphase which induces apoptosis
4. The rate-limiting side effect is severe axonal polyneuropathy

Clinical Manifestations

1. Distal extremity muscle weakness
2. Initial small fiber modality sensory loss, that in severely affected patients damages all fiber sizes
3. Constipation more frequently than urinary sphincter involvement
4. Loss of muscle stretch reflexes
5. Proximal muscle weakness and myalgia may occur

Neuropathology

1. Muscle biopsy:
 - a. Neurogenic atrophy of distal muscles
 - b. Rarely, increased lipofusion or granule accumulation
 - c. Scattered necrotic fibers in proximal muscles
2. Electron microscopy:
 - a. Myofibrillar disorganization
 - b. Subsarcolemmal osmophilic material
 - c. Myonuclei may contain membrane-bound inclusions

Laboratory Evaluation

1. Serum CK specifically in myopathic patients has not been reported
2. Muscle biopsy:
 - a. Increased insertional activity with positive sharp waves and fibrillation potentials
 - b. In distal muscles there are neurogenic pattern MUAPs
3. Nerve conduction studies:
 - a. Reduced SNAP and CMAP amplitudes
 - b. Slightly prolonged distal latencies
 - c. Mildly slow conduction velocities

Drug-Induced Mitochondrial Myopathy

Zidovudine (Azidothymidine, AZT)

General Characteristics

1. At present AZT is used in conjunction with other anti-HIV drugs in highly active antiviral therapy
2. AZT is included in combivir and trizivir
3. AZT is a thymidine analogue that selectively inhibits HIV reverse transcriptase, blocking double-stranded DNA production

4. AZT inhibits mitochondrial DNA polymerase that reduces mitochondrial DNA and causes decreased respiratory chain function
5. Other postulated mechanisms for AZT function include:
 - a. Oxidative stress
 - b. Direct inhibition of mitochondrial bioenergetics
 - c. Mitochondrial depletion of L-carnitine
 - d. mtDNA depletion due to inhibition of DNA polymerase gamma

Clinical Manifestations

1. AZT myopathy patients most often present with the insidious onset of myalgias and proximal muscle weakness
2. Other HIV-related myopathies include:
 - a. Inflammatory myopathy
 - b. Microvasculitis
 - c. Necrotizing myopathy
 - d. Type 2 muscle fiber atrophy
 - e. Toxic AZT myopathy
3. Patients with HIV myopathy may have concomitant:
 - a. Inflammatory demyelinating polyneuropathy
 - b. Symmetrical lower extremity small fiber neuropathy
 - c. Myasthenia gravis
 - d. Nemaline rod myopathy

Neuropathology

1. Muscle biopsy:
 - a. Ragged red fibers (which correlates with the cumulative dose of AZT, and supports mitochondrial dysfunction)
 - b. Necrotic fibers
 - c. Cytoplasmic bodies
 - d. Nemaline rods
 - e. Microvacuolation
 - f. In pure AZT myopathy there is absence of endomysial inflammation (should not be present in non-necrotic fibers)
2. Electron microscopy:
 - a. Mitochondrial and myofilament abnormalities

Laboratory Evaluation

1. Normal or minimally elevated serum CK levels; higher CK levels suggest HIV-associated myositis
2. Needle EMG:
 - a. Increased insertional activity with positive sharp waves and fibrillation potentials
 - b. Early recruitment of short-duration, low amplitude polyphasic MUAPs
3. Mitochondrial myopathy occurs with:
 - a. Lamivudine
 - b. Zalcitabine
 - c. Didanosine
 - i. There may be associated increased serum lactate and hepatic steatosis

Drug-Induced Inflammatory Myopathies

L-Tryptophan/Eosinophilia Myalgia Syndrome

General Characteristics

1. An outbreak of acute onset of incapacitating myalgia, some muscle weakness and marked eosinophilia ($>10^9/L$) was first described in 1989 and was traced to a single manufacturer of L-tryptophan
2. Only a fraction of persons who ingested L-tryptophan contracted the disease
3. Dosage and increased age were found to be risk factors
4. The drug was found to be a contaminant in the manufacture of the compound

Clinical Manifestations

1. Subacute onset of generalized muscle pain, tenderness and weakness
2. The onset could be delayed (weeks to possibly years after L-tryptophan ingestion)
3. Associated signs and symptoms include:
 - a. Abdominal pain
 - b. Mucocutaneous ulcers
 - c. Lymphadenopathy
 - d. Dyspnea
 - e. Myalgias
 - f. Skin rash
4. Severe polyneuropathy suggestive of Guillain-Barré syndrome or vasculitis

Neuropathology

1. Muscle biopsy:
 - a. Diffuse or perivascular inflammatory infiltrate of the perimysium, fascia and endomysium with CD8+ T-cells and macrophages
 - b. Less than 3% of the invading cells are eosinophils or B-cells
 - c. No membrane attack complex deposition or small blood vessels
2. Nerve biopsy:
 - a. Perivascular mononuclear inflammatory infiltrate
 - b. Occasional eosinophils are noted in the epineurium, endoneurium, and perineurium
 - c. Axonal degeneration
3. Eosinophil-derived proteins, MBP and EDN immunostain in the fascia, perimysium and endomysium as well as around intramuscular blood vessels and nerves
4. The pathogenesis of eosinophilic syndrome in some instances is the exposure to certain preparations of L-tryptophan in a genetically susceptible host, which triggers eosinophilic activation and degranulation that causes chronic tissue fibrosis
5. Two trace adulterants in the manufacture of L-tryptophan that are possible inducers of the syndrome:
 - a. 3-phenylamino alanine (PAA)
 - b. 1,1-ethylidenebis tryptophan (EBT)

Laboratory Evaluation

1. The serum CK level can be normal or moderately elevated
2. Absolute eosinophil count is $>10^9$ cells/L
3. EMG:
 - a. Increased insertional activity with positive sharp waves and fibrillation potentials with complex repetitive discharges
 - b. Chronic myopathic pattern was demonstrated with small and large polyphasic MUAPs and early recruitment (those with primarily isolated myopathy)
 - c. Large polyphasic MUAPs with decreased recruitment in patients with severe neuropathy
 - d. Nerve conduction studies:
 - i. Decreased amplitude of compound muscle and sensory nerve action potentials
 - ii. Normal or slightly slow motor and sensory conduction velocities in patients with polyneuropathy
 - iii. In patients with severe polyneuropathy (GBS presentation):
 1. Multifocal motor neuropathy with conduction block
 2. Slow motor and sensory conduction velocities

Rare Drug-Induced Inflammatory Myopathies**Toxic Oil Syndrome***General Characteristics*

1. A single epidemic in Spain in 1981 due to the ingestion of denatured rapeseed oil as a substitute for olive oil

Clinical Manifestations

1. Acute myalgia and proximal muscle weakness

Neuropathology

1. Muscle biopsy:
 - a. Perivascular, perimysial or endomysial inflammatory cell infiltrate
 - i. The likely toxic contaminant: 3-phenylamino-1,2-propanediol

Laboratory Evaluation

1. Elevated serum CK levels
2. EMG:
 - a. Increased insertional activity with positive sharp waves and fibrillation potentials
 - b. Myopathic pattern of MUAPs

Penicillamine*General Characteristics*

1. Primarily used to treat Wilson's disease and rarely rheumatoid arthritis
2. 0.2–1% of treated patients may develop a polymyositis clinical disorder
3. May induce myasthenia gravis

Clinical Manifestations

1. Proximal muscle weakness and myalgia
2. DM/PM-like disorder
3. Associated MG

Neuropathology

1. Perivascular, perimysial or endomysial inflammatory cell infiltrate

Laboratory Evaluation

1. Elevated serum CK
2. EMG:
 - a. Increased insertional activity with fibrillation potentials and positive sharp waves

Cimetidine*General Characteristics*

1. Cimetidine is an H₂ histamine receptor antagonist

Clinical Manifestations

1. Generalized weakness and myalgia occur rarely

Neuropathology (One Patient)

1. Muscle biopsy:
 - a. Perivascular inflammation of CD8+ lymphocytes
 - b. No immunoglobulin or complement deposition on small blood vessels
 - c. Patients with cutaneous vasculitis have been reported

Laboratory Evaluation

1. Elevated serum CK levels
2. EMG:
 - a. Increased insertional activity
 - b. Myopathic MUAPs

Procainamide*General Characteristics*

1. Rarely used now as an antiarrhythmic agent
2. May cause SLE-like (lupus-like) clinical disorder

Clinical Manifestations

1. A rare cause of proximal weakness and myalgias

Neuropathology

1. Muscle biopsy:
 - a. Perivascular inflammation and rare necrotic muscle fibers
 - b. Putative lupus-like vasculitis

Laboratory Evaluation

1. Elevated serum CK levels
2. EMG:
 - a. Myopathic pattern in a patchy distribution

Phenytoin*General Characteristics*

1. Long-term use is more often associated with a minimal lower extremity sensorimotor neuropathy, or just absent ankle muscle stretch reflexes

Clinical Manifestations

1. Proximal muscle weakness and rare myalgias

Neuropathology

1. Muscle biopsy:
 - a. Scattered necrotic and regenerating muscle fibers
 - b. Putative hypersensitivity reaction

Laboratory Evaluation

1. Elevated CK levels
2. EMG:
 - a. Insertional activity is increased
 - b. Small amplitude, short duration, polyphasic MUAPs

Alpha-Interferon*General Characteristics*

1. Alpha-interferon is used to treat chronic myelogenous leukemia and melanoma

Clinical Manifestations

1. Myositis with proximal muscle weakness and myalgia
2. Autoimmune induced myasthenia gravis

Neuropathology

1. Muscle biopsy:
 - a. Perivascular, perimysial or endomysial inflammatory cell infiltrate
 - b. Alpha-interferons have possible involvement in induction of dermatomyositis

Imatinib Mesylate (Gleevec)*General Characteristics*

1. Imatinib mesylate is the standard initial treatment for adult and pediatric patients with chronic myelogenous leukemia
2. It is the paradigm for small-molecule anticancer agents that have high selectivity against a specific molecular target
3. Imatinib is a signal transduction inhibitor that targets several protein tyrosine kinases. In the case of chronic myeloid leukemia it inhibits BCR-Abl, an oncoprotein

Clinical Manifestations

1. Approximately 20–50% of patients develop myalgias
2. Proximal muscle weakness has been reported

Neuropathology

1. CML 28 antibodies were found in one patient who developed polymyositis while taking imatinib. These antibodies

are similar to LR p46p, a component of human exosomes. Antibodies to exosome components PM-Scd100 and PM-Sc175 are also found in polymyositis which suggests an autoimmune basis for the muscle involvement with this agent

Laboratory Evaluation

1. Elevated serum CK
2. EMG:
 - a. Myopathic pattern

Myopathies Due to Impaired Protein Synthesis or Increased Catabolism**Steroid Myopathy***General Characteristics*

1. Glucocorticoid-induced myopathy is the most common type of drug-induced myopathy

Clinical Manifestations

1. Insidious onset of proximal muscle weakness and atrophy, more severe in the legs than in the arms
2. Distal extremities, extraocular muscles, and bulbar muscles are not affected
3. Myopathy usually occurs with a dosage of prednisone 30 mg/d or equivalent doses of other glucocorticoids
4. Fluorinated synthetic glucocorticoids such as triamcinolone, betamethasone, or dexamethasone may be more toxic to muscle
5. Women have a greater risk of developing the myopathy than men
6. Extra high doses (given intravenously) with neuromuscular blocking agent can cause acute quadriplegia

Neuropathology

1. Muscle biopsy:
 - a. Atrophy affects primarily fast-twitch glycolytic muscle fibers (type 2b)
 - b. Less atrophy of type 1 fibers
 - c. Lipid droplets may occur in type 1 fibers
 - d. Electron microscopy: Rare mitochondrial abnormalities
 - e. Putative mechanisms include activations of major cellular proteolytic systems that include:
 - i. The ubiquitin-proteasome system (UPS)
 - ii. The lysosomal system (cathepsins)
 - iii. Calcium-dependent calpains

Laboratory Evaluation

1. Serum CK level is normal
2. Some patients have a low serum potassium concentration
3. EMG:
 - a. Normal
 - b. NCS are normal

Finasteride*General Characteristics*

1. Finasteride is a 4-azasteroid that inhibits 5-alpha-reductase, blocking dihydrotestosterone synthesis and its resulting androgen activity
2. The agent is used to treat prostatic hypertrophy

Clinical Manifestations (One Patient)

1. Proximal greater than distal weakness
2. Sensation was normal
3. Intact muscle stretch reflexes

Neuropathology

1. Muscle biopsy:
 - a. Variation in fiber size
 - b. Increased central nuclei
 - c. Type 2 muscle fiber atrophy

Laboratory Evaluation

1. Serum CK was not elevated
2. EMG:
 - a. Small myopathic polyphasic MUAPs
 - b. NCS were normal

Emetine (Ipecac)*General Characteristics*

1. Ipecac, containing emetine and cephaeline, is an emetic that has been abused by patients with anorexia nervosa and bulimia
2. 500–600 mg/day for > than 10 days is toxic to muscles

Clinical Manifestations

1. Severe proximal myopathy and cardiomyopathy after 1–2 weeks of use
2. Myalgia, tenderness, and stiffness are seen in affected muscles
3. Normal sensation
4. Decreased muscle stretch reflexes

Neuropathology

1. Muscle biopsy:
 - a. Scattered necrotic fibers
 - b. Small atrophic and regenerating fibers
 - c. Fibers that contain cytoplasmic bodies
 - d. Oxidative stains demonstrate target and moth-eaten fibers
 - e. Electron microscopy:
 - i. Myofibrillar degeneration
 - ii. Cytoplasmic bodies that consist of compacted myofibrillar debris

Laboratory Evaluation

1. Moderate elevation of serum CK level
2. EMG:

- a. Usually increased insertional activity with positive sharp waves and fibrillation potentials
- b. Small amplitude, short duration early recruitment of MUAP
- c. Normal sensory and motor nerve conduction studies

Multifactorial Toxic Myopathies**Acute Quadriplegic Myopathy/Critical Illness Myopathy***General Characteristics*

1. Generalized weakness in intensive care patients may be due to polyneuropathy, prolonged neuromuscular blockade or myopathy that is associated with thick filament myosin loss
2. Patients frequently have a combination of all three processes
3. Acute quadriplegic myopathy may be more common than critical illness neuropathy
4. Prolonged mechanical ventilation, increased hospitalization time and persistent disability are the major complications

Clinical Manifestations

1. AQM (acute quadriplegic myopathy) often follows the use of high-dose intravenous glucocorticoids in conjunction with non-polarizing neuromuscular blocking agents
2. Patients with acute asthma attacks and organ transplant patients may be at risk
3. Approximately 10–12 days of mechanical ventilation is often utilized in patients that acquire AQM
4. There is generalized weakness of the trunk, extremities, and respiratory muscles, which is often first recognized due to difficulty in weaning patients from mechanical ventilation
5. Rarely the extraocular muscles are involved
6. Sensation is normal
7. Muscle stretch reflexes are depressed or absent

Neuropathology

1. Muscle biopsy:
 - a. Prominent type 2 muscle atrophy with or without type 1 fiber involvement
 - b. Scattered necrotic muscle fibers
 - c. Local or diffuse loss of myosin ATPase staining in type 1 > type 2 fibers that corresponds to the loss of thick filaments
 - d. Actin, titin and meloulin are relatively spared
2. Putative mechanisms
 - a. Calpain activation (calcium activated protease) may cause proteolysis of myosin
 - b. Proinflammatory cytokine effects induced by sepsis that may lead to a catabolic state of muscle

Laboratory Evaluation

1. In approximately 50% of patients there is moderate elevation of serum CK levels
2. EMG:
 - a. Nerve conduction studies:
 - i. Reduced amplitudes of CMAPs with normal distal latencies and conduction velocities
 - ii. SNAPs are normal or mildly decreased
 - iii. In AQM the muscle membrane excitability is reduced. The direct muscle stimulation and conducted CMAP are low. In critical illness, neuropathy or prolonged neuromuscular blockade, direct stimulation of the muscle membrane demonstrates normal excitability
3. EMG:
 - a. Fibrillation potentials and positive sharp waves; some patients do not have abnormal spontaneous activity
 - b. Short-duration, small amplitude polyphasic MUAPs with early recruitment

Omeprazole*General Characteristics*

1. Omeprazole is widely used to treat gastric and duodenal ulcers as well as acid reflux
2. The drug inhibits the H^+/K^+ ATPase enzyme pump at the secretory surface of the gastric parietal cell

Clinical Manifestations

1. Proximal muscle weakness with myalgia
2. Concomitant neuropathy is associated with paresthesias and stocking sensory loss more in the legs than in the arms
3. Diminished or absent biceps tendon reflexes
4. Rare rhabdomyolysis

Neuropathology

1. Muscle biopsy (2 patients):
 - a. Type 2 fiber atrophy
2. Superficial peroneal nerve biopsy:
 - a. Axonal degeneration

Laboratory Evaluation

1. Serum CK concentration may be slightly increased
2. EMG:
 - a. Small polyphasic MUAPs
 - b. NCS are normal or demonstrate an axonal sensorimotor neuropathy

Isotretinoin*General Characteristics*

1. Isotretinoin is used for the treatment of severe acne

Clinical Manifestations

1. The usually myopathic symptoms are myalgias with exercise
2. Proximal myopathy and rhabdomyolysis occur

Neuropathology

1. Muscle biopsy (one patient):
 - a. Atrophy of muscle fibers

Laboratory Evaluation

1. Serum CK levels can be markedly elevated although are usually only minimally increased
2. Low serum carnitine levels have been reported
3. EMG:
 - a. Myopathic small polyphasic MUAPs

Drug-Induced Hypokalemic Myopathy*General Characteristics*

1. Hypokalemia can be produced by a wide spectrum of medications that include diuretics, laxatives, mineral and glucocorticoids, amphotericin and lithium. Licorice has aldosterone action that is associated with hypokalemia. Hypokalemia can be caused by excessive alcohol and toluene inhalation
2. Clinical, electrodiagnostic and laboratory manifestations of hypokalemia are similar regardless of etiology

Clinical Manifestations

1. The onset may be acute or subacute generalized weakness that when severe can resemble Guillain-Barré syndrome
2. The usual potassium levels associated with muscle weakness are below 2 mg/L
3. Extraocular, bulbar and respiratory muscles are spared
4. Muscle stretch and myotactic reflexes are usually absent

Neuropathology

1. Muscle biopsy:
 - a. Scattered necrotic and regenerating fibers
 - b. Vacuoles whose origin is from T-tubules

Laboratory Evaluation

1. Serum CK concentration may be increased
2. EMG:
 - a. May be normal
 - b. Fibrillation potentials and positive sharp waves

Myopathies Associated with Anesthetics and Centrally Acting Drugs*General Characteristics*

1. Malignant hyperthermia is a genetically heterogeneous group of disorders
2. A basic mechanism in some patients is excessive calcium release from the sarcoplasmic reticulum that causes excessive muscle contraction with increased oxygen and ATPase utilization with consequent production of heat
3. Mutations have been documented in the ryanodine receptor located on chromosome 19q13.1 (MHS1) which is between the sarcoplasmic reticulum and the T tubule. These mutations may alter the calcium channel such that when

activated there is excess Ca^{2+} release into the cytoplasm. Ryanodine receptor mutations also cause central core disease

4. MHSQ has been mapped to chromosome 17q11.2-24 possibly allelic to potassium-sensitive periodic paralysis and paramyotonia congenita
5. MHS3 maps to chromosome 7q21-7q22 and may encode a subunit of a calcium channel
6. MHS4 maps to chromosome 3q13.1
7. Dihydropyridine receptor mutations which maps to chromosome 1q31 and are allelic to hypokalemic periodic paralysis cause MHS5
8. Malignant hyperthermia can occur in patients with:
 - a. Muscular dystrophies
 - b. Myotonic dystrophy
 - c. Mitochondrial myopathies
 - d. Some congenital myopathies particularly central core disease

Clinical Manifestations

1. Malignant hyperthermias most often precipitated by:
 - a. Succinyl choline, a depolarizing muscle relaxant
 - b. Inhalation anesthetics such as halothane and enflurane
2. Approximately 50% of patients have had anesthesia without complication
3. The master muscle may be the first to become rigid which is quickly followed by generalized rigidity
4. Tachycardia, cardiac arrhythmias, metabolic acidosis with tachypnea, fever and myoglobinuria rapidly occur

Neuropathology

1. Muscle biopsy:
 - a. Variation in fiber size
 - b. Central nuclei
 - c. Moth-eaten fibers
 - d. Necrotic fibers

Laboratory Evaluation

1. Serum CK is often normal or mildly elevated between attacks; during attacks the serum CK is markedly elevated
2. Severe metabolic and respiratory acidosis during attacks
3. Myoglobinuria
4. Lactic acidosis, hypoxia and hypercarbia
5. EMG:
 - a. Normal between attacks
 - b. Shortly after an attack may demonstrate increased spontaneous activity and a myopathic pattern with early recruitment of small amplitude MUAPs

Myopathies of Drug Abuse

Alcohol Myopathy

General Characteristics

1. Alcoholic myopathy occurs independently of peripheral neuropathy, malnutrition and overt lung disease

2. Myopathy is estimated to occur in approximately 50% of patients that abuse alcohol
3. Skeletal muscle is 40% of body mass and is a major component of whole-body protein turnover
4. The toxic myopathy from alcohol abuse include:
 - a. Acute necrotizing myopathy
 - b. Acute hypokalemic myopathy
 - c. Chronic alcoholic myopathy
 - d. Asymptomatic myopathy
 - e. Cardiac myopathy

Clinical Manifestations

1. Acute necrotizing myopathy
 - a. May occur following a binge and presents as:
 - i. Acute muscle pain and tenderness
 - ii. Mechanical hyperalgesia of affected muscles
 - iii. Edema
 - iv. Cramps
 - v. Primarily proximal muscle weakness
 - vi. Myoglobinuria in severe episodes with renal failure
2. Acute hypokalemic myopathy
 - a. Generalized weakness that evolves over 1–2 days
 - b. Serum potassium is usually <2 mg/L
3. Limb girdle weakness
 - a. Evolves insidiously
 - b. More severe weakness of the legs than arms
4. Asymptomatic myopathy
 - a. Elevated CK

Neuropathology

1. In patients with necrotizing myopathy
 - a. Muscle biopsy:
 - i. Muscle fiber necrosis
 - ii. Occasional tubular aggregate
 - iii. Electron microscopy:
 1. Degeneration of mitochondria
 2. Disorganized sarcomeres
2. Hypokalemic myopathy
 - a. Vacuoles within muscle fibers
3. Limb girdle weakness
 - a. Muscle biopsy:
 - i. Type 2 fiber atrophy
4. Alcohol and acetaldehyde inhibit muscle protein synthesis and both contractile and non-contractile proteins are affected
5. Muscle RNA is reduced by increased RNAase
6. Muscle protease activity is either reduced or unaltered
7. Markers of muscle membrane damage are increased possibly by reactive oxygen species
8. Low levels of alpha-tocopherol may predispose muscle to metabolic damage
9. Alcohol-induced autophagy contribute to loss in skeletal muscle mass

Laboratory Evaluation

1. Minimally elevated serum CK levels are seen in asymptomatic patients while markedly elevated levels occur in those with necrotizing myopathy
2. The potassium level is usually less than 2 mg/L in those patients with hypokalemic myopathy
3. EMG:
 - a. Positive sharp waves, fibrillation potentials
 - b. Short-duration, low amplitude MUAPs that demonstrate early recruitment (in patients with necrotizing myopathy)
 - c. Decreased amplitude of sensory > motor nerve conduction studies (in patients with concomitant neuropathy)

Myopathies from Illicit Drugs*General Characteristics*

1. The most common illicit drugs that are associated with myopathy include:
 - a. Heroin
 - b. Meperidine
 - c. Pentazocine
 - d. Phenyntion
 - e. Amphetamines
 - f. Cocaine
 - g. Toluene (severe hypokalemia)
2. Mechanisms of muscle injury include:
 - a. Direct toxic effect (Pentazocine)
 - b. Prolonged coma (pressure necrosis)
 - c. Ischemia (vasoconstriction)
 - d. Needle injury
 - e. Status epilepticus (rhabdomyolysis)

Clinical Manifestations

1. Weakness from specific muscle involvement
2. Concurrent pressure induced neuropathy from coma
3. Rhabdomyolysis with myoglobinuria (status epilepticus)
4. Hypokalemia (toluene)

Neuropathology

1. Muscle biopsy:
 - a. Necrosis of sarcomeres

Laboratory Evaluation

1. Extremely high CK
2. Myoglobulinuria
3. Associated medical complications:
 - a. Pulmonary edema (IV narcotics)
 - b. Severe malnutrition, wasting and poor dentition (amphetamine)
 - c. Fibrous destruction of muscle (pentazocine)
4. EMG:
 - a. Myopathic pattern with features of associated peripheral neuropathy

Differential Defects of Specific Muscles***Congenital Fibrosis of Extraocular Muscles****General Characteristics*

1. Kinesin family member 21A (KIF21A) gene mutation that maps to chromosome 12.12; AD and sporadic inheritance

Clinical Manifestations

1. Bilateral congenital ptosis
2. EOM defects that involve vertical extraocular muscles
3. The eyes may be fixed 20–30° below the horizontal
4. Posterior head tilt

Neuropathology

1. Decreased number of neurons in the third nerve nucleus
2. Developmental absence of the superior division of the oculomotor nerve

Laboratory Evaluation

1. Demonstrated oculomotor deficits of the superior rectus and the levator palpebrae muscles

Congenital Fibrosis of Extraocular Muscles 2*General Characteristics*

1. Aristalless homeobox, drosophila, homology of (ARIX; PHOX2A) genes, AR; that map to chromosome 11q13.4
2. Splice site and missense mutations
3. Patients described are from Saudi Arabia and Turkey

Clinical Manifestations

1. The eyes are fixed in abduction
2. Vertical movement is deficient but eyes can be raised above the horizontal; involvement may be unilateral
3. Ptosis
4. Amblyopia in the eye with a covered lid
5. Meiotic pupils with a sluggish reaction to light; pupils may be fixed

Neuropathology

1. Loss of oculomotor and fourth neurons

Laboratory Evaluation

1. Pupils may not respond to mydriatics
2. Loss of IIIrd and IVth nerve function

Congenital Fibrosis of Extraocular Muscles 3*General Characteristics*

1. Tubular Beta-3 (TUBB3) gene mutation that maps to chromosome 16q24.3; AD

Clinical Manifestations

1. Variable phenotype
2. Asymmetric

3. Deficient function of the IIIrd and IVth nerves with limited vertical movement
4. Severe involvement:
 - a. In primary gaze the eye may be eso- or exotropic with marked restriction of movement to all fields of gaze
5. Marcus-Gunn phenomenon is present
6. Deficits associated with specific mutations include:
 - a. Aberrant innervation by the trigeminal nerve
 - b. Cognitive and behavioral deficits
 - c. Paralysis of the VIIth nerve
 - d. Axonal sensorimotor neuropathy
 - e. Wrist and finger contractions

Neuropathology

1. Hypoplasia of the IIIrd nerve
2. Hypoplasia of the IIIrd nerve innervated muscles
3. Aberrant innervation of the IIIrd nerve by the VIth nerve
4. Dysgenesis of the corpus callosum, anterior commissure and internal capsule

Laboratory Evaluation

1. TUBB3 protein deficit
2. Complete to partial loss of oculomotor function in both eyes
3. MRI:
 - a. Hypoplasia of the IIIrd nerve and the muscles it innervates
 - b. Generalized loss of white matter
 - c. Boral ganglia involvement with specific mutations
 - d. Normal cortex
4. Variant syndromes include (congenital fibrosis of EOM):
 - a. CFEOM3 plus hypogonadism
 - b. TUBB3 variants with polyneuropathy
 - c. CFEOM with polymicrogyria
 - d. CFEOM with ulnar hand anomalies (Tukel syndrome)
 - e. CFEOM with congenital cranial dysinnervation disorder

Duane Syndrome

General Clinical Manifestations

1. Restriction of adduction, abduction or both
2. If adduction is restricted:
 - a. Globe retraction
 - b. Narrow palpebral fissure
3. Strabismus:
 - a. Esotropia is most common
4. Most commonly the syndrome is unilateral and sporadic
5. The bilateral syndrome manifests:
 - a. Amblyopia and strabismus most often seen in familial patients
6. Associated congenital anomalies include:
 - a. Skeletal
 - b. Ear
 - c. Ocular

- d. Neural
7. The usual pathology is in absent abduction nucleus and nerve:
 - a. The lateral rectus muscle is denervated and is aberrantly innervated by the inferior division of the oculomotor nerve which also innervates the ipsilateral medial rectus muscle

Duane Syndrome Type 1

General Characteristics

1. Sporadic inheritance; maps to chromosome 8q13

Clinical Manifestations

1. Weakness of abduction
2. Retraction of the eye and palpebral narrowing with adduction
3. Associated C2–C3 vertebral fusion (Klippel-Feil syndrome)
4. Thenar hypoplasia
5. Deafness

Neuropathology

1. Absence of the VIth nerve nucleus in the pons; absent VIth nerve; fibrosis of the lateral rectus muscle

Laboratory Evaluation

1. Ocular mobility studies demonstrate contraction of the medial and lateral rectus muscle; the globe may slip up or down under the tight lateral rectus muscle

Duane Syndrome Type 2

General Characteristics

1. $\alpha 2$ -chimaerin gene mutation (CHN1) that maps to chromosome 2q31; heterozygous missense mutations
2. Some mutations enhance $\alpha 2$ -chimaerin translocation to the cell membrane and its ability to self-aggregate

Clinical Manifestations

1. Congenital ophthalmoplegia:
 - a. Absent or reduced abduction
 - b. Adduction is decreased in some patients
 - c. Adduction produces globe retraction and ptosis (some patients)
 - d. There is a high incidence of bilateral involvement and vertical extraocular muscle weakness

Neuropathology

1. Absent abducens nucleus and nerve in the pons
2. Hypoplastic oculomotor innervated muscles; hypoplastic oculomotor nerves

Laboratory Evaluation

1. Motility function is consistent with absent or reduced abduction
2. Reduced adduction in some patients

Duane Anomaly with Radial Ray Abnormalities and Deafness

General Characteristics

1. Sal-like 4 (SALL4) gene mutations that map to chromosome 20q13.2

Clinical Manifestations

1. Hypoplasia of the thenar muscles; absence of the thumb and first metacarpal bone
2. Duane syndrome
3. Coloboma
4. Narrow external and auditory meatus; sensorineural deafness
5. Malrotation or absence of the kidney
6. Imperforate anus
7. Foot anomalies

Neuropathology

1. The SALL4 gene has been hypothesized to play a critical role in abducens motoneuron development
2. SALL4 is an oncofetal protein (zinc finger transcription factor) that has also been implicated in hepatic cancer with poor prognosis

Laboratory Evaluation

1. Ocular motility evaluation consistent with abducens deficit and absent oculomotor innervation
2. Some variants demonstrate midline brain anomalies on MRI
3. Kidney malrotations, foot anomalies as well as upper limb involvement

Bosley-Salih-Alorainy Syndrome

General Characteristics

1. Homeobox A1 (HOXA1) gene that maps to chromosome 7p15.2; AR

Clinical Manifestations

1. Bilateral Duane syndrome:
 - a. Limited horizontal gaze in both abduction and adduction
 - b. Vertical gaze preserved
 - c. Normal convergence
 - d. Globe retraction
 - e. Deafness and mutism (89% of patients)
 - f. Delayed motor development (66% of patients)
 - g. Walking after 3 years
 - h. Cognitive impairment
 - i. Autism spectrum disorder

Neuropathology

1. Absent VIth nerve
2. Carotid artery:

- a. Hypoplasia or absence of the base of the skull canal and arteries
 - b. Enlargement of the posterior communicating and basilar arteries
3. Absent cochlea, semicircular canals and vestibule
 4. Normal brainstem, cerebellum and cortex

Laboratory Evaluation

1. MRI:
 - a. Absent arterial canals at the skull base
 - b. Absent internal carotid artery with compensatory hypertrophy of the posterior communicating and basilar arteries
 - c. Absent cochlea, semicircular canals and vestibule with deficient BAER (brainstem auditory evoked response)
 - d. Ocular motility evaluation of the VIth nerve:
 - i. Duane syndrome (absent VIth nerve)

Allelic Disorder: Athabaskan (Navaho) Brainstem Dysgenesis Syndrome (ABDS)

General Characteristics

1. R26X mutation of the HOXA1 gene that maps to chromosome 7p15.2; AR

Clinical Manifestations

1. Congenital onset
2. Facial musculature weakness
3. Cerebral hypoventilation
4. Twenty percent of patients have vocal cord paralysis
5. Hypoventilations
6. Developmental delay
7. 50% of patients have seizures
8. Horizontal gaze palsy; convergence is normal

Neuropathology

1. Congenital heart defects in approximately 50% of patients that have tetralogy of Fallot and double aortic arch

Laboratory Evaluation

1. Ocular motility evaluation reveals horizontal gaze palsy
2. Abnormal brainstem auditory evoked potentials
3. MRI:
 - a. Similar to other HOXA1 defects with ICA malformation spectrum that included unilateral hypoplasia to bilateral agenesis

PEO (Horizontal Gaze Palsy) and Scoliosis

General Characteristics

1. AR: mutations in the ROBO gene that maps to chromosome 11q.24.2

Clinical Manifestations

1. Onset is congenital or within the first decade of life
2. No conjugate smooth pursuit, saccades or vestibulo-ocular reflexes

3. Vertical extraocular movements are unaffected; convergence is intact
4. Esotropia in 30% of patients
5. Pendular nystagmus
6. Cognitive impairment in 30% of patients
7. Progressive scoliosis (thoracolumbar)
8. Ipsilateral hemiparesis (uncrossed CST corticospinal fibers in some patients)

Neuropathology

1. The ROBO3 gene is important in the regulation of hind-brain axonal midline crossing, directs cell migration and is important in the lateral position of longitudinal pathways

Laboratory Evaluation

1. MRI:
 - a. DT1 demonstrates the absence of major crossing pathways in the pons and midbrain

Axenfeld-Rieger Syndrome

General Characteristics

1. AD; three chromosomal loci have been mapped with a demonstrated link to Axenfeld-Rieger syndrome and related phenotypes
2. The gene at chromosome 4q25 PITX and the FKHL7 at 6p25
3. The incidence of ARS is 1 in 200,000 of the population

Clinical Manifestations

1. Ocular anterior segment dysgenesis includes:
 - a. Heterochromia
 - b. Aniridia
 - c. Coloboma of the iris
 - d. Persistent papillary membrane
 - e. Corneal opacities
2. Proptosis
3. Hypertelorism
4. Partial absence of extraocular muscles
5. Malformation of the ears:
 - a. Mild sensorineural deafness
6. Communicating hydrocephalus
7. Cognitive impairment
8. Other malformations:
 - a. Facial
 - b. Dental
 - c. Abdominal
 - d. Cardiac defects (dextrocardia)

Neuropathology

1. ARS is an ocular anterior segment dysgenesis syndrome
2. Caused by impaired neural crest cell and ectodermal migration and differentiation during embryonic development

Laboratory Evaluation

1. Slit lamp (tears in Descemet's membrane)

2. Ocular motility studies
3. Ophthalmic ultrasonography (no posterior segment abnormality)

Congenital Ptosis Type 1

General Characteristics

1. AD; chromosome 1p32-p34/1
2. The disorder is distinct from blepharophimosis syndrome that maps to chromosome 3q and non-congenital fibrosis of extraocular muscles that map to chromosome L2

Clinical Manifestations

1. Ptosis that may be symmetric or asymmetric
2. Normal ocular movements
3. Incomplete penetrance

Neuropathology

1. Putative failure of differentiation of the levator palpebrae muscles

Laboratory Evaluation

1. Ocular motility studies are normal
2. Rarely the superior rectus may be involved

Congenital Ptosis Type 2

General Characteristics

1. Dominant; chromosome Xq24-q27.1

Clinical Manifestations

1. Congenital onset
2. Bilateral symmetric ptosis
3. Normal extraocular movements

Neuropathology

1. Failure of differentiation of the levator palpebrae
2. Levator palpebrae superioris fiber size is equal between control patients and patients with congenital ptosis
3. No change in the distribution or range of muscle fiber diameter in patients with congenital ptosis

Laboratory Evaluation

1. Ocular motility evaluation is normal

Blepharophimosis

General Characteristics

1. Definition:
 - a. Blepharophimosis is bilateral ptosis with shortened vertical horizontal palpebral fissures
2. Blepharophimosis, epicanthus inversus and ptosis, either with premature ovarian failure (BPES type I) or without (BPES type II) are caused by mutations in the FOXL2 gene which maps to chromosome 3q22.3
3. Polyalanine repeat expansion are seen in 30% of patients

Clinical Manifestations

1. Ptosis

2. Telecanthus
3. Lid phimosis
4. Epicanthus inversus which is a small skin fold arising from the lower lid and extending inwards and upwards toward the nose
5. Plus or minus ovarian failure
6. Low nasal bridge
7. Common CNS abnormalities suggest a contiguous gene syndrome
8. Some patients are cognitively impaired

Neuropathology

1. 3q23 deletion is accompanied by microcephaly, ear and nose dysmorphism, cognitive impairment and comptodactyly
2. Truncated FOXL2 encoded proteins are deficient in both type I and type II BPEX patients

Laboratory Evaluation

1. If primary amenorrhea is evident there are increased gonadotropins, and low estrogen and progesterone levels
2. MRI:
 - a. Microcephaly
 - b. Nasal bone dysmorphism
3. Rare Syndromes with congenital ptosis:
 - a. ROCA syndrome
 - b. Saethre-Chotzen syndrome
 - c. Ohdo syndrome
 - d. Dubowitz syndrome
 - e. Schwartz-Jampel syndrome
 - f. Marden-Walker syndrome

Congenital Brown's Syndrome

General Characteristics

1. Brown's syndrome is a congenital disorder of limited volitional and passive elevation of the affected eye in adduction
2. Originally proposed as mechanical restriction of the trochlear muscle or tendon sheath

Clinical Manifestations

1. Congenital superior oblique palsy

Neuropathology

1. Absence of trochlear nerve
2. Abnormal development of the trochlear nerve that results in abnormalities in the superior oblique muscle-tendon-trochlear complex
3. The tendon is either long and lax, absent or abnormally inserted that causes superior oblique paresis

Laboratory Evaluation

1. Ocular motility studies
2. MRI:
 - a. To evaluate the skull base, orbit and brain (midbrain parenchyma)

ECEL1 Related Strabismus

General Characteristics

1. ECEL1 gene (ECEL-1 endothelin-converting enzyme 1) gene maps to chromosome 2q36-37.1 and has been associated with autosomal recessive distal arthrogryposis
2. The mutations are homozygous or compound heterozygous

Clinical Manifestations

1. Distal arthrogryposis
2. Ptosis
3. Complex strabismus
4. Abnormal synkinesis

Neuropathology

1. Expression of ECEL 1 during embryogenesis in both the human spinal cord and skeletal muscle
2. Distal arthrogryposis
3. Club foot
4. Hip dysplasia

Laboratory Evaluation

1. Skeletal X-ray survey
2. MRI:
 - a. Brain and orbit
3. Ocular motility evaluation

Differential Diagnosis of the Genes Involved in Congenital Cranial Dysinnervation Disorders (CCDD)

The congenital cranial dysinnervation disorders (CCDD) are phenotypes of congenital inconstant strabismus or ptosis that are related to orbital dysinnervation.

Seven different gene mutations that are dominant or recessive cause the major described phenotypes and include:

1. Duane retraction syndrome
2. Congenital fibrosis of the extraocular muscles
3. Horizontal gaze palsy with progressive scoliosis
4. ECEL-1 related strabismus

The identified genes include:

1. CHN1
2. SALL4
3. HOXA1
4. KIF21A
5. TUBB3
6. ROBO3
7. ECEL1

Congenital Facial Paresis

Hereditary Congenital Facial Paresis (HCFP1)

General Characteristics

1. Several loci for HCFP1 have been identified and mapped to chromosome 3q, 10q and the HOXB1 gene on chromosome 17q21
2. Although there is clinical overlap HCFP is considered to be different than Moebius syndrome

Clinical Manifestations

1. There may be unilateral or less frequently bilateral facial weakness
2. No extraocular muscle involvement

Neuropathology

1. HCFP may be a primary disorder of the fourth rhombomere from which facial motoneurons originate
2. Decreased neurons in the facial nerve nuclei (vicinity) that can be uni- or bilateral
3. Facial nerve roots and nerves are poorly developed (few fibers)

Laboratory Evaluation

1. Absent stapedial reflex (some patients)
2. EMG:
 - a. Enlarged polyphasic MUAP and prolonged distal latencies
3. MRI:
 - a. Normal brainstem without hypoplasia or malformation

Moebius Syndrome*General Characteristics*

1. The definition and diagnostic criteria for Moebius syndrome are controversial. As defined by a conference at the Moebius Syndrome Foundation in 2007:
 - a. A congenital non-progressive facial weakness with limited abduction of one or both eyes
 - b. Additional cranial nerve and neurodevelopmental features
2. Some patient families have a gene defect mapped to chromosome 13q12.2-q13

Clinical Manifestations

1. Patients may have unilateral or bilateral involvement; bilateral > unilateral
2. There is often asymmetric facial involvement; in some series there may be relative sparing of muscles in the lower half of the face
3. A significant number of patients have feeding problems at birth due to palatal and pharyngeal involvement
4. Impairment of ocular abduction; some patients have been described with oculomotor and trochlear nerve involvement
5. Additional manifestations include:
 - a. Tongue hypoplasia
 - b. Nasal dysarthria
 - c. Delayed language development
 - d. Mastication muscle involvement
 - e. Partial defect of sensory components of the trigeminal nerve
 - f. Craniofacial dysmorphisms:
 - i. Epicanthal folds
 - ii. Flattened nasal bridge

- iii. Microgathia
 - iv. High arched palate
 - v. External ear defects
 - vi. Teeth defects
 - vii. Hypertelorism
- g. Extremity malformations:
 - i. Brachydactyly
 - ii. Clinodactyly
 - iii. Syndactyly
 - iv. Metacarpal abnormalities
 - v. Pes planus
 - vi. Hypoplasia of the lower legs
 - vii. Talipes equinovarus
 - viii. Arthrogryposis multiplex
 - ix. Approximately 10% with Poland syndrome
6. Poor coordination

Neuropathology

1. Towfighi classification:
 - a. Hypoplasia of cranial nerve nuclei due to congenital rhombencephalon development
 - b. Neuronal loss and degeneration secondary to defects in the facial peripheral nerve
 - c. Decreased neurons, degeneration of the facial nerve with gliosis and calcifications in the brainstem nuclei from vascular insufficiency or infection
 - d. Primary myopathic changes without lesions in the cranial nerve nuclei or nerves
2. A complex regional developmental disorder

Laboratory Evaluation

1. EMG:
 - a. A spectrum of electrophysiological abnormalities at supranuclear, nuclear or peripheral levels
2. MRI:
 - a. Brainstem hypoplasia and cranial nerve atresia
 - b. Absence or hypoplasia of cranial nerve VI and VII may be the most common defect in sporadic Moebius syndrome
 - c. Evaluation of a novel familial Moebius-like syndrome revealed:
 - i. Hypoplasia of extraocular muscles that were abnormally inserted.

Cayler Cardiofacial Syndrome*General Characteristics*

1. The Cayler cardiofacial syndrome in some instances is due to 22q11 deletion and is paternally derived

Clinical Manifestations

1. Facial weakness of variable severity:
 - a. Mild cases have unilateral lower lip weakness
 - b. Severe involvement causes complete facial paresis
2. Cardiac anomalies:
 - a. Arterial septal defect

- b. Ventricular septal defect
- c. Situs inversus totalis
- 3. Skeletal defects:
 - a. Adducted thumbs
 - b. Cervical vertebral body fusion
 - c. Facial dysmorphism
- 4. Approximately 10% of patients have:
 - a. Microcephaly
 - b. Cognitive impairment
- 5. Ear microtia
- 6. Asymmetric crying facies
- 7. Bifid uvula

Neuropathology

1. 22q11 deletion syndrome

Laboratory Evaluation

1. EKG and echocardiography:
 - a. ASD and VSD
 - b. Greater than 40% of patients have heart abnormalities
 - c. Tetralogy of fallot
 - d. Patent ductus arteriosus
2. Immune system:
 - a. T-cell abnormalities
 - b. Thymic hypoplasia
3. Skeletal survey:
 - a. Cervical vertebral fusion
 - b. Adducted thumbs
4. MRI:
 - a. Microcephaly
5. Myopathy
 - a. Normal strength
 - b. May have high CK

Congenital Diaphragmatic Hernia (CDH)

General Characteristics

1. Congenital diaphragmatic hernia (CDH) is characterized by the herniation of abdominal viscera into the chest cavity due to incomplete formation of the diaphragm
2. CDH affects 1 in 3000 births
3. Chromosomal anomalies that include whole chromosome and segmental aneuploidies are the most common genetic cause of CDH
4. The CDH may occur as an isolated defect but is associated with anomalies 40% of the time
5. Mutations in GATA binding protein 6 that maps to chromosome 18q11.2:
 - a. GATA factors are transcriptional regulatory proteins that have distinct developmental and tissue specific profiles

Clinical Manifestations of GATA 6 Mutations

1. Usually associated with congenital heart disease
2. Pancreatic agenesis

3. Congenital absence of the pericardium
4. Manifestations of diaphragmatic weakness:
 - a. Infants are more clinically affected than adults
 - b. Unilateral involvement:
 - i. 50% of patients are asymptomatic
 - ii. 25% have mild exertional dyspnea
 - iii. Vital capacity is 75% of predicted value
 - c. Bilateral involvement:
 - i. Severe exertional dyspnea
 - ii. Orthopnea
 - iii. Nocturnal hypoxemia
 - iv. Hypercapnea
 - v. Vital capacity less than 45% of predicted value

Neuropathology

1. GAT6 is involved in the development of the diaphragm and the pericardium

Laboratory Evaluation

1. EKG and echocardiography to evaluate for congenital heart disease (VSD, patent ductus arteriosus and absence of the pericardium)
2. Abdominal CT:
 - a. Agenesis of the pancreas
3. Chest CT:
 - a. Pulmonary hypoplasia and pulmonary hypertension

Types of Congenital Diaphragmatic Hernia

1. Bochdalek:
 - a. 70–90% of CDH patients
 - b. Most often left-sided
 - c. Posterolateral herniation
2. Morgagni:
 - a. Anterior retrosternal
3. Central:
 - a. 1–2% of CDH
 - b. Midline of the septum transversum

Differential Diagnosis of Specific Syndromes with Diaphragmatic Hernia

1. Fryns (coarse facies, cloudy cornea, absence of lung lobulation and distal limb deformities)
2. Simpson-Golabi-Behmel:
 - a. Xq26.2 with mutation in the glypican 3 (GPC3 gene)
 - b. Coarse facies, congenital heart disease, enlarged tongue and short hands and fingers
3. Tetrasomy 12p
4. Brachmann-deLange syndrome:
 - a. AD or duplication of the long arm of chromosome 3
 - b. Growth retardation; short stature
 - c. Severe cognitive deficits
 - d. Depressed nasal bridge
 - e. Bushy eyebrows that meet in the midline
 - f. Hirsutism
 - g. Malformation of the hands

5. Lethal multiple pterygium:
 - a. The syndrome is caused by mutations in the gamma or fetal subunit of the nicotinic acetylcholine receptor that maps to chromosome 2q37.1
 - b. It is a multiple congenital anomaly syndrome that includes:
 - i. CHD
 - ii. Pterygia (webbing) of the neck, elbows and knees
 - iii. Joint contractures (arthrogryposis)
6. SMARD1
7. EMARDO (early myopathy, arreflexia, respiratory distress and dysphagia)
8. MDC1B
9. Myotubularin female carriers (elevated hemidiaphragm)
 2. Radius is absent or hypoplastic in 64% of patients
 3. Contracture of the elbow and wrist
 4. Severe patients may have total absence of the arm (phocomelia)
 - ii. Cardiac defects:
 1. ASD, VSD
 2. AV block
 3. Atrial fibrillation
 4. Sinus node dysfunction
 - iii. Thenar abnormalities:
 1. Distal displacement of the thenar eminence with or without a triphalangeal digit
 2. Patients may have an aplastic thumb on one side with a triphalangeal thumb contralaterally

Differential Diagnosis of Genetic Cause of Congenital Diaphragmatic Hernia

1. DIH1 (chromosome 15q26.1)
2. DIH2 (chromosome 8p23.1):
 - a. Most often unilateral
 - b. Associated with hypoplasia of the left lung
 - c. Atrial septal defect
3. DIH3:
 - a. The mutations occur in the zinc finger protein multiple 2 gene (ZFPm2) that maps to chromosome 8q23.1
4. Diaphragmatic defects with skull ossification and limb anomalies (or) AR
5. Congenital anterior diaphragmatic hernia:
 - a. X-linked
 - b. High mortality

Congenital Hand Muscle Abnormalities

Holt-Oram Syndrome

General Characteristics

1. This developmental hand disorder is caused by mutations in the TBX5 gene that maps to chromosome 12q24.21. The dominant phenotype is the result of haploinsufficiency of TBX5. The gene encodes the T-box transcription factor

Clinical Manifestations

1. Absent or hypoplastic muscles include:
 - a. Thenar muscles (100% of patients)
 - b. Non-opposing thumbs
 - c. Trapezius muscle
 - d. Rarely:
 - i. Deltoid, biceps, triceps
 - ii. Wrist extensors, ulnar abductors, and the supinators
 - iii. Normal
 - e. Normal lower limbs
 - i. Skeletal dysgenesis:
 1. Defects may be bilateral; the left side is more often affected than the right in 70% of patients

Neuropathology

1. TBX5 mutation that results in haploinsufficiency, encodes a protein that lacks T-box residues and causes limb and heart abnormalities
2. T-box gene family encodes transcription factors. The T-box domain is the DNA-binding domain

Laboratory Evaluation

1. EKG:
 - a. Atrial fibrillation
 - b. Brachycardia (sinus dysfunction)
 - i. Echocardiography:
 1. Primarily ASD and VSD
 2. Secundum defects
 - ii. X-ray of hands and upper extremities:
 1. Congenital anomalies of the thumb and upper extremity

Axial Musculature

Poland Syndrome

General Characteristics

1. Usually sporadic inheritance; familial patients have been reported
2. Male: female 2.4:1
3. Right to left 1.7:1
4. Prevalence is 1 in 30,000 patients
5. Onset may be in the sixth week of gestation

Clinical Manifestations

1. Unilateral absence or hypoplasia of the pectoralis muscles that most frequently involves the sternocostal portion
2. Anomalies of the breasts and nipples
3. Ipsilateral hand and digit abnormalities that include symbrachydactyly; short fingers
4. Occasional absence of the trapezius, supraspinatus and serratus anterior muscles

5. The anomalies may occur bilaterally
6. The lower limb equivalent has been described with unilateral gluteal hypoplasia and brachysyndactyly
7. Craniofacial anomalies:
 - a. Moebius syndrome
 - b. Ptosis
 - c. Mandibular prognathism
 - d. Craniofrontal nasal dysplasia
 - e. Parry-Romberg syndrome (progressive facial hemiatrophy)
 - f. External ear anomalies
8. Skeletal defects:
 - a. Scoliosis
 - b. Hemivertebrae
 - c. Agenesis of ribs
 - d. Klippel-Feil syndrome
 - e. Sprengel's deformity
 - f. Pectus excavatum and carinatum
9. Lower limbs:
 - a. Popliteal webs
 - b. Club foot
 - c. Toe syndactyly
10. Gastrointestinal complications:
 - a. Ulcerative colitis
 - b. Pyloric stenosis
 - c. Liver herniation
11. Genitourinary anomalies:
 - a. Renal agenesis
 - b. Ureteral reflex
 - c. Undescended testes
12. Cardiovascular anomalies:
 - a. Dextrocardia
 - b. ASD
 - c. Vascular malformations
13. Possible neoplastic associations:
 - a. Thoracic teratoma
 - b. Pleural fibroma
 - c. Leukemia and lymphoma

Neuropathology

1. Putative interruption of the early embryonic blood supply in the subclavian arteries, the vertebral arteries and/or their branches
2. It has been suggested that Poland syndrome, Klippel-Feil anomaly, Moebius syndrome, isolated absence of the pectoralis major muscle with breast hypoplasia, isolated transverse limb defects and Sprengel's anomaly are the spectrum for this early embryonic loss of subclavian and vertebral artery blood supply

Laboratory Evaluation

1. 3-D CT imaging of the chest to evaluate anomalies
2. MRI:
 - a. MRI evaluation of the brain if Moebius syndrome is evident
3. Echocardiography:
 - a. ASD or other cardiac anomalies

Abdominal Musculature

Prune Belly Syndrome

General Characteristics

1. A homozygous frameshift mutation has been identified in the CHRM3 gene that maps to chromosome 1q43 (1 Turkish family)
2. Most patients have autosomal recessive inheritance
3. CHRM3 protein is the major receptor that mediates urinary bladder contraction with micturition

Clinical Manifestations

1. The full syndrome is more common in males
2. Congenital onset
3. Severe abdominal distension due to absent abdominal musculature
4. Autonomic deficits:
 - a. Deficient pupillary light reflex
 - b. Dry mouth
5. Genitourinary deficits:
 - a. Bladder outflow obstruction
 - b. Cryptorchidism
6. Imperforate anus
7. Pectus excavation, club foot and hip dislocation
8. Patent ductus arteriosus

Neuropathology

1. Putative hypothesis that the entity is due to marked distention of the abdomen in the fetal period due to obstruction of the urinary tract from posterior urethral valves

Laboratory Evaluation

1. Abdominal ultrasound:
 - a. Absence of abdominal muscles
2. CT of the abdomen:
 - a. Determination of associated malformations and visceral position
3. Urinary tract evaluation
4. Chest X-ray:
 - a. Multiple segmentation defects:
 - i. Bilateral cervical ribs
 - ii. T8 to T12 and S3 hemivertebrae

Lower Extremity CHILD Syndrome

General Characteristics

1. The CHILD syndrome is caused by an X-linked dominant mutation in the NSDHL gene that maps to chromosome Xq28 and in the EBP gene
2. The CK syndrome is allelic and has a less severe phenotype
3. NADCPJ steroid dehydrogenase-like (NSDHL) gene:
 - a. Encodes a 3B-hydroxy steroid dehydrogenase in the cholesterol biosynthetic pathway

Clinical Manifestations

1. The CHILD occurs overwhelmingly in females because the disorder is X-linked dominant
2. Most often the right side of the body is poorly developed. This deficient development involves the ribs, neck, vertebrae and limbs. Internal organs may be affected
3. At birth or shortly thereafter, erythroderma (red, inflamed patches) and flaky scales (ichthyosis) are noted in the hemidystrophic side of the body. Hair loss may be noted
4. Limb anomalies:
 - a. Fingers on the hand or toes of the foot are missing on the affected side
 - b. Rarely an arm or leg may be shortened or missing
5. Hypoplasia occurs in:
 - a. The psoas muscle
 - b. Cranial nerves V, VII, XI, and X
 - c. Anomalies in the pons medulla, cerebellum and spinal cord
6. Hypoplasia of the lung and thyroid gland

Clinical Manifestations of the CK Syndrome

1. Affected males:
 - a. Weak fetal movements
 - b. Severe cognitive deficits
 - c. Seizures
 - d. Spasticity
 - e. Atrophy of the optic nerve
 - f. Strabismus
 - g. Micrognathia
 - h. High nasal bridge

Neuropathology

1. Putatively, some patients with CHILD syndrome may have less activity of 2 peroxisomal enzymes, catalase and dihydroxyacetone
2. A decrease of the 3-beta-hydroxysterol dehydrogenase may allow toxic metabolites of cholesterol synthesis to accumulate that disrupts growth and development of body parts

Laboratory Evaluation

1. Skin biopsy of the characteristic ichthyotic skin lesion
2. MRI:
 - a. Hypoplasia:
 - i. Cranial nerves V, VII, VIII, IX and X
 - ii. Pons, cerebellum and cortex

Differential Diagnosis of Congenital Absence or Hypoplasia of Muscles

1. Extraocular muscles:
 - a. Congenital cranial dysinnervation
 - b. Axenfeld-Rieger syndrome
 - c. Blepharophimosis
 - d. Congenital fibrosis of EOM:

- i. CFEOM1 (K1F21A; 12q12)
 - ii. CFEOM2 (PHOX2A; 11q13)
 - iii. CFEOM3 (TUBB3; 16q24)
 - iv. CFEOM4 (Tukel21qter)
 - v. CFEOM5 (COL25A1; 4q25)
 - vi. CFEOM (TUBB2B; 6p25)
- e. Duane syndromes:
 - i. DURS1 (8q13)
 - ii. DURS2 (CHN1, 2q31)
 - iii. DURS (SALL4, 20q13)
 - iv. Navajo (HOXA1; 7p15)
 - v. DA5E (PIEZ02; 18p4)
 - vi. CCDD (COLA25A1; 4q25)
 2. Moebius syndrome
 3. PEO (horizontal gaze palsy with scoliosis); ROBO3
 4. Absence of the superior rectus muscle
 5. Axenfeld-Rieger anomaly
 6. Hereditary congenital ptosis:
 - a. Type 1 (1p32-34)
 - b. Type 2 (Xq24-q27)
 7. Blepharophimosis syndromes:
 - a. Blepharophimosis-ptosis-epicanthus inversus syndrome (BPES type I) (FOXL2; 3q22.3)
 - b. BPES type II (Saethre-Chotzen syndrome [TWIST; chromosome 7p21.1])
 - c. Blepharophimosis with short stature; autosomal recessive
 - d. Ohdo syndrome (deletion of the short arm of chromosome 3)
 8. Face:
 - a. Hereditary congenital facial paralysis (3q; HOXB1 17q21)
 - b. Cardiofacial syndrome (22q11.2)
 - c. Moebius syndrome
 9. Diaphragm:
 - a. Congenital (X-linked)
 - b. Associated with specific syndromes:
 - i. Fryns
 - ii. Tetrasomy 12p
 - iii. Simpson-Golabi-Behmel
 - iv. SMARD1
 - v. EMARDD
 - vi. MDC1B
 - vii. Female carriers of myotubularin
 - c. Diaphragmatic hernias:
 - i. D1H1 (15q.26.1)
 - ii. D1H2 (8p23.1)
 - iii. D1H3 (ZFPM2; 8q23.1)
 - iv. Diaphragmatic defects with skull ossification and limb anomalies (AR)
 - v. Congenital anterior diaphragmatic hernia (X-linked)

Hand Muscle Hypoplasia or Absence

1. Holt-Oram syndrome (TBX5; 12q24.1)
2. Absence of the Palmaris longus muscle (AD)

Axial Musculature

1. Pectoral muscles (Poland syndrome)
2. Trapezius (8q12.2–q21.2)
3. Superior transverse scapular ligament calcification (AD)
4. Prune belly syndrome (CHRM3; 1q43; recessive and sporadic)

Lower Extremity

1. CHILD syndrome (Xq28) with absent psoas muscle

Putative Gluteal Muscle Atrophy as the Lower Extremity Component of Moebius Syndrome

1. Absence of the peroneus tertius muscle (AR)

Rhabdomyolysis and Myoglobinuria**Overview**

Rhabdomyolysis is the lysis of skeletal muscle whose major features are myalgia of the affected muscle, pigmenturia and elevated serum creatine kinase. Acute renal failure, cardiac arrest and nerve damage from compartment syndromes are the major systemic complications. In general, muscle enzymes are elevated to five times normal and serum and urinary myoglobin are present.

The balance of extracellular and intracellular calcium across the muscle membranes is maintained by:

1. Sodium-potassium pumps regulated by sodium/potassium activated adenine-triphosphatase
2. Calcium channels
3. Specific calcium-ATPase
4. Sodium-calcium exchanges

Disruption of the muscle and sarcoplasmic reticular membrane occurs (possible osmotic mechanism due to failure of the Na pump mechanism) and calcium homeostasis is lost which causes a dramatic rise in intracellular calcium. This calcium overload activates phospholipase-A2 and neutral proteases which further destroy muscle membranes. The elevated cytoplasmic calcium induces myofibrillar hypercontractures by enhanced action of myosin filament interaction.

Rhabdomyolysis causes myoglobinemia and myoglobinuria. The latter at levels above 300 mg/liter causes renal failure (at levels of 1000 mg/liter in greater than 82% of patients). The clearance of myoglobin through the kidneys is rapid as well as its conversion to bilirubin. Serum values may return to normal after an attack of rhabdomyolysis between 1–4 hours. Myoglobin levels in the serum precede an increase in CK. Myoglobin levels may be detected by radioimmunoassay, pigmented casts in the urine, absence of red cells and a normal haptoglobin.

The most sensitive test for rhabdomyolysis is the serum CK which is often 5 times normal. Approximately 200 grams of muscle needs to be involved to affect a rise in serum

CK. The CK isoenzyme CKMM (cardiac greater than skeletal muscle) is also elevated. CK-BB is found in brain tissue. Serum CK rises 2–12 hours after the onset of rhabdomyolysis, peaks in 1–3 days and decreases 3–5 days after the muscle damage. Immunologic measurement of carbonic anhydrase III is a very specific marker of skeletal muscle injury and is not present in cardiac tissue.

Rhabdomyolysis is associated with hyperkalemia, hypocalcemia and hyperphosphatemia. Approximately 150 grams of muscle destruction releases 15 millimoles of potassium which may elevate plasma levels and can contribute to or cause cardiac arrhythmias. Hypocalcemia seen in early rhabdomyolysis has been attributed to the deposition of calcium in affected muscle. Hypocalcemia may also be secondary to a decrease of 1, 25-dihydroxycholecalciferol due to hyperphosphatemia. In later stages of rhabdomyolysis, hypercalcemia may be seen as calcium is mobilized from necrotic tissue.

Rhabdomyolysis is also associated with elevated aldolase, lactic dehydrogenase, aminotransferase, creatine and uric acid. Troponin I and troponin T may be elevated.

Muscle signs and symptoms are generally similar for all causes of rhabdomyolysis. Patients suffer muscle pain and edema, have thin, shiny skin, weakness, stiffness and eventually experience contractures. The most commonly affected muscles are the quadratus lumborum (paraspinal muscles), the quadriceps and major muscles of the upper extremities. Rarely, muscles of the chest, abdomen, throat and masseter muscles are affected. All striated muscles may be affected focally or diffusely depending on specific etiology.

Rhabdomyolysis ranges from an asymptomatic illness with elevation of CK to severe elevation of serum CK, electrolytic disturbance, acute renal failure and disseminated intravascular coagulation. In general, a CK level of >5000 units/L portends serious muscle injury.

Approximately 10–50% of patients with rhabdomyolysis develop acute renal failure (ARF) and rhabdomyolysis occurs in up to 85% of patients with traumatic injuries.

Burst muscle activity such as sprinting utilizes anaerobic metabolism and Type 2 muscle fibers. Prolonged less than maximal intensity exercise (measured by oxygen utilization) requires glucose derived from glycogen stores as the primary energy source. Prolonged exercise such as distance running, utilizes free fatty acids (FFA) for ATP production. Many mitochondrial myopathies suffer weakness and exercise intolerance with minimal activity. Exhaustion of glycogen is correlated with fatigue and myoglobinuria which is seen with energy failure and muscle breakdown from any cause of inadequate ATP production with or without exercise.

Episodic weakness of muscle occurs with:

1. Phosphorylase deficiency
2. Phosphofructokinase deficiency
3. Carnitine palmitoyl transferase deficiency (CPT₂)
4. Acid maltase deficiency

5. Debrancher deficiency
6. Brancher deficiency

Disorders of Glycogen Metabolism

1. Type II – Acid maltase deficiency
2. Type III – Amylase 1, glycositase deficiency (brancher)
3. Type IV – Amylase, 4-6 1, 6 transglycosylase deficiency (brancher)
4. Type V – Myophosphorylase deficiency (McArdle disease)
5. Type VII – Phosphofructose kinase deficiency (PFK)
6. Type VIII – Myophosphorylase kinase
7. Type IX – phosphoglycerate kinase deficiency (PGK)
8. Type X – Phosphoglycerate mutase deficiency (PGM)
9. Type XI – Lactate dehydrogenase deficiency (LDH)
10. Type XII – Aldolase A deficiency
11. Type XIII – β -enolase deficiency

Lysosomal Glycogen Storage Myopathies

1. Danon disease (X-linked vacuolar cardiomyopathy and myopathy)
2. X-linked myopathy with excessive autophagy

Disorders of Purine Nucleotide Metabolism

1. Myoadenylate deaminase (MAD) deficiency

Disorders of Lipid Metabolism

1. Carnitine transporter deficiency (Primary carnitine deficiency)
2. CP2 deficiency
3. VLCAD deficiency
4. LCAD deficiency
5. MCAD deficiency
6. SCAD deficiency
7. Long-chain HAD deficiency
8. ETF-ETF-QO deficiency

Mitochondrial Dysfunction

1. Exercise intolerance
 - a. All mitochondrial disorders
2. Mitochondrial disorders with progressive weakness
 - a. Kearns-Sayre syndrome
 - b. ATPase deficiency
 - c. Cytochrome-c-oxidase deficiency
 - d. MERRF
 - e. MELAS
 - f. AD-PEO

Myoglobinuria

General Characteristics

1. Myoglobinuria may develop with:
 - a. Severe and excessive stress upon the fuel reserves of working muscle
2. During moderate exercise muscles utilize:

- a. High energy phosphate to generate ATP
- b. Muscle glycogen for the first 5–10 minutes
3. 15–20 minutes of exercise:
 - a. Blood glucose is derived from liver glycogen
 - b. Requires insulin for uptake
4. Greater than 90 minutes of exercise:
 - a. Glucose
 - b. Free fatty acids
5. Myoglobin:
 - a. Facilitates rapid diffusion of O_2 from capillaries to mitochondria in exercising muscles

Clinical Manifestations Associated with Rhabdomyolysis

1. Swelling of affected muscles
2. Pigmenturia with myalgia
3. Weakness of the involved muscle groups
4. Pain free episodes may still be associated with pigmenturia and leakage of muscle enzymes

Neuropathology

1. Myoglobinemia and myoglobinuria may occur with strenuous exercise performed under conditions of high temperature and humidity
2. Hypokalemia increases the risk of rhabdomyolysis with myoglobinuria
3. Myoglobinuria with serum levels greater than 300 mg/liter may cause renal failure
4. Two crucial factors in the development of myoglobinuric ARF are:
 - a. Hypovolemia/dehydration
 - b. Aciduria
5. Mechanisms of heme protein toxicity include:
 - a. Renal vasoconstriction that causes decreased renal circulation
 - b. Intraluminal cast formation
 - c. Direct heme protein toxicity:
 - i. Scavenging of nitric oxide which is a vasodilator
6. Activation of endothelin receptors due to free radical formation that is induced by heme protein (causes vasoconstriction)

Laboratory Evaluation

1. Myoglobin is cleared rapidly through the kidneys:
 - a. May return to normal 1–6 hours after muscle injury
 - b. Concomitantly metabolized to bilirubin
2. Myoglobin:
 - a. The urine dipstick reacts with hemoglobin and myoglobin; possibly detects myoglobin at the same concentration as hemoglobin (3 mg/liter)
 - b. Myoglobin gives urine its red-brown color at concentrations above 300 mg/L
 - c. Positive toluidine blue test
 - d. Colorless serum
 - e. Normal haptoglobin
 - f. RIA
 - g. ELISA assays

Differential Diagnosis of Genetic Causes of Rhabdomyolysis and Myoglobinuria

Rhabdomyolysis Associated Mutations in LP1N1

General Characteristics

1. Mutations in the LP1N1 gene that maps to chromosome 2p25.1
2. May be a common cause of recurrent rhabdomyolysis in children

Clinical Manifestations

1. Onset is in early childhood >5 years
2. Recurrent attacks of rhabdomyolysis associated with muscle pain and weakness that are followed by excretion of myoglobin in the urine
3. There is no relation to exercise
4. Attacks are triggered by intercurrent illness, most often upper respiratory tract infections
5. Episodes may last 7–10 days

Neuropathology

1. Lipin 1 dephosphorylates, phosphatidic acid to form diacylglycerol (phosphatidic acid and phosphohydrolase; PAP)
2. PAP is a transcriptional regulatory protein that controls metabolic gene expression
3. Muscle biopsy:
 - a. Rhabdomyolysis
 - b. Deficient PAP activity

Laboratory Evaluation

1. Myoglobinuria
2. Glycolytic Defects
 - a. Myophosphorylase deficiency
 - b. Phosphofructokinase
 - c. Phosphoglycerate mutase
 - d. Phosphoglycerate kinase
 - e. Lactic dehydrogenase
 - f. Phosphorylase kinase
 - g. Lipid metabolic defects with myoglobinuria and rhabdomyolysis
 - h. Primary carnitine deficiency
 - i. CPT2 deficiency
 - j. VLCAD deficiency
 - k. LCAD deficiency
 - l. MCAD deficiency
 - m. SCAD deficiency
 - n. Long-chain HAD deficiency
 - o. ETF and ETF-QO deficiencies (glutaconic aciduria type 2)

Differential Diagnosis of Rhabdomyolysis and Myoglobinuria from Drug Use

1. Opioids:
 - a. Clinical signs and symptoms may be delayed
 - b. Lower limbs affected to a greater degree than upper limbs
 - c. Transverse myelitis is associated
 - d. Pulmonary edema after IV use
2. Barbiturates:
 - a. Myonecrosis may occur with one large oral dose
 - b. Barbiturate coma may be associated with bullous skin lesions
3. Amphetamines:
 - a. Thin patients
 - b. Agitated; attention and problems with concentration
4. Meprobamate:
 - a. Dilated unresponsive pupils
 - b. Depression
5. Diazepam
6. Phencyclidine (PCP):
 - a. Severe nystagmus
 - b. Self-mutilation
 - c. Acute dystonic reaction
7. Beta blockers:
 - a. Slow heart rate
8. Clofibrate:
 - a. Generalized cramps, weakness and muscle tenderness
9. 3-hydroxy-3methyl glutaryl coenzyme A reductase inhibitors (3HMG-CoA reductase)
 - a. Rhabdomyolysis may be acute or delayed
 - b. Triggers are intercurrent illness, strenuous exercise and drug interaction
10. Phenformin/fenfluramine:
 - a. Right heart valve lesions
 - b. Pulmonary hypertension
11. Hypokalemic-induced myonecrosis:
 - a. Patients utilizing purgatives and diuretics
 - b. Acute potassium loss from:
 - i. Amphotericin
 - ii. Licorice and carbenoxolone
 - iii. Azathioprine
12. Chloroquine:
 - a. Doses of 250–500 mg daily for months (usually in the treatment of autoimmune disorders)
 - b. Face may be affected
 - c. Heart involvement
 - d. Macular retinopathy
 - e. Slow progressive muscle weakness
13. Emetine hydrochloride:
 - a. Generalized muscle weakness, pain and tenderness
14. Vincristine:
 - a. Minimal muscle weakness
 - b. Small fiber neuropathy
15. Colchicine:
 - a. Weakness and atrophy of all muscle groups of the lower extremities
16. Succinylcholine:
 - a. Associated malignant hyperthermia

17. Strychnine:
 - a. An adulterant with IV heroin
 - b. Extreme continuous extensor positions while maintaining consciousness
18. Cocaine:
 - a. Common cause of both traumatic and non-traumatic rhabdomyolysis
 - i. Prolonged vasoconstriction
 - ii. Direct toxic effect that causes myofibrillar degeneration
 - iii. Coma with muscle compression
 - iv. Prolonged generalized clonic-tonic seizures
19. Immunosuppressive drugs:
 - a. Primarily cyclosporin
 - b. Setting of solid organ transplantation
20. Rapeseed oil ingestion (toxic oil syndrome):
 - a. Initial symptoms of a respiratory illness
 - b. Myalgias and numbness of the extremities
 - c. Muscle weakness and atrophy (3rd–4th week)
 - d. Severely affected patients:
 - i. Sclerodermal features
 - ii. Hypertension
 - iii. Respiratory failure
 - iv. CTS (carpal tunnel syndrome)
21. Penicillamine:
 - a. Autoimmune induced myositis
22. Acute alcoholic myopathy (myonecrosis or rhabdomyolysis)
 - a. 5–10% of severely intoxicated alcoholics
 - b. Alcoholics of long duration
 - c. Previous attacks of long duration with pain and swelling of affected muscle
 - d. Acute attacks occur during:
 - i. Bouts of heavy drinking
 - ii. Withdrawal
 - iii. Sustained heavy drinking
 - e. Abrupt onset
 - f. Pain and tenderness may occur without cramps:
 - i. Usually cramps last 20–30 seconds but may last for hours
 - g. Process may affect single muscle groups; rarely the rectus abdominus muscle
 - h. Occasionally one or most of one extremity is involved
 - i. Pain, tenderness and swelling lasts 1–2 weeks; weakness lasts 10–14 days
 - j. One attack increases susceptibility to future attacks

Differential Diagnosis of Severe Hypokalemia

1. Severe Hypokalemia with Myoglobinuria at a level of 0.6–23 mEq/L
 - a. Renal tubular acidosis
 - b. Amphotericin B therapy
 - c. Primary aldosteronism
 - d. Regional enteritis

- e. Nasogastric suction and hyperalimentation
- f. Laxative abuse
- g. Hyponatremia
- h. Water intoxication

Differential Diagnosis of Direct Toxic Effects on Muscle Membrane with Myoglobinuria and Rhabdomyolysis with Envenomation

1. Sea snake (*Enhydra schistosa*) envenomation (SE Asia)
2. The Australian tiger snake (*Pseudechis*)
3. North and South American rattlesnake (*Crotalus viridis*):
 - a. Myotoxin
 - b. Phospholipases A
4. Hornet sting:
 - a. Alteration of the sarcoplasmic reticulum
5. Spiders:
 - a. Damage to the endoplasmic reticulum
6. Scorpions
 - a. Damage to the endoplasmic reticulum

Differential Diagnosis of Rhabdomyolysis with Myoglobinuria with Heat and Exercise

1. Exertional myoglobinuria:
 - a. Specific repetitive exercise (squat jump)
 - b. Military recruits
 - c. Long distance runners
 - d. Determining factors:
 - i. State of fitness of the individual
 - ii. Ability to terminate the exercise if severe cramps or pain develop
 - iii. Core temperature during the exercise
 - iv. Ambient temperature
 - v. Ischemia of specific muscles in particular positions
 - vi. Myoglobinuria during violent muscle contractions:
 1. Status epilepticus
 2. Electroshock therapy
 3. Delirium tremens
 4. Prolonged myoclonus
 5. Tetanus
 6. Prolonged dystonic postures
 7. Status asthmatics
 8. Cross country soldiers
 9. Anterior tibial syndrome
 10. Wrestling
2. High body temperature and excessive muscle work:
 - a. Exercise in hot, humid climate
 - b. Malignant hyperthermia
 - c. Neuroleptic malignant syndrome
 - d. Strychnine poisoning
 - e. Amphetamine intoxication
 - f. Heat stroke with myoglobinuria
 - g. Toxic shock syndrome with myoglobinuria (staphylococcus toxin)

Differential Diagnosis of Rare Toxins Causing Myoglobinuria and Rhabdomyolysis

1. Licorice ingestion:
 - a. Licorice abuse
 - b. Muscle pain
 - c. Neck weakness
 - d. Quadriplegia
 - e. Depressed but maintained reflexes
2. Cicuta (water hemlock):
 - a. Seizures
 - b. Myoglobinuria renal failure
3. Toluene:
 - a. Leukoencephalopathy
 - b. Dorsal column involvement
4. Clozapine:
 - a. Basal ganglia involvement
5. Gasoline vapor (Huffer's disease):
 - a. Leukoencephalopathy
6. Carbon monoxide:
 - a. Involvement of the globus pallidus, cerebellum and cortex
7. Haff disease:
 - a. East Prussia, Sweden and Russia
 - b. Ingestion of fish
8. Hellebore (veratrum alkaloid):
 - a. Ingestion of quail

Differential Diagnosis of Crush Injury and Ischemia with Rhabdomyolysis and Myoglobinuria

1. Intoxicated patients that have suffered prolonged muscle compression
2. Elderly patients that have suffered a fall
3. Trauma and crash injuries
4. Motor vehicle accidents
5. Collapse of buildings
6. Patients that struggle against restraints

Differential Diagnosis of Infections with Rhabdomyolysis and Myoglobinuria

1. Bacterial infections:
 - a. Shigella
 - b. Salmonella
 - c. E. coli
 - d. Legionnaire's disease
 - e. Leptospirosis
 - f. Clostridium perfringens
2. Viral infections:
 - a. Influenza
 - b. Herpes simplex
 - c. Herpes zoster
 - d. Epstein-Barr
 - e. Coxsackie
 - f. Adenovirus
 - g. Enteroviruses (ECHO 9,21,24)
3. Cysticercosis

Differential Diagnosis of Agents That Cause Focal Rhabdomyolysis

1. Tetracycline
2. Paraldehyde
3. Colistimethate
4. Ceftriaxone
5. Talwin (pentazocine)
6. Meperidine
7. Penicillin

Differential Diagnosis of Acid Maltase Deficiency

The infantile form of the disease presents with severe weakness and hypotonia. The differential diagnosis includes Werdnig-Hoffman disease (SMA1) and other congenital metabolic and myopathic disorders. The major differential feature is severe congestive heart failure and macroglossia. Mitochondrial disorders such as COX deficiency may involve proximal muscles and the heart but not to the same degree. Macroglossia is not a feature of mitochondrial disease.

Debrancher deficiency presents with massive hepatomegaly and hypoglycemia. There is no rise of blood glucose to epinephrine. Phosphorylase kinase deficiency may present with severe cardiomegaly in infancy, but lacks muscle weakness. Duchenne dystrophy has clear X-linked genetics, more prominent calf hypertrophy and the EMG does not demonstrate initiative features. Carnitine deficiency does not have the same degree of cardiac dysfunction or macroglossia.

Congenital myopathies occasionally present with a similar body habitus and include myotubular myopathy, central core disease and nemaline myopathy. Thinness, high arched palate, and long facies are characteristics of nemaline myopathy while bilateral symmetrical ptosis is present. Muscle biopsy clearly differentiates these congenital myopathies.

Adult acid maltase deficiency is frequently misdiagnosed as limb-girdle muscular dystrophy or polymyositis. The early respiratory muscle involvement as well as paraspinal myotonic discharges and complex repetitive action potentials differentiate the entities.

The adult variants of autophagic vacuolar myopathy have a similar phenotype. One variant with cardiomyopathy and cognitive deficiency due to a mutation of the gene for lysosome associated membrane protein-2 (LAMP-2 gene) and the other with myopathy and multisystem involvement. Muscle biopsy differentiates the vacuoles from PFK. Glycogen positive acid phosphatase containing vacuoles in acid maltase disease distinguishes this entity from chloroquine vacuolar myopathy which may also have concomitant macular retinopathy.

Differential Diagnosis of Myophosphorylase Deficiency

The major myopathies that comprise the differential diagnosis are other metabolic myopathies and the terminal glycolysis which include:

1. PFK (phosphofructokinase)
2. PGK (phosphoglycerokinase)
3. PGAM (phosphoglyceromutase)
4. LDH (lactate dehydrogenase)

Patients with PFK differ from those with McArdle's disease in that they manifest:

1. Less of a second wind phenomenon; intravenous glucose may be deleterious for them during testing
2. Severe nausea and vomiting occurs during exercise induced cramps
3. Less myoglobinuria
4. Increased bilirubin in the serum
5. An increased reticulocyte count

Patients with terminal glycogenosis, PGAM, PGK, and LDH have an abnormally low lactate rise during the ischemic forearm exercise test, but is not absent.

Carnitine palmitoyl transferase deficiency Type II is the most common cause of recurrent adult myoglobinuria. It occurs not only with exercise, but also during fasting without exertion. The forearm ischemic exercise test is negative in CPT2 deficiency. In myophosphorylase deficiency the myoglobinuria occurs with and following intense exercise. Exercise induced myoglobinuria may also occur with DMD, BMD and malignant hyperthermia. The autosomal recessive genetic pattern, interval rather than consistent elevated CK and clinical presentation rule out the dystrophinopathies. Malignant hyperthermia is AD and there is often a family history of death during anesthesia or unexpected anesthetic complications.

Undue fatigue with exercise and without myoglobinuria occurs with terminal glycogenosis as well as with adenosine monophosphate deaminase (AMPD) deficiency. In this myopathy, the forearm ischemic exercise test demonstrates a normal rise in lactate but no increase in ammonia.

Differential Diagnosis of Carnitine Deficiency

1. Chanarin-Dorfman
2. Lipid storage myopathy
3. Polymyositis
4. Debrancher enzyme deficiency
5. Infantile acid maltase deficiency
6. Fructose-1, 6-diphosphate deficiency (intermittent encephalopathy)
7. Phosphoenolpyruvate carboxy kinase deficiency

Seminal Points in the Differential Diagnosis

1. Carnitine deficiency:
 - a. Recurrent encephalopathy resembling Reye's syndrome
 - b. Recurrent hypoglycemia with or without keto acidosis precipitated by:
 - i. Caloric deprivation
 - ii. Exercise
 - iii. Infection
 - iv. Pregnancy

- c. Myalgias and exacerbated fatigue with exercise
- d. Lactic acidemia with exercise
- e. Cardiomyopathy:
 - i. High precordial T-waves
 - ii. Left axis deviation
- f. Unexplained hepatomegaly
- g. Hypertrophic cardiomyopathy with or without family history of sudden death
- h. Established organic aciduria
2. Chanarin-Dorfman disease:
 - a. AR
 - b. Inability of cells to degrade endogenously synthesized triglycerides
 - c. Clinical Manifestations:
 - i. Congenital ichthyosis
 - ii. Age of onset is the second decade
 - iii. Ichthyosis:
 1. Lamellar ichthyosis
 2. Accentuated over the skin creases
 3. Mild erythema in affected areas
 4. Ectropion (eyelids)
 - iv. Steatorrhea
 - v. Muscle weakness:
 1. Proximal greater than distal
 2. Cranial muscles are spared
 3. Moderate severity
 - vi. Associated ataxia, nystagmus, and neurosensory hearing loss
 - vii. Laboratory Evaluation:
 1. Increased liver enzyme
 2. Increased serum CK
 3. No ketone body formation during a fast
 4. Sudanophilic droplets in granulocytes
 - viii. Neuropathology:
 1. Triglyceride storage in all tissues
3. Sporadic myopathic carnitine deficiency versus polymyositis:
 - a. Both disorders have proximal myopathy and increased serum CK
 - b. Dysphagia in some PM patients
 - c. Absence of fibrillation potentials on EMG and muscle biopsy excludes an inflammatory myopathy
4. Carnitine deficiency versus debrancher enzyme deficiency:
 - a. Common to both entities:
 - i. Intermittent episodes of hypoglycemia
 - ii. Abnormal liver function tests
 - iii. Lactic acidemia
 - iv. Hyperuricemia
 - b. Debrancher enzyme deficiency:
 - i. Glycogen is stored in tissue rather than lipid
 - ii. Distal weakness occurs in debrancher enzyme deficiency
 - iii. EMG demonstrates more irritative features than in carnitine deficiency

5. Infantile maltase deficiency versus secondary carnitine deficiency that occurs in maltase deficiency
 - a. Enlarged tongue with fibrillation potentials occur in infantile maltase deficiency
 - b. Progressive weakness is not associated with episodic metabolic crises (maltase deficiency)
 - c. Cardiac myopathy (more severe with maltase deficiency)
 - d. Irritative EMG with pseudomyotonic discharges (maltase deficiency)
 - e. Glycogen rather than lipid accumulates in skeletal muscle
6. Systemic carnitine deficiency with intermittent encephalopathy versus urea cycle deficits:
 - a. Metabolic acidosis does not occur in urea cycle defects
 - b. Branched chain aminoacidurias may also suffer protein intolerance
 - c. Secondary carnitine deficiencies:
 - i. Plasma levels of arginine and citrulline are normal (elevated in urea cycle defects) in carnitine deficiency
7. Fructose 1, 6 diphosphatase deficiency and phosphoenolpyruvated carboxykinase deficiency:
 - a. Impaired gluconeogenesis
 - b. Have episodes of hypoglycemia
 - c. Fatty liver
 - d. Ketoacidosis
 - e. Hypotonia
- a. DNA polymerase gamma (POLG, POLG2)
- b. Twinkle
5. The gene products function directly at the mtDNA replication fork. Adenine nucleotide translocator 1, thymidine phosphorylase thymidine kinase 2, deoxyglucosamine kinase, ADP-forming succinyl-CoA synthetase, ligase, MPV17 (supply the mitochondria with deoxyribonucleotide triphosphate pools for mtDNA replication)
6. The most common mutated genes that phenotypically present with adult onset mitochondrial depletion syndromes (MDS) include:
 - a. POLG1
 - b. TK2
 - c. TYMP
 - d. RRM2B
 - e. PEO/twinkle
7. Adult MDS has the same phenotype spectrum as early onset MDS. Adult mitochondrial depletion syndrome may present with mild manifestations
8. Human mitochondrial DNA encodes 13 of the 82 structural proteins of the electron transport chain. There is a constant need for mitochondrial nucleotide synthesis due to the requirements of mitochondrial maintenance
9. De novo enzymes are not present in mitochondria and therefore synthesis proceeds through the salvage pathway
10. Defective mtDNA synthesis and maintenance is manifest by multiple deletions or by depletion of the mitochondrial genome
11. mtDNA depletion is usually a disease of infants whose phenotype is severe muscle weakness, hepatic failure or renal tubular failure
12. In families with multiple mtDNA deletions there are defects in proteins that are involved in mtDNA replication from mutations in the mitochondrial DNA polymerase gene, the twink gene (helicase), the adenine nucleotide translocator and the thymidine phosphorylase gene. Mutations involved in the nucleotide salvage pathways are the deoxyguanosine kinase gene and thymidine kinase gene that are also involved in mtDNA replication

Differential Diagnosis of Lipid Storage Myopathies

1. Type I glycogenesis (Von Gierke disease)
2. Pyruvate decarboxylase deficiency
3. Familial beta-hypolipoproteinemia
4. Arthrogryposis multiplex congenita (rare)
5. Scapuloperoneal dystrophy pattern (rare)
6. Autoimmune dysfunction (rare)

Mitochondrial Depletion Syndrome (MDS)

General Characteristics

1. Mitochondrial DNA depletion is caused by mutations in the nuclear genes that maintain mtDNA or deoxyribonucleotide pools and mtDNA biogenesis
2. mtDNA depletion syndrome (MDS) categories include:
 - a. Progressive External Ophthalmoplegia (PEO)
 - b. Predominant myopathy
 - c. Mitochondrial NeuroGastro-intestinal Encephalomyopathy (MNGIE)
 - d. Sensory Ataxic Neuropathy, Dysarthria and Ophthalmoplegia (SANDO)
 - e. Hepatoencephalopathy
3. The most common organs involved in MDS are the brain, liver and muscles
4. The most common involved genes are divided into two groups:

Specific Mitochondrial Depletion Syndromes of Adults

PEO1

General Characteristics

1. The mitochondrial helicase Twinkle gene is an essential component of mitochondrial replication. Heterozygous mutations in its coding gene (PEO1) are a cause of progressive external ophthalmoplegia. It is inherited as an autosomal dominant disorder

Clinical Manifestations

1. The onset is usually prior to the fifth decade, but may be in childhood

2. Slowly progressive symmetrical ptosis
3. Ophthalmoplegia
4. Rare diplopia
5. Proximal myopathy
6. Cataracts
7. Tremor
8. Ataxia
9. Peripheral neuropathy
10. Rare respiratory involvement

Neuropathology

1. Ragged red muscle fibers
2. COX deficient muscle fibers
3. Multiple mtDNA deletions are detected in muscle

Laboratory Evaluation

1. Creatine kinase and lactate are normal
2. EMG:
 - a. Normal
3. Optical coherence tomography:
 - a. Normal optic nerve and retina

Differential Diagnosis of CPEO

1. Oculopharyngeal muscular dystrophy
2. Kearns-Sayre syndrome (KSS)
3. MNGIE
4. Myasthenia gravis
5. Progressive supranuclear palsy
6. Spinocerebellar ataxia Type III

Mitochondrial Neurogastrointestinal Encephalomyopathy

General Characteristics

1. MNGIE is caused by mutations in the TYMP gene that maps to chromosome 22q13.33. It is a rare autosomal recessive disorder
2. The gene encodes Thymidine Phosphorylase (TP). Loss of the enzyme causes an accumulation of thymidine and deoxyuridine nucleotides that are incorporated by the mitochondrial salvage pathway. Their accumulation causes deoxynucleotide triphosphate pool imbalance thought to cause mtDNA instability
3. A few patients with MNGIE have been associated with POLG gene and MTTK gene mutations

Clinical Manifestations

1. Onset is prior to age twenty (range is 2.5–22 years)
2. Distal greater than proximal weakness
3. Gastrointestinal dysmotility (pseudo-obstruction)
4. Stocking and glove sensory loss
5. Decreased muscle stretch reflexes
6. Ptosis and extraocular muscle weakness
7. Rare patient has cognitive deficits
8. Pigmentary retinopathy
9. Sensorineural hearing loss
10. Facial weakness
11. Hoarseness and dysphasia

Neuropathology

1. Muscle biopsy:
 - a. Ragged red fibers
 - b. Ragged blue fibers
 - c. COX-negative fibers
 - d. Neurogenic atrophy of distal muscles
2. Sural nerve biopsy:
 - a. Loss of myelinated fibers
 - b. Demyelination with remyelination with rare onion bulbs
 - c. Electron microscopy:
 - i. Abnormal mitochondria
 - ii. Paracrystalline inclusions in both muscle fibers and Schwann cells
 - iii. Enzymatic assay of muscle fibers:
 1. COX and other respiratory enzyme deficits
 - iv. Autopsy:
 1. Endoneurial fibrosis and demyelination in peripheral nerves
 2. White matter abnormalities in the cerebral cortex and cerebellum
 3. Cranial nerve and spinal roots are demyelinated to a degree
 4. Loss of neurons and fibrosis of the autonomic ganglia, celiac and myenteric plexuses

Laboratory Evaluation

1. Serum CK levels are normal or slightly elevated
2. Increased lactate, pyruvate and CSF protein is typical
3. EKG:
 - a. Conduction defects in some asymptomatic patients
4. EMG:
 - a. Increased insertional activity, positive sharp waves and fibrillation potentials
 - b. Decreased recruitment of MUAPs may be seen in distal muscles
 - c. Proximal muscles reveal small brief duration MUAPs
5. NCS:
 - a. Slow motor and sensory nerve conduction velocities to the demyelinating range with prolonged F-wave latency
 - b. Reduced amplitudes of sensory nerve action potentials
 - c. Rare reduced amplitude of CMAPs
6. MRI:
 - a. Abnormalities of cerebral and cerebellar white matter (leukoencephalopathy)
7. Gastrointestinal radiology:
 - a. Dilation and dysmotility of the esophagus, stomach and small intestine

Polymerase Gamma 1 (POLG1)

General Characteristics

1. POLG1 is a nuclear gene that maps to chromosome 15q.26.1 which causes disease by affecting mtDNA
2. It encodes the catalytic subunit of the mtDNA polymerase gamma that is required for mtDNA replication

Clinical Manifestations

1. Alpers syndrome
2. PEO with or without myopathy
3. Ataxia-neuropathy syndrome
4. Epilepsy
5. Childhood progressive encephalopathy
6. Parkinsonism
7. Stroke-like episodes
8. Isolated exercise intolerance
9. Propofol-related infusion syndrome

Neuropathology

1. Muscle biopsy:
 - a. COX deficient ragged red fibers
2. Analysis of mtDNA of clinically affected tissue reveals deletion, multiple deletions, or point mutations

Laboratory Evaluation

1. Resting pyruvate and lactate levels may be elevated
2. EMG:
 - a. Usually normal

RRM2B*General Characteristics*

1. RRM2B (ribonucleotide reductase small subunit 2-like) maps to chromosome 8q22.3
2. The RRM2B gene encodes the small subunit of p53-inducible ribonucleotide reductase
3. The heterotetrameric enzyme converts ribonucleotide diphosphates into deoxynucleoside diphosphates that are critical for DNA synthesis
4. Mutations in RRM2B are the third most common cause of multiple mitochondrial deletions in adults
5. Transcription of RRM2B is regulated by the tumor suppression protein p53
6. Mutations in the RRM2B gene have been documented with dominant and recessive inheritance
7. Recessively inherited RRM2B mutations have a more severe phenotype

Clinical Manifestations

1. Ophthalmoparesis is severe and most often associated with ptosis (90%)
2. Proximal muscle weakness
3. Bulbar dysfunction (42%):
 - a. Dysarthria and dysphagia
 - b. Dysphonia
 - c. Facial weakness
 - d. Neck flexor muscle weakness
 - e. Sensorineural hearing loss (36%)
 - f. Gastrointestinal dysfunction (19%)
 - g. Cerebellar ataxia (39%)
 - h. Stroke-like episodes (10%)
 - i. Cardiac complications

Neuropathology

1. Muscle biopsy:
 - a. COX deficient ragged red fibers
 - b. EMG:
 - i. Normal
 - c. Multiple mtDNA deletions in affected tissue

Laboratory Evaluation

1. Normal or elevated resting lactate and pyruvate levels
2. Muscle biopsy:
 - a. Ragged red fibers
 - b. COX deficient fibers
3. EKG:
 - a. Cardiac conduction defects

Thymidine Kinase Deficiency (Myopathic Type)**TK2***General Characteristics*

1. Thymidine Kinase (TK2) is a mitochondrial deoxyribonucleotide that is encoded by the TK2 gene that maps to chromosome 16p21
2. It phosphorylates thymidine, deoxycytidine, and deoxyuridine
3. TK2 along with DGUOK are important in mitochondrial salvage pathway enzymes that are critical for the maintenance of balanced mitochondrial dNTP concentrations

Clinical Manifestations

1. TK2 related mitochondrial DNA depletion syndrome has a wide phenotypic spectrum
2. In infants and children:
 - a. There is generalized hypotonia and proximal muscle weakness
 - b. Loss of previously acquired motor skills
 - c. Poor feeding and respiratory failure after a few years
 - d. A form in infants is characterized by rapidly progressive proximal muscle weakness, encephalopathy, epilepsy and an early demise that resembles spinal muscular atrophy
 - e. A variant early presentation is progressive myopathy with sensorineural hearing loss and hepatomegaly
 - f. Late or adult onset forms include:
 - i. Progressive proximal muscle weakness
 - ii. Chronic progressive ophthalmoplegia (with multiple mtDNA deletions and no DNA depletion)

Neuropathology

1. Muscle Biopsy:
 - a. Increased SDH activity (succinic dehydrogenase) with low to absent COX (cytochrome oxidase activity)
 - b. Severely decreased mitochondrial DNA copy number (5% to 30%) of control values
 - c. Ragged red fibers

Laboratory Examination

1. Elevated CK concentration that is usually 5–10 times normal
2. Pulmonary function abnormalities in the infantile and early childhood forms (may also be present in adults)
3. Normal serum lactate may occur concomitantly with high CK Levels

Adult Mitochondrial DNA Depletion Symptoms with Mild Manifestations*General Characteristics*

1. Report of an adult patient with mitochondrial depletion syndrome with mild clinical symptomatology

Clinical Manifestations

1. Onset at 47 years of age
2. Positive family history for mitochondrial disease
3. Daytime sleepiness
4. Exercise intolerance
5. Myalgia in the lower extremities
6. Painful neck muscles
7. Bilateral ptosis
8. Decreased Achilles tendon reflexes

Neuropathology

1. Muscle Biopsy:
 - a. Detached lobulated fibers with subsarcolemmal NADH and SDH staining
 - b. Depletion of mtDNA to 9% of normal

Laboratory Evaluation

1. Hyperlipidemia; pyruvate and lactic acid were normal
2. EMG:
 - a. Normal

The Differential Diagnosis of the Genes Involved in DNA Replication and Maintenance

1. The mechanism that underlies mitochondrial maintenance disorders is offset by either replication machinery of the biosynthesis pathways of deoxyribonucleotide 5' triphosphates that is critical for mtDNA synthesis
2. Mitochondrial DNA is replicated by:
 - a. POLG
 - b. POLG2
 - c. DIOD or F2, and
 - d. MGME1 (mitochondrial genome maintenance exonuclease 1). The products of these genes function directly at the mtDNA replication fork
3. Genes involved in the supply of the mitochondria with deoxyribonucleotide triphosphate pools that are needed for mtDNA replication include:
 - a. Adenine nucleotide translocator 1 (ANT 1)
 - b. Thymidine phosphorylase
 - c. Thymidine Kinase 2

- d. Deoxyguanosine kinase
- e. ADP forming succinyl CoA synthetase ligase
- f. MPV17
- g. RRM2B

POLG

1. DNA polymerase gamma in conjunction with its accessory proteins that include:
 - a. Mitochondrial DNA helicase
 - b. Single-stranded DNA-binding protein
 - c. Topoisomerase
 - d. Initiating factors
2. Genes directly involved in replication:
 - a. POLG
 - b. POLG2
 - c. Twinkle gene
 - d. MGME1
 - e. C10 or F2
3. Genes whose products supply the mitochondria with deoxyribonucleotide triphosphate pools for mtDNA replication:
 - a. Adenine nucleotide translocator 1 (ANT 1)
 - b. Thymidine phosphorylase
 - c. Thymidine kinase 2
 - d. Deoxyguanosine kinase
 - e. ADP-forming succinyl CoA synthetase ligase
 - f. MPV17

Differential Diagnosis of Mitochondrial Myopathy

Any adult patient that presents with exercise intolerance, easy fatiguable, bilateral symmetrical ptosis, ophthalmoplegia, diabetes, short stature, and sensorineural hearing loss and migraine should alert the clinician to the possibility that he is dealing with a mitochondrial myopathy. There is a wide spectrum of clinical manifestations from the same mutation and great variability of the severity of the disorder among family members and between families. Rarely, mitochondrial myopathies that are usually restricted to infants and childhood are seen in adults. Some have adult onset. A specific genetic defect may cause different phenotypes. Primary carnitine deficiency primarily presents in infancy with hypoketotic hypoglycemia and hepatomegaly although secondary forms are seen with many diseases and may present with severe weakness. Carnitine palmitoyl transferase deficiency (CPT2) may present with proximal myopathy and cardiomyopathy. Coenzyme Q deficiency has several presentations that include: 1. encephalopathy, seizures and ataxia (infants and childhood), 2. multisystem involvement, 3. cardiomyopathy, encephalopathy and renal failure, 4. Leigh phenotype and 5. isolated primarily proximal myopathy. All defects in the respiratory chain cause failure of generation of ATP. Complex II has an elevated serum CK, spasticity, and leukoencephalopathy. Complex II manifests as exercise intolerance. Complex IV has a wide clinical spectrum from an isolated

myopathy to multisystem disease. Its onset is from infancy to adulthood. Most severe forms manifest lactic acidemia, a Leigh's disease presentation with white matter abnormalities, basal ganglia lesions and cerebellar atrophy. Complex V may present with psychomotor retardation, growth retardation, leukoencephalopathy, lactic acidemia and 3-methyl glutaconic aciduria. The benign form of pyruvate carboxylase deficiency may have normal strength but episodes of metabolic acidosis with increased serum levels of lactate, pyruvate, lysine, proline and beta-hydroxybutyrate. Pyruvate decarboxylase deficiency is primarily seen in infants and manifests with hypotonia with subsequent psychomotor retardation, seizures, facial dysmorphisms, metabolic and lactic acidosis. Defects of oxidative phosphorylation coupling occur with Luft disease which manifests a hypermetabolic state characterized by profuse sweating, exercise intolerance, fever, generalized weakness and heat intolerance. Mitochondrial depletion syndromes are characterized by myopathy, encephalopathy and hepatocerebral symptomatology.

There are few neurologic disorders that demonstrate bilateral ptosis and ophthalmoplegia in concert with heart block. Syncope may be the presenting feature of Kearns-Sayre syndrome (KSS). Congenital myasthenic syndromes have no cardiac symptomatology although interstitial myocarditis may occur in adult patients with myasthenia and thymoma. The ptosis an ophthalmoparesis in myasthenia is asymmetric. Niemann-Pick Type C has failure of upgaze and a supranuclear palsy, but ptosis and heart conduction defects do not occur.

Oculopharyngeal muscular dystrophy may demonstrate the same pattern of weakness as KSS but begins in the fourth to sixth decade, where KSS starts prior to age 20. There are no cardiac defects with oculopharyngeal dystrophy. AD-PEO with multiple mtDNA depletion has prominent ptosis associated with face, neck flexor and proximal weakness, but no other manifestations of KSS. AR-PEO has ocular manifestations, no myopathy but an often severe hypertrophic cardiomyopathy, cataracts and early death. MNGIE's most dominant feature is gastrointestinal dysmotility and peripheral neuropathy, whereas ARCO is dominated by a severe cardiomyopathy rather than conduction defect.

Leigh's syndrome is usually a pediatric disease but occasionally presents in adulthood. There is a wide clinical spectrum that includes hypotonia, recurrent vomiting and psychomotor deficits in childhood with generalized weakness, ophthalmoplegia, ptosis, hearing loss and optic atrophy in later life.

The sentinel features of MERRF are the myoclonic seizures, dementia and lipomatosis (some patients).

MELAS is characterized by stroke-like episodes that are out of a vascular distribution and may evolve rather than present abruptly. Most patients are symptomatic in adolescence but rarely may it present very late in adulthood. In addition to the stroke-like episodes there is generalized muscle weakness and high serum and CSF lactate levels. Some mitochondrial myopathy patients only have exercise induced

muscle pain, reduced muscle bulk and occasional recurrent myoglobinuria. In general, they are of short stature and may have sensorineural hearing loss. Dementia is prominent in MELAS, MERRF and KSS. Ptosis and ophthalmoplegia in AD-PEO, Leigh's syndrome, KSS, MNGIE and ARCO. Rarely, it occurs in MELAS that is differentiated from other mitochondrial disorders by associated posterior leukoencephalopathy and migraine. The stroke-like episodes are differentiated from ischemic events by: 1. not being restricted to a vascular territory (often parietal and posterior territories); 2. evolving over hours to days rather than presenting with an apoplectic onset and 3. with recurrence and recovery. Pigmentary retinopathy is seen in KSS, MELAS and MERRF. Optic atrophy occurs with LHON, MERRF and Leigh's disease. Peripheral neuropathy is seen in NARP and MNGIE but the gastrointestinal dysmotility dominates the later disorder. An unusual condition is hypoparathyroidism that may be seen with KSS.

Differential Diagnosis of Chronic Progressive Ophthalmoplegia

1. Oculopharyngeal muscular dystrophy:
 - a. Bulbar symptomatology is more severe than in AD-PEO
2. KSS (Kearns-Sayre syndrome):
 - a. Heart block with syncope may dominate the clinical picture
 - b. Younger age than PEO
 - c. Pigmentary retinopathy
3. Myasthenia gravis:
 - a. Fluctuation of cranial nerve signs; may be induced at the bedside
 - b. Asymmetrical ophthalmoplegia and ptosis
 - c. Diplopia; most PEO patients have minimal diplopia or none
4. Progressive supranuclear palsy (PSP):
 - a. Dramatic vertical gaze deficits
 - b. Falls
 - c. Parkinsonian features (not responsive to L-Dopa)
 - d. Cognitive decline
 - e. Head held in extension (idiopathic Parkinson's disease the head is invariably flexed)
5. MNGIE:
 - a. Severe GI dysmotility
6. Spinocerebellar ataxia (Type III):
 - a. Cerebellar degeneration and ataxia are the most prominent features

Defects of Oxidative Phosphorylation Coupling

Luft Disease

General Characteristics

1. Hypermetabolism and abnormal muscle respiration
2. The hypermetabolism is caused by extensive uncoupling of mitochondrial respiration in skeletal muscle

Clinical Manifestations

1. Onset in adolescence
2. Fever
3. Heat intolerance
4. Profuse sweating
5. Exercise intolerance
6. Hypermetabolic state
7. Polyphasia and polydipsia
8. Tachycardia
9. Death in middle age
10. Generalized weakness

Neuropathology

1. Muscle biopsy:
 - a. Peripheral aggregates of abnormal mitochondria:
 - i. Overabundant tightly packed disorganized cristae of the mitochondria
 - ii. The mitochondrial cristae form a zigzag pattern
2. Electron microscopy:
 - a. Small electron dense osmophilic bodies are identified in the mitochondria
 - b. Occasional paracrystalline inclusions
3. The mitochondrial enzymes function normally
4. The zigzag mitochondrial structural conformational change is caused by an absence of some tricarboxylic acid cycle enzyme from the cristae which exposes the interior of the cristae to the matrix flux
5. Leakage of protons from the cristae impairs coupling of respirational and ATP synthesis

Laboratory Evaluation

1. The basal metabolic rate is dramatically elevated

Defects of the Mitochondrial Respiratory Chain***Mitochondrial Complex I****General Characteristics*

1. Complex I deficiency involves mutation in NADH-CoQ reductase
2. Two electrons are removed from NADH and transferred to a lipid-soluble carrier, ubiquinon (Q); the reduced product is ubiquinol
3. Ubiquinol (QH₂) diffuses within the membrane and translocates four protons (H⁺) across the membrane which produces the mitochondrial proton gradient
4. Mitochondrial gene mutations encode defective subunit 4 of complex I

Clinical Manifestations

1. Fatal infantile multisystem disorder
2. Congenital lactic acidosis
3. Cognitive deficits
4. Hypotonia

5. Most often death in infancy from cardiorespiratory failure
6. Myopathy with associated carnitine deficiency:
 - a. Onset in childhood or adult life
 - b. Exercise intolerance
 - c. Muscle pain
 - d. Progressive primarily proximal muscle weakness
 - e. Female affected relatives

Neuropathology

1. Muscle biopsy:
 - a. Accumulation of lipid
 - b. Ragged red fibers

Laboratory Evaluation

1. Low plasma and muscle carnitine
2. EMG:
 - a. Normal

Complex Deficiency with Normal Carnitine Levels*General Characteristics*

1. NADH is oxidized to NAD⁺ by reducing flavin mononucleotide to FMN in electron steps from the FMN to Fe-S clusters and then to ubiquinone
2. Complex I is a major site for the production of reactive oxygen species (superoxide)

Clinical Manifestations

1. Age at onset is between 16–46 years of age
2. Fatigue
3. Muscle pain
4. Weakness
5. Remittent paralysis (rare) associated with lactic acidosis
6. Heart failure (rare)
7. Dementia, dystonia, blindness (one patient)

Neuropathology

1. Muscle biopsy:
 - a. Ragged red fibers

Laboratory Evaluation

1. Metabolic acidosis
2. Hypoglycemia
3. Lactic acidemia
4. Increased serum CK
5. EMG:
 - a. Normal

Mitochondrial Complex II (Succinate Dehydrogenase or Succinate – CoQ Reductase)*General Characteristics*

1. Complex II delivers additional electrons into the quinone pool that originate from succinate and are transferred via FAD to Q
2. Complex II is composed of four protein subunits

3. Although complex II is a parallel electron transport pathway (to complex I) it does not transport protons to the inner mitochondrial space
4. SDH is a nuclear encoded enzyme
5. AR inheritance; involvement of the Fe-S unit of the complex

Clinical Manifestations

1. May present in adulthood
2. Optic atrophy
3. Proximal myopathy
4. Growth retardation
5. Spasticity
6. Pulmonary edema
7. Kearns-Sayre-like presentation

Neuropathology

1. Ragged red fibers and small arteries stain less intensely with SDH stains
2. Accumulation of lipid droplets in abnormal fibers

Laboratory Evaluation

1. Excessive and prolonged lactate production and increased venous oxygen saturation with the forearm exercise test
2. EMG:
 - a. Usually normal

Coenzyme Q10 (CoQ) Deficiencies

General Characteristics

1. Primary coenzyme Q10 deficiency-1 (CoQ10D1) is caused by homozygous or compound heterozygous mutation in the CoQ2 gene that maps to chromosome 4q21; AR
2. Coenzyme Q10 is ubiquinone which is a mobile lipophilic electron carrier of the inner mitochondrial membrane respiratory chain
3. Multiple genes may be mutated that encode proteins directly involved in the synthesis of coenzyme Q
4. Secondary CoQ10 deficiency is associated with glutaric aciduria type IIC (ETFDH gene on chromosome 4q) and mutation in the APTX gene in chromosome 9p13 that causes ataxia syndrome (AOA-1)
5. CoQ10 transfers electrons from complex I and II to complex III

Clinical Manifestations

1. There are 5 major phenotypes:
 - a. Encephalomyopathic:
 - i. Seizures
 - ii. Ataxia
 - b. Multisystem infantile form:
 - i. Encephalopathy, cardiomyopathy and renal failure
 - c. Cerebellar form with ataxia and cerebellar atrophy
 - d. Leigh's syndrome with growth retardation
 - e. Isolated myopathic form:
 - i. Proximal weakness
 - ii. Exertional recurrent myoglobinuria
 - iii. Exercise intolerance
 - iv. Some patients have bilateral ptosis in childhood

Neuropathology

1. Muscle biopsy:
 - a. Ragged red fibers
 - b. Cytochrome C, oxidase deficient fibers
 - c. Excess lipid droplets
 - d. Muscle tissue demonstrates low levels of CoQ10

Laboratory Evaluation

1. Serum CK, lactic acid and pyruvate levels can be normal to moderately elevated
2. Excessive and prolonged lactate production with increased venous oxygen saturation during and following exercise

Mitochondrial Complex III (Mutation in the Cytochrome b Gene)

General Characteristics

1. Cytochrome b is a protein that is encoded by the MT-CYB gene
2. It is a subunit of the respiratory chain protein ubiquinol cytochrome c reductase. The complex is composed of the products of one mitochondrially encoded gene MT-CYB and ten nuclear genes
3. The complex is involved in the electron transport complex and the pumping of protons to form the proton gradient
4. The complex leaks electrons to molecular oxygen to form the reactive oxygen species superoxide

Clinical Manifestations

1. Encephalopathy:
 - a. Infant presentation (fatal)
2. Childhood or adult presentation:
 - a. Myopathy:
 - i. Exercise intolerance
 - ii. Fixed proximal weakness
 - iii. Cardiomyopathy (histiocytoid cardiomyopathy in infancy)
3. Pigmented retinopathy
4. Sensory neuropathy
5. May respond to vitamin K3 (menadione)

Neuropathology

1. Muscle biopsy:
 - a. Ragged red fibers
 - b. Lipid accumulation

Laboratory Evaluation

1. Serum lactate and pyruvate may be elevated at rest and are exacerbated by the forearm exercise test

Cytochrome C Oxidase Deficiency (Complex IV)*General Characteristics*

1. Cytochrome c oxidase deficiency can be caused by mutation in several nuclear encoded and mitochondrially encoded genes
2. The mitochondrial gene mutations include:
 - a. COX
 - b. MTCO1
 - c. MTCO2
 - d. MTCO3
 - e. MTTS1 (mitochondrial tRNA)
 - f. MT-TL1 (transfers leucine)
3. Mutations in nuclear genes include:
 - a. COX20 (1q44)
 - b. COAS (2q11.2)
 - c. FASTKE2 (2q33.3)
 - d. COX14 (12q13.12)
 - e. APOPT1 (14q32.33)
 - f. COX10 (17p12)
 - g. TACO1 (17q23.3)
 - h. PET100 (19p13.2)
 - i. COX6B (19q13.2)
4. The mitochondrially encoded proteins in the cytochrome oxidase complex are the catalytic subunits and also function in electron transport
5. Isolated COX deficiencies have autosomal recessive inheritance and are caused by mutations in nuclear-encoded genes

Clinical Manifestations

1. The deficiency of cytochrome c oxidase is clinically very heterogeneous
2. Onset may be from infancy to adulthood
3. Myopathic phenotypes:
 - a. Fatal infantile form:
 1. Lactic acidosis
 2. Respiratory distress
 3. Renal failure
 4. Death in the first year
 - b. Benign form:
 1. Patients improve and are normal by age three
 2. Return of COX in muscle
 3. Subunit VII, Z, b and II are involved
 - c. Adolescent form:
 1. Exercise induced myoglobinuria
 2. Normal neurological examination between attacks
 3. Mild proximal muscle weakness
 4. No multisystem involvement
 5. Fatigue and myalgia with exercise

Neuropathology

1. Muscle biopsy:
 - a. Ragged red fibers
 - b. Increased lipid accumulation

2. Magnetic resonance spectroscopy:
 - a. Rapid decrease of creatine phosphate and an abnormal increase of inorganic phosphate with exercise
 - b. Delay of phosphocreatine to baseline concentrations regeneration after exercise

ATP Synthase Deficiency (Complex V)*General Characteristics*

1. ATP synthase deficiency nuclear type 2 may be caused by homozygous mutations in the TMEM70 gene that maps to chromosome 8q21.11; subunit 6 (mtDNA 8993)
2. A large percentage of patients have been described from Roma families

Clinical Manifestations (MC5DN2)

1. Intrauterine growth retardation
2. Severe hypotonia at birth
3. Some children developed pulmonary arterial hypertension in the neonatal period
4. Hypertrophic cardiomyopathy
5. Microcephaly
6. Dysmorphism
7. Hypospadias
8. Growth retardation
9. Cryptorchidism

Clinical Manifestations in Patients with Subunit 6 (mtDNA 8993)

1. Mild progressive muscle weakness
2. Fatigue on exertion
3. Growth retardation
4. Sensorineural hearing loss
5. Recurrent vomiting
6. Pigmentary retinopathy
7. Cognitive impairment
8. Peripheral sensory neuropathy
9. Cerebellar ataxia
10. Multisystem involvement

Neuropathology (mtDNA 8993)

1. Muscle biopsy:
 - a. Ragged red fibers
 - b. Lipid accumulation (often exacerbated by secondary carnitine deficiency)
 - c. Electron microscopy:
 - i. Paracrystalline deposits in the inner mitochondrial membrane

Laboratory Evaluation

1. Lactic acidosis
2. 3-methylglutaconic aciduria
3. MRI:
 - a. Cerebellar atrophy; leukoencephalopathy
 - b. Basal ganglia calcification (mtDNA 8993 mutation)

Defects of Mitochondrial Substrate Utilization and Gluconeogenesis

Pyruvate Carboxylase Deficiency

General Characteristics

1. Categorized into 3 phenotypic subgroups:
 - a. North American patients (group A)
 - b. Patients from France and the UK (group B)
 - c. Group C is relatively benign
2. Mutations in the pyruvate carboxylase gene have been mapped to chromosome 11q13.2

Clinical Manifestations in Group A (North American Patients)

1. Cognitive impairment
2. Proximal renal tubule acidosis
3. Leigh-type necrotizing encephalopathy
4. Episodes of lactic acidosis
5. Developmental delay
6. Muscle hypotonia
7. Some patients with clonus or athetosis

French Form

1. Neonatal and congenital lactic acidosis
2. Cognitive impairment
3. Macrocephaly
4. More severe phenotypes than the North American form
5. Hepatomegaly

Benign Form

1. Normal motor and cognitive abilities
2. Episodes of metabolic acidosis
3. Mild cognitive impairment (in 1 patient)

Neuropathology

1. Necropsy (North American and French forms):
 - a. Severe ischemic brain lesions (2 patients) associated with periventricular leukomalacia
 - b. Periventricular cysts and diffuse hypomyelination

Laboratory Evaluation

1. Severe forms Type A and B:
 - a. Increased plasma lactate pyruvate, glutamic acid, proline and alanine
 - b. Low pyruvate carboxylase activity in skin fibroblasts
2. French form:
 - a. Hyperammonemia
 - b. Lysinemia
 - c. Citrullinemia
3. Benign form:
 - a. Metabolic acidosis with elevated lactate, pyruvate, alanine, beta-hydroxybutyrate, acetoacetate
4. MRI (Type A and B):
 - a. Periventricular leukomalacia and cysts
 - b. Stroke-like lesions (2 patients)

Pyruvate Dehydrogenase (E-1 Alpha Deficiency (PDHAD))

General Characteristics

1. PDHAD is caused by mutations in the PDHAD gene that is localized to chromosome Xq 22.12
2. Mutations in the E-1 alpha-subunit gene are the most common but PDH deficiency is also caused by mutations in genes coding for other subunits of the PDH complex and include:
 - a. PDHX gene (11p)
 - b. PDHB gene (3p)
 - c. DLAT gene (11q)
 - d. PDP1 gene (11q)
 - e. LIAS gene (4p14)
3. Components of the PDH complex are:
 - a. Pyruvate decarboxylase (E-1)
 - b. Dihydrolipoyl transacetylase (E2)
 - c. Dihydrolipoyl dehydrogenase (E3)
4. There are two regulatory enzymes of the complex:
 - a. Pyruvate dehydrogenase kinase
 - b. Pyruvate dehydrogenase phosphatase

Clinical Manifestations

1. There are two major clinical presentations of PDH deficiency:
 - a. Metabolic:
 - i. Severe lactic acidosis of the newborn with mortality
2. Neurologic manifestations:
 - a. Intermittent ataxias
 - b. Intermittent movement disorders
 - c. Clinical neurologic manifestations depend on the severity of the deficit and not on the subunit or enzyme that is deficient
3. Presentation at birth with:
 - a. Psychomotor retardation
 - b. Progressive encephalopathy
 - c. Seizures
 - d. Generalized hypotonia
 - e. Metabolic and lactic acidosis
 - f. Rapid respiration
 - g. Facial dysmorphisms
 - h. Ataxia

Neuropathology

1. Necropsy of a 50 year old patient:
 - a. Cerebellar degeneration
 - b. Necrosis around the IIIrd ventricle and aqueduct similar to that seen in Leigh's or Wernicke's encephalopathy
2. Structural changes in children:
 - a. Cerebral atrophy
 - b. Cystic lesions of the cortex, basal ganglia and brain stem; lesions similar to Leigh's disease

Laboratory Evaluation

1. Metabolic acidosis (newborns)

2. Elevated blood and CSF lactate and pyruvate levels
3. Identification of specific subunit mutations in mitochondrial fractions
4. Increased lactate, pyruvate and alanine can be determined in the urine
5. If there is decreased dihydrolipoyl dehydrogenase activity (CE3):
 - a. Increased blood levels of branch chain amino acids and α -ketoglutarate

Mitochondrial Importation Defects

General Characteristics

1. Transport of nuclearly encoded proteins from the cytoplasm into mitochondria:
 - a. Targeted to different intramitochondrial compartments
2. Defects of translocation steps:
 - a. Address signals:
 - i. Amino terminal leader peptides
 - ii. Cytoplasmic heat shock proteins
 - iii. Peptide transport proteins
 - iv. Leader-peptide receptor interaction at the mitochondrial membrane
 - v. Energy dependent translocation through the mitochondrial membrane
 - vi. Intramitochondrial cleavage of leader peptides by peptidases

Clinical Manifestations

1. Infantile encephalopathy, lactic acidosis, defective heat shock proteins
2. Methylmalonic aciduria:
 - a. Mutation that causes defective methylmalonic CoA-mutase:
 - i. Defective leader peptide
 - ii. Inability to enter the mitochondrion
3. Friedreich's ataxia:
 - a. Trinucleotide expansion of intron 9 on chromosome 9q21.11
 - b. Defective encoded protein is frataxin
4. Loss of regulation of iron transport into the mitochondrion
5. Dysfunction of enzymes that contain iron sulfur subunits:
 - a. Aconitase
 - b. Complex I, II, III
6. Paraplegia (spastic):
 - a. Chromosome 16q
 - b. AR
 - c. Regulation of metalloproteinase
7. Reye's syndrome:
 - a. Putative defect of translocation associated with multiple mitochondrial enzyme dysfunction

Neuropathology

1. Dependent on the specific disorder

Laboratory Evaluation

1. Dependent on the specific disorder

Inflammatory Myopathies

Diagnostic Criteria for Dermatomyositis

1. Clinical inclusion criteria:
 - a. Onset in childhood or adulthood
 - b. Subacute or insidious onset
 - c. Symmetric proximal weakness:
 - i. Legs > arms
 - ii. Neck flexors > neck extensors
 - d. Rash:
 - i. Heliotrope
 - ii. Gottron's papules
 - iii. V-sign
 - iv. Shawl sign
 - v. Holster sign
2. Exclusion criteria:
 - a. Oculomotor involvement
 - b. Isolated dysarthria
 - c. Neck extensor > neck flexor weakness
3. Muscle biopsy:
 - a. Perifascicular atrophy (definite DM)
 - b. Probable DM:
 - i. Myxovirus resistance 1 protein (or other type 1 interferon regulated proteins) that are deposited in small blood vessels or muscle fibers
 - ii. MAC deposition on small blood vessels
 - iii. Tubuloreticular inclusions in endothelial walls by electron microscopy
 - iv. MHC-1 expression of perifascicular fibers
 - v. Perifascicular, perineurial inflammatory cell infiltrate
4. Amyopathic DM criteria:
 - a. No subjective or objective muscle weakness
 - b. Normal serum CK
 - c. Normal EMG
 - d. Typical DM rash
 - e. Skin biopsy:
 - i. Reduced capillary density, deposition of MAC on small blood vessels at the dermal-epidermal junction
5. Dermatomyositis without rash
 - a. Clinical criteria for DM but without a rash
 - b. Muscle biopsy:
 - i. Perifascicular atrophy
 - ii. MAC deposition on small blood vessels or muscle fibers
 - iii. Reduced capillary density
 - iv. Electron microscopy:
 1. Tubuloreticular inclusions in endothelial cell walls
 - v. MHC-1 expression of perifascicular fibers
 - c. Elevated CK plus one other laboratory criterion for DM that includes myositis antibodies
6. Non-specific myositis:

a. Clinical Manifestations

i. Inclusion criteria:

1. Onset in childhood or adulthood
2. Subacute or insidious onset
3. Symmetrical proximal > distal weakness

ii. Exclusion criteria:

1. Rash typical of DM
2. Clinical features of IBM
3. Extraocular muscle involvement
4. Isolated dysarthria
5. Neck extensor weakness > than flexor
6. Allergies to myotoxic drugs
7. Endocrinopathy
8. Amyloidosis
9. SMA
10. Dystrophies

iii. Muscle biopsy:

1. Perivascular, perimysial inflammatory cell infiltrate but without perifascicular atrophy, perifascicular MHC-1 expression, MAC deposition on small blood vessels, reduced capillary density and no tubuloreticular inclusions
2. There may be scattered endomysial CD8+ T-cells infiltration which does not surround or invade muscle fibers
3. Exclusion of:
 - a. Necrotizing myopathies
 - b. Dystrophies
 - c. IBM

iv. Elevated CK

v. One of three other laboratory criteria:

1. Myositis – specific antibodies
2. Skeletal muscle MRI
3. Positive EMG criteria for myositis

Immune-Mediated Necrotizing Myopathy

1. Inclusion criteria:

- a. Onset usually after 18 years of age
- b. Subacute or insidious onset
- c. Symmetrical proximal > distal weakness

2. Exclusion criteria:

- a. Typical DM rash
- b. Clinical exclusion criteria of PM

3. Muscle biopsy:

- a. Predominance of necrotic muscle fibers
- b. Minimal inflammatory cell response with slight perivascular perimysial infiltrate
- c. MAC deposition on small blood vessels
- d. Rare tubuloreticular inclusions in endothelial cells
- e. Electron microscopy:
 - i. Pipestem capillaries
- f. No mononuclear inflammatory cell invasion of non-necrotic fibers
- g. No perifascicular atrophy

4. Serum CK is elevated

5. One laboratory criteria (EMG, skeletal MRI or myositis-specific antibodies)

Differential Diagnosis of Dermatomyositis

1. Polymyositis
2. Amyopathic DM
3. DM size dermatitis (solitary)
4. Non-specific myositis
5. Immune-mediated myopathy
6. Necrotizing myopathy
7. Muscular dystrophies
8. IBM
9. Active endocrinopathies:
 - a. Hyper- or hypothyroidism
 - b. Hyperparathyroidism
10. Myotoxic drugs
11. Amyloidosis
12. Spinomuscular atrophy (SMA)

Diagnostic Criteria for Polymyositis

1. Clinical Manifestations

a. Inclusion criteria:

- i. Onset most often after 18 years of age
- ii. Subacute or insidious
- iii. Symmetric proximal > distal weakness

b. Exclusion criteria:

- i. Clinical features of IBM that include
 1. Asymmetric weakness
 2. Wrist and finger flexor weakness equal to or worse than that demonstrated in the deltoids, knee extensors and/or ankle dorsi flexors; same or greater weakness in hip flexors
 3. Extraocular muscle weakness, isolated dysarthria, neck extensor > than neck flexor weakness
 4. Exposure to myotoxic drugs, active endocrinopathy that affects muscle, amyloidosis, and a family history of muscular dystrophy or proximal motor neuropathies (SMA)

2. Elevated creatine kinase in the serum

3. One of three positive laboratory studies:

a. EMG:

i. Inclusion criteria:

1. Increased insertional and spontaneous activity
2. Short duration, small amplitude, polyphasic MUAPs

ii. Exclusion criteria:

1. Prominent myotonic discharge consistent with proximal myotonic dystrophy or other channelopathy
2. Long duration, large amplitude MUAPs
3. Decreased recruitment MUAP pattern

b. Skeletal muscle MRI:

- i. Diffuse or patchy increased signal (edema) within muscle tissue or STIR images

c. Myositis specific antibodies in the serum

4. Muscle biopsy:

- a. Endomysial inflammatory cell infiltrate (T-cells) that surround and invade non-necrotic muscle fibers

- b. Exclusion criteria:
 - i. Rimmed vacuoles, ragged red fibers, cytochrome oxidase-negative fibers (supportive of IBM)
 - ii. Perifascicular atrophy, deposition of MAC on small blood vessels, reduced capillary density tuboreticular inclusions in endothelial cells; pipestem capillaries (support DM or another form of humorally mediated microangiopathy)
 - iii. Dystrophic features or MAC deposition

Differential Diagnosis of Polymyositis

1. IBM
2. Dermatomyositis
3. An immune-mediated necrotizing myopathy
4. Infectious inflammatory myopathy
 - a. HIV
 - b. HTLV-1
 - c. Hepatitis B and C
5. Metabolic myopathies with rhabdomyolysis
6. Muscular dystrophies:
 - a. Facioscapulohumeral
 - b. Congenital
 - c. Dysferlinopathies
 - d. Limb girdle dystrophies
7. Myotonic dystrophy type 2
8. Amyloid myopathy:
 - a. Light chain
 - b. Familial
9. Endocrine myopathies:
 - a. Hypo- and hyperthyroidism
 - b. Hyperparathyroidism
 - c. Diabetic muscle infarction
10. Drug-induced myopathies
 - a. Statins and other cholesterol lowering agents
 - b. Cyclosporine
 - c. Chloroquine
 - d. Amiodarone
 - e. Colchicine
 - f. D-penicillamine
 - g. Cocaine
11. Juvenile or adult-onset spinal muscular atrophy
12. Kennedy's disease
13. Polymyalgia rheumatica
14. Mixed connective tissue disease (MCT)

Diagnostic Criteria for Inclusion Body Myositis

1. Clinical inclusion criteria:
 - a. Duration of illness > 6 months
 - b. Age of onset > 30 years
 - c. Muscle weakness is predominant in the proximal and distal muscles of the arms and legs; patients must have at least one of the following manifestations:
 - i. Finger flexor weakness
 - ii. Wrist flexor > wrist extensor weakness
 - iii. Quadriceps muscle weakness

Laboratory Evaluation

1. Serum creatine kinase < 12 times normal
 - a. Inflammatory myopathy in which there is mononuclear cell invasion of non-necrotic muscle fibers
- b. Vacuolated muscle fibers:
 - i. Intracellular amyloid deposits
 - ii. 15-18-nm tubulofilaments are identified with electron microscopy
- c. EMG:
 - i. Consistent with features of an inflammatory myopathy (long-duration potentials are allowed)
- d. Family history:
 - i. Rarely IBM is observed in families
 - ii. Familial IBM requires:
 - a. Documentation of mononuclear inflammatory cells that invade non-necrotic muscle fibers
 - b. Vacuolated muscle fibers and intracellular amyloid deposits on 15-18-nm tubulofilaments
- e. Associated disorders; usually immune-mediated
- f. Definite IBM:
 - i. A definitive diagnosis of IBM can be made if patient's muscle biopsy has all of the features of IBM that include:
 - a. Invasion of non-necrotic muscle fibers by mononuclear cells
 - b. Vacuolated muscle fibers
 - c. Intracellular amyloid deposits or 15-18 tubulofilaments

Differential Diagnosis of Inclusion Body Myositis

1. PM
2. ALS
3. Hereditary inclusion body myopathy
4. LGMD-1A (myotilinopathy)
5. LGMD-2
6. Welander distal myopathy

Diagnostic Criteria for Non-Specific Myositis

1. Clinical Manifestations
 - a. Inclusion criteria:
 - i. Onset in childhood and adulthood
 - ii. Subacute or insidious onset
 - iii. Proximal > distal weakness
 - b. Exclusion criteria:
 - i. DM rash
 - ii. Similar to those for DM
2. Muscle biopsy:
 - a. Perivascular and perimysial inflammatory cell infiltrate without
 - i. Perifascicular atrophy
 - ii. Perifascicular MHC-1 expression
 - iii. MAC deposition in small blood vessels
 - iv. Reduced capillary density
 - v. Tubuloreticular inclusions in EM

- b. A scattered endomysial CD8+ T-cell infiltrate may be present but does not:
 - i. Surround or invade non-necrotic muscle fibers
- c. Requires exclusion of:
 - i. Necrotizing myopathy
 - ii. IBM
 - iii. Dystrophies
- 3. Elevated serum CK
- 4. One corroborating laboratory test:
 - a. EMG
 - b. Skeletal muscle MRI
 - c. Myositis specific antibodies

Differential Diagnosis of Non-Specific Myositis

- 1. PM
- 2. DM (dermatomyositis)
- 3. IBM
- 4. Muscular dystrophy
- 5. Necrotizing myopathy

Diagnostic Criteria for Immune-Mediated Necrotizing Myopathy

Clinical Manifestations

- 1. Inclusion criteria
 - a. Onset over 18 years of age
 - b. Subacute or insidious onset
 - c. Symmetric proximal > distal weakness
- 2. Exclusion criteria
 - a. Rash
 - b. Similar to those for PM

Laboratory Evaluation

- 1. Muscle biopsy:
 - a. Multiple necrotic muscle fibers
 - b. A perimysial infiltrate
 - c. Few perivascular inflammatory cells
 - d. MAC deposition on small blood vessels
 - e. No mononuclear cell invasion of non-necrotic muscle fibers
 - f. No perifascicular atrophy
 - g. Electron microscopy:
 - i. Rare or absent tubuloreticular endothelial cell inclusions
 - ii. Pipestem capillaries
- 2. Elevated serum CK
- 3. One of three corroborating laboratory criteria (EMG, muscle MRI and myositis-specific antibodies)

Differential Diagnosis of Non-Specific Myositis

- 1. DM
- 2. PM
- 3. IBM
- 4. Toxic myopathies

- 5. Endocrine myopathies
- 6. Infectious myopathies
- 7. Amyloidotic myopathy
- 8. Congenital myopathies
- 9. Mitochondrial myopathies
- 10. Dystrophies
- 11. Proximal neuropathies
- 12. Proximal myotonic dystrophy

Neural Disorders of Skeletal Muscle Overactivity

Overview of Cramps and Fasciculations

A muscle cramp is a sudden involuntary and painful contraction of the whole or part of a muscle. It terminates within seconds to minutes and is frequently associated with a palpable lump in the muscle. The exact etiology of cramps has not been defined, but it is clear that they occur from either peripheral or central mechanisms. Cramps may be elicited from hyperexcitability of motor neurons that are elicited by afferent input. Support for this mechanism includes:

- 1. The triceps surae H-reflex is enhanced after a cramp of the homologous muscle
- 2. Voluntary contraction of antagonistic muscles contralateral to the cramping muscle induces reciprocal inhibition or cross-reflex effects which modify the EMG findings associated with cramps. Spinal involvement in cramp generation is further supported by the finding that cramp generated EMG and voluntary EMG are both inhibited by stimulation of tendon afferents

Support for the peripheral generation of cramps is that it has been demonstrated that they can be elicited by electrical stimulation distal to a peripheral nerve block which may be the result of spontaneous motor nerve discharges or abnormal excitability of the terminal branches of motor axons. Cramps may be preceded and followed by fasciculations which are thought to originate primarily from the terminal portions of motor axons. Cramps can be elicited with or without proximal nerve block.

Those elicited during nerve block in healthy subjects:

- 1. Require greater stimulus frequency
 - 2. Last for a shorter interval
 - 3. Demonstrate different motor unit characteristics
- This evidence demonstrates spinal involvement in both the origin and maintenance of cramps.

Another recent pathophysiological mechanism suggested to explain cramps is that increased afferent muscle spindle activity occurs with decreased inhibition from the golgi tendon organ which causes an increase in alpha motor neuron discharge. The firing frequencies are comparable to those seen during normal voluntary contractions. Muscle cramps most often occur at short muscle lengths and are relieved by muscle stretch. In shortened muscle, the inhibition of the golgi tendon organ is depressed at the same time there is a lowered excitation threshold at motor end plates.

Fasciculations are random spontaneous discharges of all muscle fibers of a given motor unit. They are most often benign when confined to a simple muscle and when they occur in isolation. Fasciculation potentials are the electrodiagnostic correlate of fasciculations. They are ominous if widespread and associated with atrophy and weakness. Most fasciculations originate distally in the motor nerve in both normal subjects and patients with motor neuron disease.

Cramps

General Characteristics

1. A muscle cramp is a sudden involuntary and painful contraction of a muscle (or part of one) with visible and palpable muscle hardening. There may be associated abnormal position of joints. They may be acutely relieved by massage or stretching. They usually spontaneously extinguish within seconds or minutes
2. Their estimated prevalence on a weekly basis is 35% of a normal population

Clinical Manifestations

1. Cramps occur with greater frequency in the elderly, during pregnancy and those who do not exercise
2. Gastrocnemius soleus complex muscle is the most commonly involved, particularly at night in the elderly
3. Cramps are most often associated with benign processes. They portend a serious neuromuscular disorder if accompanied by weakness, atrophy or are elicited with muscle activity
4. They may occur with disease at any level of the motor unit

Neuropathology

1. ALS and other motor neuron diseases including Kennedy's disease and SMAD
2. Toxic myopathies
3. Metabolic disorders that include:
 - a. Carbohydrate
 - b. Lipid
 - c. Mitochondrial
 - d. Purine
 - e. X-linked Becker's muscular dystrophy

Laboratory Evaluation

1. Specific to the underlying pathology
2. Persistent cramps may cause an elevation of CK in the serum that lasts for 3–8 days
3. EMG:
 - a. A physiologic contraction is associated with muscle shortening and electrical silence
 - b. A cramp discharge:
 - i. Involuntary discharge of multiple normal different action potentials
 - ii. Fasciculations:
 - a. Simple, random and spontaneous discharges of normal appearing but different motor unit action potentials

Cramp-Fasciculation Syndrome

General Characteristics

1. Clinical features occur most often in healthy subjects but can be disabling

Clinical Manifestations

1. Myalgias
2. Stiffness
3. Cramps
4. Myokymia
5. Fasciculations
6. Exercise intolerance

Neuropathology

1. Antibodies to potassium channels have been reported in some patients
2. Possible limited form of neuromyotonia
3. Some patients have neurogenic features in muscle biopsy

Laboratory Evaluations

1. Persistent cramps can cause an elevation of serum CK
2. EMG:
 - a. Cramp discharges
 - b. Fasciculation potentials
 - c. Repetitive stimulation of peripheral nerves:
 - i. After discharges in some patients similar to Isaacs' syndrome

Isaacs' Syndrome

General Characteristics

1. The syndrome is frequently referred to as that of continuous muscle fiber activity or generalized myokymia
2. Most often it is sporadic; some families with AD inheritances

Clinical Manifestations

1. Diffuse muscle stiffness
2. Widespread and continuous myokymia and cramps
3. Abnormal postures include:
 - a. Carpopedal spasm (rare)
 - b. Plantar flexion of the foot
 - c. Exaggerated lordosis
 - d. Facial grimacing
 - e. Flexion of the elbows, wrists, hips and knees
4. Distal > axial and proximal muscles are affected
5. Abnormal movements may persist during sleep
6. Increased muscular activity may be focal
7. Muscle stiffness increases with activity
8. Pseudomyotonia may be prominent (difficulty relaxing muscles after maximal contraction)
9. Physical Examination
 - a. Slight trunk flexion, shoulder abduction and elevation with elbow flexion

- b. Prominent myokymia is apparent in the face, pectoral and calf muscles after muscle contraction
- c. Sensation is normal
- d. Muscle stretch reflexes are normal or depressed
- e. Chvostek's and Trousseau's signs are present

Neuropathology

1. Primarily an autoimmune but occasionally a paraneoplastic disorder
2. Voltage gated potassium channel antibodies are primarily directed against associated proteins that complex with the VGKC rather than the channels themselves
3. Isaacs' syndrome has been reported with:
 - a. Small cell carcinoma of the lung
 - b. Thymoma
 - c. Plasmacytoma
 - d. Hodgkin's disease
4. Sural nerve biopsy:
 - a. Normal or a reduction of myelinated fibers

Laboratory Evaluation

1. Radioimmunoassay may detect antibodies directed against VGKC complexes in both the serum and CSF
2. Associated autoimmune markers include:
 - a. Immunoglobulins
 - b. Oligoclonal bands in the CSF
3. EMG:
 - a. Usually the motor and sensory NCS are normal in both the idiopathic and familial forms of the disease although there may be a polyneuropathy in some patients
 - b. Repetitive after-discharges are noticed both with standard EMG recordings and by microneurographic studies in both motor and sensory nerves
 - c. Neuromyotonic discharges are prominent in skeletal, facial and extraocular muscles. They are high frequency (200–300 Hz) and not self-sustaining
 - d. Frequent myokymic discharges are noted:
 - i. Grouped discharges of a single motor unit that occur spontaneously in bursts
 - ii. There are intervening periods of electrical silence
 - e. Neuromyotonic discharges are characterized by:
 - i. Interpotential intervals of 2–5 milliseconds
 - ii. Interburst frequencies of > 150 Hz to 500 Hz which may be triggered by exercise, muscle movement, limb ischemia or mechanical nerve stimulation. They have abrupt onset and offset
 - f. Isaacs' syndrome may demonstrate combinations of individual or grouped discharges that include
 - i. Fasciculation potentials
 - ii. Doublet and triplet discharges
 - iii. Multiplex and complex repetitive discharges
 - iv. Myokymic and nerve myotonic discharges
 - g. Experimental studies support neuromyotonic discharges as originating in the terminal nerve arborization

- h. In some patients there has been a reduction of abnormal muscular activity that suggests:
 - i. The existence of impulse generators in both the peripheral and central nervous systems
- i. Differential diagnosis of neuromyotonic discharges
 - i. Myasthenia gravis
 - ii. Amyloidosis
 - iii. CIDP
 - iv. Graft-versus-host disease
 - v. Radiation therapy
 - vi. Hereditary neuropathies
 - vii. Pontine demyelination (most often glioma; associated myokymia around the orbit)
 - viii. Rattle snake envenomation (may be very long lasting)
 - ix. ALS
 - x. Penicillamine treatment
- j. Both myokymia and neuromyotonic discharges have been reported in patients with antibodies to VGKC complexes

Morvan's Syndrome

General Characteristics

1. Morvan's syndrome is primarily neuromyotonia with an associated encephalopathy

Clinical Manifestations

1. Hallucinations, confusion and insomnia
2. Respiratory muscle involvement with dyspnea
3. Hoarseness and dysphagia
4. Hyperhidrosis
5. Loss of weight
6. Ocular neuromyotonia that causes diplopia
7. Numbness and paresthesia
 - a. Overactive sensory nerves
 - b. Associated sensory neuropathy

Neuropathology

1. CASPR2 (Contactin-associated protein-2) complex
 - a. Primarily involved in the hippocampus and paranodally at the node of Ranvier in peripheral nerves

Laboratory Evaluation

1. CASPR2 antibody complex levels in the serum
2. EMG:
 - a. Neuromyotonic discharges
 - b. Continuous muscle fiber activity
 - c. Myokymia

Satoyoshi Syndrome

General Characteristics

1. Most patients are Japanese but the systemic disorder has a worldwide distribution

Clinical Manifestations

1. Onset in adolescence

2. Female predominance
3. Painful muscle spasms of the extremities, usually the legs, that progressively involves the trunk, neck and muscles of mastication
4. The spasms last for a few minutes then recur often
5. Distortion of posture
6. Alopecia
7. Diarrhea
8. Growth retardation
9. Endocrine dysfunction
10. Amenorrhea:
 - a. Hypogonadotropic hypogonadism from primary ovarian failure (in some patients)
11. Skeletal defects (secondary to spasms)
12. May occur in adults

Neuropathology

1. Presumed to be immunologically mediated
2. Skin biopsy (one patient) in an area of hyperpigmentation demonstrated lymphocytic infiltration

Laboratory Evaluation

1. Anti-acetylcholine, anti-GAD as well as anti-nuclear antibodies have been reported in isolated patients
2. Female sex hormones are low and gonadotrophins are elevated in post-pubescent young women
3. Mildly elevated serum CK levels
4. EMG (surface recordings during involuntary contractions)
 - a. High amplitude, synchronous motor unit discharges that are widespread throughout the muscle
5. Hyperexcitability of the H-reflex (one patient) that suggests the spinal cord as the origin of spasms

Stiff Person Syndrome

General Characteristics

1. A heterogeneous syndrome that is thought to be due to dysfunction of inhibitory synaptic transmission of motor neurons in the brainstem and spinal cord

Clinical Manifestations

1. The onset is most often in middle age with lower axial muscle involvement
2. Patients note the insidious onset of muscle stiffness associated with painful spasms that are triggered by movement, touch, emotional and auditory stimuli
3. The rigidity and spasms concomitantly affect both agonist and antagonist muscles
4. Spasms are relieved by general anesthesia, neuromuscular blockade and sleep
5. Dysautonomic features are seen during episodes of severe spasms and include:
 - a. Diaphoresis
 - b. Hypertension

- c. Tachycardia
- d. Tachypnea and pupillary dilation
6. Paraspinal and abdominal muscle contraction cause hyperlordosis
7. Spasms may be severe enough to break bones, dislocate joints and produce opisthotonus
8. Facial and oculomotor involvement may occur
9. Stiff person syndrome (SPS) – plus (stiff person subtypes) includes:
 - a. Stiff-limb form in which the disorder is limited to the lower extremities
 - b. Jerking stiff-person syndrome that is manifested by chronically progressive stiffness and myoclonus
 - c. Acute onset and progressive encephalomyelitis with rigidity and myoclonus (PERM). It's associated manifestations include:
 - i. Myoclonus
 - ii. Nystagmus
 - iii. Opsoclonus
 - iv. Dysarthria
 - v. Dysphagia
 - vi. Corticospinal tract signs
 - vii. Seizures
10. Associations of SPS:
 - a. Approximately 5% of patients have an underlying malignancy that include Hodgkin's disease, thymoma, breast, colon and small cell cancer of the lung
 - b. There is an increased incidence of other immune-mediated disorders which is particularly high in patients with GAD antibodies
 - c. The comorbidities may occur in 80% of patients and include:
 - i. Encephalomyelitis with seizures, cerebellar syndrome and myasthenia gravis
 - ii. Hypo- and hyperthyroidism
 - iii. Pernicious anemia
 - iv. Celiac disease
 - v. Systemic lupus erythematosus
 - vi. Adrenal insufficiency
 - vii. Ovarian failure
 - viii. Vitiligo
 - ix. Diabetes mellitus (may occur in up to 70% of patients)

Neuropathology

1. Most patients with SPS have antibodies directed against glutamic acid decarboxylase, the rate-limiting enzyme in the production of γ -amino butyric acid (GABA)
2. Antibodies against glycine γ 1 receptor and GABA receptor-associated protein have also been detected
3. Anti-GAD65 antibodies are frequently detected in type 1 diabetes that is associated with SPS in 30–40% of patients
4. Anti-amphiphysin antibodies are seen in breast cancer, thymoma, small cell cancer of the lung and ovarian cancer

- a. Amphiphysin is a membrane protein that functions in synaptic vesicle endocytosis
- b. Amphiphysin and GAD are located in the cytosolic surface of synaptic vesicles in nerve terminals that are identified targets in CNS autoimmunity
- c. Experimental antibody transfer models support the association of amphiphysin and SPS
- d. Autopsy evaluation:
 - i. Loss of anterior horn cells and interneurons
 - ii. Loss of both small alpha and gamma motor neurons in the spinal cord
 - iii. In the encephalomyelitic subtype:
 1. Perivascular inflammation in the spinal cord, brainstem and brain

Laboratory Evaluation

1. Serum and CSF antibodies that include:
 - a. GAD-65 (possibly 90% of patients with classic SPS)
 - i. These antibodies have also been detected in:
 1. Cerebellar syndromes
 2. Palatal myoclonus
 3. Epilepsy
 4. Ceroid lipofuscinosis
2. Patients with breast cancer:
 - a. Antibodies to 128KD protein amphiphysin consolized to synapses
3. Patients with SPS (encephalomyelitic type) with Opso-clonus:
 - a. Anti-Ri antibodies
4. Antibodies against gephyrin:
 - a. Gephyrin is a protein associated with receptors for glycine and GABA
5. Oligoclonal bands occur in the CSF
6. EMG:
 - a. Routine nerve conduction in studies are normal
 - b. In symptomatic muscles:
 - i. Spontaneous discharge of normal MUAPs which also occur in the antagonist muscle; both discharge spontaneously and concomitantly
 - ii. There should be no myotonic, myokymic or neuromyotonic discharges
 - iii. Vibration induced inhibition of the H-reflexes (GABA-ergic) may be abnormal
 - iv. Enhanced blink reflex
 - v. Increased and widespread response to the startle reflex

Tetanus

General Characteristics

1. Tetanus is decreasing both in industrial nations and in the developing world
2. The World Health Organization estimated that there has been a 93% decrease in newborn fatality from the late 1980's to 2010

3. Tetanus is caused by the obligatory anaerobic Gram-positive bacillus clostridium tetani
4. The threat is still extant among farm workers and intravenous drug addicted patients

Clinical Manifestations

1. The disease is most often associated with a penetrating wound that inoculates the anaerobic organism
2. The usual incubation period is eight days but may be as long as two months; the majority of patients become symptomatic within 30 days of exposure
3. Disease progression is usually 10–14 days; a shorter duration portends severe disease; recovery begins within one month
4. Clinical symptomatology depends upon:
 - a. The site of the wound
 - b. The patient's immunization status
 - c. The extent of toxin spread
5. In generalized tetanus, the initial symptoms include
 - a. Irritability
 - b. Akathisia
 - c. Diaphoresis
 - d. Tachycardia
6. The predominant sign and symptom of tetanus is painful muscle stiffness:
 - a. Onset is often in the paraspinal and masseter muscles ("trismus")
 - b. Facial muscle involvement causes "risus sardonicus"
 - c. Masseter spasm may be triggered from mechanical stimulus of the posterior pharyngeal wall
 - d. The order of muscle involvement is usually cranial, trunk and lastly, extremities
 - e. Tetanus may remain local, affecting muscles proximal to the site of injury ("cephalic tetanus")
 - f. Generalized tetanus involves both the abdominal and paraspinal muscles which may cause respiratory insufficiency
 - g. Opisthotonus may occur in severe patients which is extremely mechanical, emotional and sensory sensitive
 - h. Spasm of bulbar musculature causes dysarthria, dysphagia and laryngospasm
 - i. Dysautonomia is manifest by hypertensive episodes, cardiac arrhythmia, sialorrhea and hyperhidrosis
 - j. Fever
 - k. Alteration of consciousness may occur from hypoxia
 1. Local tetanus may occur from anaerobic infections in the middle ear, paranasal sinuses that cause trismus and cranial nerve dysfunction
 - m. Uterine tetanus may occur from non-hygienic abortion

Neonatal Tetanus

1. Primarily seen in developing countries from umbilical stump infection, whose mother was not immunized
2. Symptoms occur within the first two weeks of life that manifest as poor suck and muscle twitching
3. Cranial nerve involvement may be prominent

Neuropathology

1. Portals of entry in patients that have acquired tetanus from *C. tetani* most often are:
 - a. Contaminated puncture wounds
 - b. Parental drug abuse
 - c. Septic abortion
 - d. Compound fractures
2. Clinical manifestations are due to the release of tetanus toxin
 - a. It may be diffused locally where it binds to peripheral nerve terminals and is retrogradely transported in motor nerves to the CNS. It may also spread hematogenously
 - b. Trans-synaptic migration occurs from the perikaryon of the motor nerves to presynaptic terminals where the toxin binds irreversibly to the presynaptic inhibitory interneurons in the brainstem and spinal cord
 - c. The toxin inhibits GABA in the brainstem and glycine in the spinal cord which disinhibits anterior horn cells both from sensory stimuli and descending motor tracts
 - d. The intermediolateral column of the sympathetic nervous system is similarly disinhibited

Laboratory Evaluation

1. *Clostridium tetani* can be cultured from wounds in approximately 1/3 of patients
2. There may be elevated CSF protein and immunoglobulin
3. EMG:
 - a. Continuous discharge of motor units with normal morphology in agonist and antagonist muscles
4. Secondary complications include:
 - a. Inappropriate secretion of ADH
 - b. Renal failure
 - c. Rhabdomyolysis with myoglobinuria

Differential Diagnosis of Skeletal Muscle Overactivity

1. Tetany
 - a. Decreased serum ionized calcium with or without a decreased serum 24 hydroxyvitamin D levels
 - b. Tetany induced by hyperventilation:
 - i. Decreased PCO₂ and elevated pH (respiratory alkalosis)
 - c. Chvostek's and Trousseau's signs are prominent
 - d. EMG demonstrates spontaneous grouped discharges of normal MUAPs that constitute doublets, triplets and multiplets
2. Trismus
 - a. Dental trauma or infection
 - b. Paraneoplastic or inflammatory causes of brain stem encephalitis
3. Drug-induced dystopia
 - a. Oculogyric crises
 - b. Writhing rather than tonic movements
4. Hyperekplexia

a. General Characteristics

- i. Hyperekplexia may be caused by heterozygous, homozygous, or compound heterozygous mutations in the GLRA1 gene that localizes to chromosome 5q32
- ii. Hyperekplexia may be caused by heterozygous, homozygous or compound heterozygous mutations in the GLRA1 gene that localizes to chromosome 5q32
- iii. It has also been described in association with autoimmune encephalomyelitis

b. Clinical Manifestations

- i. Genetic forms often have a neonatal onset
- ii. Exaggerated startle response to sudden unanticipated auditory or tactile stimuli
- iii. Patients have brief episodes of intense generalized hypertonia in response to stimulation
- iv. Adults may experience drop attacks
- v. Neonates may suffer impaired swallowing and breathing

c. Neuropathology

- i. In AD patients there is defective alpha-1 subunit of the glycine receptor
- ii. AR disorders have defective beta subunits of the glycine receptor
- iii. Non-familial patients demonstrate the pathology of the underlying illness which is usually an autoimmune-mediated encephalomyelitis such as PERM

d. Laboratory Evaluation

- i. Glycine receptor antibodies in PERM and related syndromes
- ii. Genetic testing in familial patients for mutations in the GLRA1 and GLBR genes

5. Meningoencephalitis:

- a. Muscle and paraspinal rigidity
- b. Seizures
- c. Altered mental status
- d. Diagnostic CSF studies

6. Metabolic muscle disease:

- a. No involvement of cranial nerve or paraspinal muscles
- b. Electrically silent EMG of a rigid muscle

7. Multiple sclerosis

- a. Most often confused with stiff person syndrome
- b. SPS upper and lower motor nerve findings
- c. Diagnostic MRI for MS; SPS has little pathology on brain and spinal cord imaging

8. Neuroleptic malignant syndrome:

- a. Severe metabolic acidosis
- b. History of exposure to phenothiazine or butyrophenones
- c. Dysautonomic features
- d. High CK
- e. Fever and altered mental status

9. Rabies

- a. Possibly confused with cephalic tetanus
 - b. Severe bulbar involvement
 - c. Altered mental status
 - d. Lymphocytic pleocytosis of the CSF
 - e. Dysautonomic involvement (cholinergic)
10. Abdominal tetanus:
- a. Setting of possible peritonitis
 - b. More often umbilical stump infection of neonates
11. Strychnine:
- a. Rat poison and adulterant in i.v. heroin abuse
 - b. CNS glycine antagonist
 - c. Similar to tetanus although there is no trismus
 - d. Reflex spasms are superimposed on tonic rigidity
 - e. Most often there is a clear mental status

Differential Diagnosis of Rare Disorders of Muscle Overactivity

1. Neuroleptic malignant syndrome
2. Malignant hyperthermia
3. Glycogen storage disease
4. Lipid storage disease
5. Myotonic disorders
6. Rippling muscle disease
7. Brody disease

Differential Diagnosis of Congenital Muscular Dystrophies

MDC1A

1. Laminin-X-2 chain (Merosin deficiency in chromosome 6q22-23)
2. Neck, shoulder, hip girdle weakness
3. Contractions
4. Normal intelligence
5. Seizures
6. White matter changes on MRI

Merosin-Positive Classic MDC

1. Some partial merosin deficiencies map to chromosome 1q42
2. More benign

Ullrich Disease

1. Contractions of the proximal joints
2. Hyperextensive distal joints
3. Protruberant calcanei
4. Normal intelligence

Fukuyama Congenital Muscular Dystrophy

1. Allelic to LC and 2L; fukutin (chromosome 9q31-33)
2. Proximal > distal weakness at birth
3. Calf pseudohypertrophy (50%)
4. Arthrogryposis (some children)
5. Severe brain structural abnormalities (Microcephaly, dysplasia and lissencephaly)

Walker-Warburg Syndrome

1. DONT1; (chromosome 9q3c)
2. Severe generalized weakness and hypotonia in infancy
3. Ocular malformation
4. Migrational and developmental abnormalities
5. Hypoplasia of the brain stem and veins
6. Seizures

Muscle-Eye-Brain Disease

1. POMGnT1 (chromosome 1p32)
2. MEB is less severe than WWS
3. Slow motor development
4. Eye abnormalities (glaucoma, cataracts)
5. Cognitive impairment
6. Hypoplasia of the vermis and pons; abnormalities of the midline structure

MDC1C

1. MDC1C is allelic to LGMD2I; mutation in the gene FKRP that maps to 19q13
2. Northern European ancestry
3. Onset is from infancy to the fourth decade
4. Weakness similar to MDC1A (rare WWS phenotype)
5. Early cardiac and respiratory muscle involvement

MDC1D

1. Mutation of the LARGE gene (chromosome 22q12-13.1)
2. Generalized weakness, cognitive impairment and developmental delay
3. Nystagmus (one patient)

Rigid Spine Syndrome

1. Selenoprotein (chromosome 1p35-36)
2. Rigid spine muscular dystrophy manifests in infancy
3. Hypotonia, proximal weakness and delayed milestones
4. Limited spine mobility with scoliosis and contracture of the knees and elbows
5. Respiratory involvement from rib cage restriction and diaphragm weakness
6. Similar phenotype is seen with:
 - a. EDMD
 - b. Ullrich CMD
 - c. Bethlem myopathy
 - d. Scapuloperoneal syndrome

Mutations in Genes That Produce Abnormal Glycosylation of X-Dystroglycan

1. POMT1 (9q34)
2. POMT2 (14q24)
3. POMGnT1 (1p34)

C5

1. Fukutin (9q31)
2. FKRP (19q13)
3. LARGE (22q12)

4. ISPD (7p21)
5. GTDC2 (3p22)
6. TMES (12q14.2)
7. BSGALNT2 (1q42)
8. SGK 196 (8p11)
9. B3GNT 1 (11q13)
10. GMPPB (3p21)

Congenital Muscular Dystrophy with Integrin X-7 Mutations

General Characteristics

1. Integrin X-7 (ITGA7) gene mutations that map to chromosomes 2q13.2; recessive
2. Codes for the X-7B1 integrin protein
3. X-7B1 integrin is the primary integrin in muscles

Clinical Manifestations

1. Hypotonia
2. Delayed milestones
3. Some patients walk by age 3
4. Proximal muscle weakness
5. Respiratory involvement during disease progression

Neuropathology

1. Muscle biopsy
 - a. Variation in fiber size
 - b. Decreased staining for integrin X-7
2. Laminin receptor; links the cytoskeleton to the extracellular matrix
3. Important in the formation of myotendinous function, the postsynaptic membrane and myoblast migration

Laboratory Evaluation

1. CK is mildly elevated
2. Normal brain MRI

Differential Diagnosis of Rare Congenital Muscular Dystrophies

1. Congenital MD with joint hyperlaxity
2. Congenital MD with CNS atrophy and absent large myelinated peripheral nerve axons
3. Walker-Warburg syndromes
 - a. The gene disorders generally produce abnormal glycosylation of x-dystroglycan
 - b. The systems that are affected are:
 - i. Brain
 - ii. Muscle
 - iii. Eye
 - c. Mutations in:
 - i. POMT1 (chromosome 9q34)
 - ii. POMT2 (14q24)
 - iii. POMGnT1 (1p34)
 - iv. Fukutin (9q31)
 - v. FKRP (19q13)

- vi. LARGE (22q12)
- vii. ISPD (7p21)
- viii. GTDC3 (3p22)
- ix. TMEM5 (12q14.2)
- x. B3GALNT2 (1q42)
- xi. SGK196 (8p11)
- xii. B3GNT1 (11q13)
- xiii. GMPPB (3p21)

4. Congenital muscular dystrophy with familial junctional epidermolysis bulbosa
5. Congenital muscular dystrophy with mitochondrial (megaconical) structural abnormalities
6. Congenital muscular dystrophy with early spine rigidity
7. Congenital muscular dystrophy with respiratory failure and muscular hypertrophy
8. Early-onset myopathy with areflexia, respiratory distress and dysphagia
9. Congenital muscular dystrophy with muscle hypertrophy
10. Scleroatonic muscular dystrophy (Ullrich)
11. Congenital muscular dystrophy with mental retardation and abnormal glycosylation
12. Congenital muscular dystrophy with adducted thumbs, ophthalmoplegia and mental retardation
13. Congenital muscular dystrophy and myasthenic syndrome

Differential Diagnosis of Duchenne and Becker Muscular Dystrophy

Duchenne Dystrophy

1. Weakness apparent at 2–3 years
2. Calf enlargement
3. Gowers' sign
4. Neck flexor weakness > than with Becker
5. Loss of walking by age 12
6. Severe systemic involvement

Becker Dystrophy

1. Age at onset 5–15 years
2. Milder involvement than DMD but same pattern
3. Patients survive to 30–60 years
4. Neck flexors are affected later in the course
5. May walk throughout the course
6. A few patients manifest with only myalgia, myoglobinuria and cardiomyopathy

Outliers of DMD and BMD

1. Phenotype between DMD and BMD
2. Walk after the age of 12
3. Maintain antigravity neck muscle strength

Female Carriers of DMD and BMD

1. The daughters of men with BMD and the mothers of affected children with a family history of DMD or BMD are obligate carriers
2. Usually asymptomatic
3. Manifesting carriers have a limb girdle pattern of weakness

Limb Girdle Muscular Dystrophies

1. The absence of cognitive deficit
2. Less frequent cardiomyopathy
3. Less marked calf hypertrophy
4. Autosomal dominant inheritance rules out dystrophinopathy

Limb Girdle Presentation in a Girl

1. Rule out DMD or BMD with 45XO
2. Non-random X chromosome inactivation

Acid Maltase Deficiency

1. Calf hypertrophy
2. Fibrillation tongue
3. Early cardiomyopathy

Spinal Muscular Atrophy

1. May have prominent proximal weakness in childhood
2. CK is minimally elevated
3. Neuropathic EMG

Emery-Dreifuss Muscular Dystrophy

1. AD not X-linked inheritance
2. No pseudohypertrophy
3. Early elbow and heel contractures
4. Mild CK elevation
5. Prominent early cardiac abnormalities

Unexplained Persistent Elevation of Liver Enzymes Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST)

1. May represent dystrophinopathy in:
 - a. Women who become symptomatic (DMD/BMD)
 - b. Asymptomatic carriers
2. Other dystrophies
3. CK is elevated highest of the other enzyme elevations are from muscle

Isolated Dilated Cardiomyopathy

1. Need to rule out dystrophinopathy

DMD, Glycerol Kinase Deficiency and Adrenal Hypoplasia Congenital

1. Severe psychomotor delay
2. Episodic stupor (GKL)
3. Proximal weakness from the DMD component

Muscle Cramp with Myoglobinuria*General Characteristics*

1. Female relatives of boys with DMB/BMD
 - a. Heterozygous carriers with mutated dystrophies gene
 - i. Random "X" inactivation
2. Inversions

Clinical Manifestations

1. Clinically evident weakness is seen in 2.5–10% of carriers (proximal muscles)
2. May have calf hypertrophy
3. A family with cardiomyopathy and muscle cramps without clinical weakness has been reported

Neuropathology

1. Muscle biopsy:
 - a. A mosaic of fibers with either normal or absent dystrophin
 - b. Exons 40–44 and 45–47 of the dystrophin gene may be mutated

Laboratory Evaluation

1. Approximately 70% of female carriers have elevated CK

Differential Diagnosis of Autosomal Dominant LGMD

1. LGMD1A
 - a. Myotilin (5q22.3-31.3)
 - b. Proximal weakness early or late adult life
 - c. Scapula humeral pelvic muscles
 - d. Early contracture of elbow and heel cord
 - e. Cardio myopathy
 - f. Calf hypertrophy is rare
2. LGMD1B
 - a. Lamin AC (1q11-21)
 - b. Girdle weakness of humeral peroneal muscle cramp
 - c. Cardiac conduction defects (severe)
3. LGMD1C
 - a. Caveolin-3 (3p25)
 - b. Childhood or adult onset
 - c. Proximal weakness or exertional myalgia
 - d. Calf hypertrophy
 - e. Rippling muscle disease (anterior tibial or gastrocnemius weakness)
 - f. Asymptomatic CK-emia
4. LGMD1D
 - a. Chromosome 6q23
 - b. Slowly progressive weakness
 - c. Associated cardiomyopathy
5. LGMD1E
 - a. Chromosome 7q
 - b. Onset late adult life
 - c. Dysphagia and extremity weakness
6. LGMD1F
 - a. Chromosome 7q32.1-32.2
 - b. Onset infancy to adulthood
 - c. Slowly progressive proximal muscle weakness

Differential Diagnosis of Autosomal Recessive LGMD

1. LGMD1A
 - a. Calpain-3 (chromosome 15q15.1-21.1)

- b. Onset early childhood to mid-adulthood
- c. Pelvic muscles and posterior thigh muscle early involvement; later periscapular and humeral
- d. Deltoid/brachioradialis and distal leg and supraspinati relational response
- e. Mild weakness of neck muscles
- f. Early contracture of elbow and calves
- g. Rare calf hypertrophy
- 2. LGMD2B
 - a. Dysferlin (chromosome 2p13)
 - b. Onset early teens or early 20s
 - c. Limb girdle or early involvement of the posterior calf muscles, or early anterior tibial muscles
 - d. Miyoshi phenotype with gastrocnemius/soleus weakness and atrophy
 - e. Rare rigid spine
 - f. Early loss of Achilles tendon reflex
- 3. Sarcoglycanopathies
 - a. VF-LGMD2C-V-sarcoglycan (chromosome 13q12)
 - b. LGMD2D-X-sarcoglycan (chromosome 17q12-21.3)
 - c. LGMD2E-B-sarcoglycan (chromosome 4q12)
 - d. LGMD2F-F-sarcoglycan (chromosome 5q33-34)
 - i. Similar to dystrophinopathies
 - ii. Some with early onset similar to DMD and others with later onset and slower progression similar to BMD
 - iii. Early proximal muscle weakness
 - iv. Cardiomyopathy
- 4. Congenital fibrosis of the extraocular muscles
 - a. Chromosome 12p11.2
 - b. Congenital fibrosis of the extraocular muscles
- 5. LGMD2G
 - a. Telethonin (chromosome 17q11-q12)
 - b. Early quadriceps and anterior tibial muscle weakness
 - c. Onset mean is 12.5 years
 - d. Miyoshi pattern occurs (calf weakness occurs)
- 6. LGMD2H
 - a. E3-ubiquitin ligase (TRIM 32) (chromosome 9q31-q33)
 - b. Onset 8–27 years of age
 - c. Manitoba Hutterites
 - d. Can walk with assistance to 40 years of age
- 7. LGMD2I
 - a. Fukutin-related protein (FKRP) (chromosome 19q13)
 - b. Onset in infancy (MDC1C) to the fourth grade
 - c. Variable limb girdle pattern (arm vs. legs)
 - d. Hypertrophy calves
 - e. Dilated cardiomyopathy
 - f. Respiratory muscle involvement
- 8. LGMD2J
 - a. Titin gene mutation (chromosome 2q31)
 - b. Late adult onset
 - c. Childhood presentation may be limb girdle; involvement of the upper limbs, others posterior calves
- 9. LGMD2K

- a. POMT protein (chromosome 9q3)
- b. Most often Walker-Warburg phenotype
- 10. LGMD2L
 - a. Fukutin (chromosome 9q31-33)
 - b. Fukuyama muscular dystrophy
- 11. LGMD2M
 - a. POMGnT1 protein (chromosome 1p32)
 - b. Muscle-eye-brain disease

Differential Diagnostic Points of Dystrophies

- 1. DMD/BMD
 - a. Calf hypertrophy
 - b. High CK
 - c. Systemic complications
- 2. DMD/glycerol kinase/adrenal hypoplasia congenital
 - a. Severe cognitive deficit
 - b. Intermittent catatonic stupor
 - c. Muscle weakness
- 3. LGMD1A
 - a. May be adult onset
 - b. Scapula-humeral-pelvic pattern
 - c. Early contracture elbow/heel
- 4. LGMD1B
 - a. Humeral-peroneal pattern
 - b. Cardiac conduction defects
- 5. LGMD1C
 - a. May have adult onset
 - b. Calf hypertrophy
 - c. Rippling muscle
- 6. LGMD1D
 - a. Adult onset
 - b. Cardiomyopathy
- 7. LGMD1E
 - a. Late adult onset
 - b. Dysphagia
- 8. LGMD1F
 - a. Onset infancy to adulthood
- 9. LGMD2A
 - a. No calf hypertrophy
- 10. LGMD2B
 - a. Early thigh or posterior calf involvement (Miyoshi phenotype)
- 11. Sarcoglycanopathies (LGMD2C, LGMD2D, LGMD2E, LGMD2F)
 - a. Similar to dystrophinopathies
 - b. No cardiac involvement
- 12. LGMD2G
 - a. Quadriceps and anterior tibial involvement
- 13. LGMD2H
 - a. Manitoba Hutterites
- 14. LGMD2I
 - a. MDC1C to fourth decade
- 15. LGMD2J
 - a. Titin (chromosome 2q31)

- b. Late adulthood
- c. Anterior tibial weakness
- 16. LGMD2K
 - a. POMT (chromosome 1p32)
 - b. Walker-Warburg syndrome
- 17. LGMD2L
 - a. Fukutin (chromosome 9q31-33)
- 18. LGMD2M
 - a. POMGnT1 (chromosome 1p32)
 - b. Muscle-eye-brain disease

Differential Diagnosis of Distal Myopathy/Muscular Dystrophy

Welander Myopathy

1. AD; mutation in the T1A1 gene that maps to chromosome 2p13
2. Late onset 5th decade
3. Site of onset
 - a. Finger and wrist tensors that progresses to toe and ankle dorsiflexors
 - b. Proximal involvement in some families
 - c. No neck flexor weakness
 - d. Loss of brachioradialis and Achilles
4. Normal to slightly elevated CK; Myopathic EMG
5. Rimmed vacuoles

Markesbery-Griggs Distal Myopathy

1. AD; 2 ASP; chromosome 10q22, 3-23.2;
2. Late onset
3. Initially involves the anterior compartment of the legs; some patients develop wrist and finger extensor weakness
4. Cardiomyopathy
5. Rimmed vacuoles and features of myofibrillar myopathy

Udd Distal Myopathy

1. AD; titin gene mutation that maps to chromosome 2q31
2. Onset after age 35
3. Weakness of the anterior compartment of the legs; begins in the toe extensors
4. May progress to intrinsic hand muscles
5. Facial muscles are spared; rare involvement of bulbar musculature
6. Decreased Achilles reflex
7. Rimmed vacuoles may be seen in muscle biopsy

Nonaka Distal Myopathy

1. AD; mutations in GNE that maps to chromosome 9p1-q1; allelic to AD IBM
2. Weakness of the anterior compartment of the distal lower extremity; foot drop in the second or third decade of life
3. With time neck flexor and proximal muscle weakness
4. Quadriceps relatively spared
5. Rimmed vacuoles on muscle biopsy; absent inflammatory infiltrate

Miyoshi Distal Myopathy

1. AR; dysferlin gene that maps to 2p13
2. Early adult onset of calf atrophy and weakness
3. Distal upper and lower extremities are affected; intrinsic hand muscles are spared
4. Gastrocnemius and soleus are severely affected
5. Markedly increased CK; muscle biopsy demonstrates myopathic and dystrophic changes

Laing Distal Myopathy

1. AD; mutated gene is MYH7 that maps to chromosome 4q1,2
2. Initial weakness in the anterior compartment of the distal lower extremities and neck flexor
3. Onset is between 4 and 25 years
4. Finger extensors may be affected; finger flexors and hand extrinsic muscles are spared
5. Muscle biopsy reveals deposits of myosin long chain (MyHC) in subsarcolemmal areas of type 1 fibers

Distal Myopathy with Pharyngeal and Vocal Cord Paralysis

1. AD
2. Onset fourth to sixth decade
3. Anterior tibial and vocal cord paralysis

Differential Diagnosis of Distal Myopathy

Myotonic Dystrophy

1. Severe ptosis
2. Mental and behavioral abnormalities
3. Stellate cataracts; (posterior)
4. Severe facial muscular atrophy
5. Systemic manifestations

Emery-Dreifuss Muscular Dystrophy

1. Contracture
2. Cardiac abnormalities

Oculopharyngeal Dystrophy

1. French connection
2. Severe ptosis and dysphagia

Scapuloperoneal Dystrophy

1. Early and more symmetrical involvement of the shoulder girdle and anterior compartment of the legs

Distal Myopathy with Vocal Cord Paralysis

1. Late onset
2. Vocal cord and pharyngeal weakness

Differential Diagnosis of Regional Muscular Dystrophies

Facioscapulohumeral Dystrophy (FSHD)

1. AD; contraction of the D4Z4 macrosatellite repeat in the subtelomeric region of chromosome 4q35
2. Variable age onset

3. Facial muscles are affected early (orbicularis ocula, zygomaticus and orbicularis oris)
4. Weakness of scapular stabilizers with scapular winging and trapezium hump
5. Stenocostal head of the pectoralis major is weak and atrophic that results in lateral displacement of clavicle (more horizontal)
6. Tibialis anterior is affected earliest in the lower extremity
7. Inflammatory infiltrate of the endomysium confused with polymyositis

Scapuloperoneal Muscular Dystrophy

1. AD; mutation in the desmin gene that maps to 2q35
2. Foot drop followed by scapular weakness
3. Compensatory hypertrophy of the extensor digitorum brevis (subset of patients)
4. Ankle contractions
5. Relative sparing of humeral muscles
6. Greater involvement of peroneal muscles than FSHD
7. Variants
 - a. Davidenkov
 - i. Scapuloperoneal weakness
 - ii. Distal sensory loss on the extremities
 - iii. Pes cavus
 - iv. Depressed reflexes
 - v. Decreased motor and sensory nerve conduction velocities
 - b. Kaeser variant
 - i. 12 members over 5 generations
 - ii. Anterior horn cell loss is the primary pathology

Emery-Dreifuss Muscular Dystrophy

1. X-linked EMG
2. EDMD caused by mutations in STA that map to Xq28
3. Contractions of Achilles tendons, elbows and posterior cervical muscles
4. Humeral peroneal distribution of weakness
5. Cardiac arrhythmia

Autosomal Dominant

1. EDMD2/LGMD1B
 - a. AD; mutations in lamin A/C gene that maps to chromosome 1q11-23
 - b. Similar phenotype to X-linked EDMD1
 - c. Mutations in the rod domain of LMNA cause a dilated cardiomyopathy (there may not be skeletal muscle involvement)

Autosomal Recessive EDMD3

1. Contracture and severe spinal rigidity
2. Onset in the first 2 years of life
3. Mutation in the LMNA

EDMD Phenotype form Mutations in

1. SYNE 1 (chromosome 6q34)
2. SYNE 2 (chromosome 14q23)

Differential Diagnosis of Weakness in the Facioscapular Distribution

1. Scapuloperoneal syndrome
 - a. Neurogenic and myogenic forms
 - b. May have mild facial weakness
 - c. Some FSHD patients may have mild facial weakness
2. Hereditary proximal spinal muscular dystrophy
 - a. No facial involvement
 - b. The entire shoulder girdle including the deltoid muscle is involved
3. Restricted polymyositis
 - a. The cause may be similar to that of FSHD
 - b. AD inheritance has been described in two patients
 - c. Facial, scapular and anterior tibialis muscles may be involved
 - d. Muscle biopsy and EMG are compatible with polymyositis
 - e. Facial weakness and atrophy is much more prominent in FSHD
 - f. Polymyositis has minimal facial weakness
4. Coats' disease (VIIIth nerve defects retinal disease)
 - a. Begins in infancy
 - b. Uni- or bilateral sensorineural hearing loss
 - c. Retinal telangiectasia and detachment
5. Limb girdle dystrophies
 - a. Less prominent facial weakness
 - b. Proximal upper and lower extremity weakness
6. Emery-Dreifuss muscular dystrophy
 - a. Prominent contractures
 - b. Early long finger flexion contractures
 - c. Quadriceps involvement
7. Mitochondrial myopathy
 - a. Ophthalmoplegia
 - b. Fatigue with exercise
 - c. Short stature
 - d. Symptomatic VIIIth nerve deficits
 - e. Severe dilated cardiomyopathy
8. Acid maltase deficiency
 - a. Enlarged fibrillation tongue
 - b. Congestive heart failure
 - c. Membrane instability on EMG
9. Desmin myopathy
 - a. Weakness and atrophy of the distal muscles of the lower limbs
 - b. Progression to the hands, then to the trunk, neck and face
10. Congenital centronuclear myopathy
 - a. Prominent ptosis
 - b. Limb girdle weakness
 - c. Less prominent cardiac defects
11. Bethlem Myopathy
 - a. Allelic and mild variant of Ullrich congenital muscular dystrophy
 - b. AD; 21q22 and 2q37 that encode collagen 6A1 and 6A3

- c. Onset birth or early childhood
 - d. Delayed but attained motor milestones
 - e. Proximal > distal muscle weakness; extensors > flexors
 - f. Early contracture of elbows and ankles; late wrist and finger contractures
 - g. Heart is involved in 10% of patients
 - h. Ventilatory muscle involvement
12. Bent spine/Dropped head syndrome
- a. Involvement is prominent in the cervical musculature; rarely the thoracic and paraspinal musculature is involved
 - b. Neck extensor weakness onset is after 60 years of age
 - c. Involvement of thoracic paraspinal musculature causes severe kyphoscoliosis most prominent with standing
 - d. When supine the posture is normal
 - e. Myasthenia gravis and ALS both may have a dropped head
13. Oculopharyngeal Dystrophy (OPMD)
- a. AD; GCG expansion repeat within PABN (gene that maps to chromosome 14q11.1)
 - b. Presents in the fourth to sixth decade
 - c. Bilateral often asymmetric ptosis; extraocular muscle involvement in 50% of patients (rare diplopia)
 - d. Dysphagia that when severe leads to weight loss and aspiration
 - e. Rare facial and masticatory weakness as well as proximal > distal muscle involvement
 - f. No heart, cognitive and VIIIth nerve involvement that occurs with mitochondrial myopathies
14. OPMD Variants
- a. Infantile or early childhood variant
 - i. Ptosis and ophthalmoparesis
 - ii. Severe generalized weakness
 - iii. Respiratory failure
 - b. Oculopharyngeal distal variant
 - i. Earlier weakness
 - ii. Distal OPMD with pseudo-obstruction (one patient)

Differential Diagnosis of Oculopharyngeal Dystrophy (OPMD)

- 1. Myotonic muscular dystrophy
 - a. Systemic manifestation
 - b. Myotonia
 - c. Cardiac involvement
- 2. AD distal myopathy
 - a. Welander
 - b. Markesbery/Griggs/Udd
 - c. Nonaka
 - d. Specific leg compartment atrophy
 - e. Less swallowing difficulty than OPMD
 - f. No ophthalmoplegia
- 3. Myasthenia gravis

- a. Fluctuating signs and symptoms
 - b. Pattern of weakness (MG > proximal than distal)
 - c. Severe extraocular muscle involvement that fluctuates
4. Mitochondrial myopathy with or without external ophthalmoplegia
- a. Severe cardiac involvement
 - b. Fatigue with exercise
 - c. VIIIth nerve deficit
 - d. Short stature
5. Polymyositis and progressive bulbar palsy
- a. No ptosis and extraocular muscle involvement
6. Recessive OPMD
- a. Late onset ptosis and dysphagia

Differential Diagnosis of Rare Muscular Dystrophies

- 1. Myofibrillar myopathy
 - a. Heterogeneous with a wide phenotype spectrum
 - b. Onset 25–45 years of age
 - c. Proximal distal or generalized weakness; scapuloperoneal pattern
 - d. Cardiac involvement
 - e. Some patients develop severe respiratory insufficiency
 - f. Muscle biopsy demonstrates hyaline and non-hyaline structures
- 2. Hereditary inclusion body myopathies
 - a. AD and AR forms
 - b. AR form is allelic to Nonaka distal myopathy; mutations in the GNE gene that maps to chromosome 9p1-q1
 - c. AR form is in Iranian and Afghani-Jewish patients; North American families

Differential Diagnosis of Myopathy by Genetics and Pattern of Weakness

- 1. Male with proximal weakness
 - a. X-linked or sporadic
 - i. DMD/BMD
 - b. No mutation; non-rimmed vacuoles
 - i. Danon disease
 - ii. XMEA
- 2. Sporadic or AR female or male with proximal weakness
 - a. Early cardiac/respiratory involvement
 - b. English or Northern European ancestry
 - c. LGMD2I or MDC1C with FKRP mutation
 - d. No FKRP mutation
 - i. EDMD and LGMD1B if there are early contractures
 - ii. MFM
 - iii. Pompe disease
 - e. Scapular muscle wing; thigh adductor weakness; thin calves
 - f. Eastern and southern European ancestry
 - g. Calpain 3 mutation with LGMD2A
 - h. No mutation identified

- i. FSHD (limb girdle phenotype)
- i. Onset in late teens to age 30
- j. Early calf atrophy
- k. Absent dysferlin
 - i. LGMD2B
 - ii. Miyoshi myopathy
- l. Early cardiomyopathy and contractures
- m. Emerin lamin A/C mutations
 - i. EDMD
- 3. Sporadic or AR female or AR male with distal muscle weakness
 - a. Early calf atrophy and weakness
 - i. Dysferlin is absent
 - 1. LGMD2B
 - 2. Miyoshi myopathy
 - b. Early anterior atrophy
 - i. Rimmed vacuoles on muscle biopsy
 - 1. h IBM
 - c. Hyaline/non-hyaline inclusions:
 - i. Myofibrillar myopathy
- 4. Autosomal Dominant with proximal weakness
 - a. Scapular winging with facial weakness
 - i. FSHD
 - b. Early contractures with no cardiomyopathy
 - i. Bethlem myopathy
 - ii. LMNA/C
 - 1. LGMD1B/EDM2
 - c. Rippling muscles, distal leg weakness with proximal weakness; no cardiac or respiratory weakness
 - i. LGMD1C
- 5. Childhood to late adult onset with or without cardiac or respiratory involvement
 - a. Myofibrillar myopathy
 - b. LGMD1A (myotilinopathy)
 - c. ZASP-related myofibrillar myopathy
 - d. Desminopathy
- 6. Autosomal Dominant with early anterior tibial weakness
 - a. Late adult onset
 - i. Tibial myopathy
 - ii. LGMD2J

Differential Diagnosis by Muscle Biopsy

- 1. Immunohistochemistry
 - a. Emerin – EDMD
 - b. Desm/Myotilin/ZASP
 - i. MFM
 - c. Myosin heavy chain
 - i. Myosin storage myopathy
 - d. Alpha-actinin/nebulin
 - i. Nemaline myopathy
 - e. LAMP-2 and membrane attack complex
 - i. Danon disease
 - ii. XMEA
 - iii. Associated with non-rimmed vacuoles in a male

- 2. Immuno blot
 - a. Dystrophin
 - b. Dysferlin
 - c. Calpain
- 3. Electron microscopy
 - a. Myofibrillar myopathy
 - b. Danon disease
 - c. XMEA
 - d. Storage diseases
 - e. Mitochondrial myopathies
- 4. Immunohistochemistry
 - a. Dystrophin (dystrophinopathies)
 - b. Sarcoglycan
 - c. Beta-dystroglycan
 - d. Merosin
 - e. Dysferlin
 - f. Caveolin 3

Differential Diagnosis of Congenital Myopathies

Central Core Myopathy

- 1. AD; Ryanodine receptor gene (RYR1) that maps to chromosome 19q13.1
- 2. Infant or childhood onset; rare adult onset
- 3. Proximal muscle weakness
- 4. Skeletal abnormalities:
 - a. Congenital hip dysplasias
 - b. Scoliosis
 - c. Foot deformities
- 5. Malignant hyperthermia

Multi/Minicore Myopathy

- 1. AD, AR and sporadic
- 2. AR; Selenoprotein; N1/1p36 (some patients)
- 3. Infancy or childhood onset
- 4. Weakness proximal > distal; moderate weakness and wasting of the hands; respiratory muscles
- 5. Hyperlaxity of joints of the hands; patellar, hip and knee dislocations
- 6. Heel contractures; rare arthrogryposis
- 7. Risk for malignant hyperthermia

Nemaline Myopathy

- 1. AR – mutations in nebulin gene NEM2 that maps to chromosome 2q21.20q22
 - a. Infantile form (severe)
- 2. AR/AD – mutations in the X-Actin (ACTA 1) gene that maps to chromosome 1q42
- 3. AR/AD – X-Tropomyosin (TMP3) gene that maps to chromosome 1q21–q23
- 4. AD – B-Tropomyosin (TPM2) gene that maps to chromosome 9q13
- 5. AR-slow troponin (TNNT1) gene that maps to chromosome 11q13
- 6. AR/AD – X-tropomyosin (TMP1) gene that maps to chromosome 15q21-23

7. AD – cofilin-2 gene (CFL2) that maps to chromosome 14q12

Infantile Forms (Nebulin, X-Actin, X-Tropomyosin, B-Tropomyosin)

1. Infantile onset with severe generalized hypotonia and weakness
2. Respiratory weakness
3. Skeletal defects
4. Fatal first year of life

X-Tropomyosin (TMP1 Gene) That Maps to 15q21-q23

1. Encodes Relch-repeat and BTB (PO2) domain containing 13 (KBT BD13) AD
 - a. Childhood onset
 - b. Proximal weakness that includes neck flexor
 - c. Unable to run; poor postural connection; slow movements

Cofilin-2 Gene; AR; Maps to Chromosome 14q12

1. Onset in infancy or childhood
2. Mild generalized hypotonia and weakness; facial muscles are involved as are EOM in some patients
3. High arched palate
4. Thorax deformities

Nemaline Myopathy – Adult Onset

1. Some sporadic; often no family history
2. Onset is 3rd to 9th decade
3. Proximal > distal weakness
4. 50% of patients have posterior cervical involvement
5. Respiratory failure 30%; may be presenting feature
6. Myalgia
7. Cardiomyopathy

Centronuclear Myopathy

1. X-linked
 - a. Myotubularin (MTM1) gene that maps to Xq28; recessive
 - i. Severe neonatal hypotonia and weakness
 - ii. Respiratory insufficiency
 - iii. Ptosis and extraocular muscle involvement
 - iv. Large ear (70%); narrow face (80%); long digits (60%)
 - v. Death at <6 months

Centronuclear Myopathy (Neonatal or Late Infantile)

1. Sporadic, AR or AD
2. Dynamin-2
 - a. Allelic to dominant Charcot-Marie-Tooth type B
 - b. D1-CmTB (on chromosome 19p13.2)
 - c. Onset late infancy or early childhood
 - d. Generalized weakness and hypotonia
 - e. Facial weakness, ptosis, extraocular muscle weakness
 - f. Facial dysmorphisms
 - g. Later onset may not have ophthalmoparesis

Autosomal Dominant Centronuclear Myopathy Late Childhood or Adult Type

1. Dynamin-2 gene; maps to chromosome 19p13.2; allelic to D1-CmTB
2. Onset in late childhood or adulthood
3. Mild proximal or distal weakness
4. Ptosis
5. Variable weakness of facial and extraocular muscles
6. No skeletal abnormalities or facial dysmorphisms

Centronuclear Myopathy (BINI)

1. Mutations in bridging integrator 1 (BINI: Amphiphysin 2) gene that maps to chromosome 2q14.3
2. BINI protein functions
 - a. Membrane remodeling
 - b. Regulated by phosphoinositide
 - c. Organization of T-tubules
3. Onset from birth to childhood
4. Mild proximal weakness
5. Some patients have ptosis and ophthalmoparesis
6. Bulbar, facial involvement; dysarthria
7. No respiratory failure
8. Diffuse muscle atrophy
9. Mild facial dysmorphism

Congenital Fiber Type Disproportion 1

1. Sporadic AD or AR; 43% have a family history
2. CFTD 1
 - a. X-actin (ACTA 1) gene that maps to chromosome 1q42.13; dominant
 - b. Clinical Manifestations of the severe phenotype
 - i. Onset with congenital weakness that is severe and affects respiratory muscles
 - ii. No ophthalmoparesis
 - iii. Respiratory failure < 4 years
3. Differential of other X-actin diseases
 - a. Nemaline rod myopathy
 - b. Intramuscular rod myopathy
 - c. Rod myopathy with cores
 - d. Actin myopathy (congenital myopathy with an excess of thin filaments)

Congenital Fiber Type Disproportion 2

1. Chromosome xq13.1–q22.1; recessive
2. Onset is congenital
3. Bilateral ptosis
4. Facial weakness
5. Weak suck and cry
6. Generalized hypotonia
7. Respiratory insufficiency
8. Dilated cardiomyopathy
9. Death by respiratory failure in 6–14 weeks

Congenital Fiber Type Disproportion 3

1. Selenoprotein N1 (SEPN 1) gene that maps to chromosome 1p36; recessive

2. SEPN 1-like syndrome
 - a. Early trunkal hypotonia
 - b. Early neck flexor weakness
 - c. Respiratory impairment starts from adolescence to early adulthood
 - d. Minimal limb strength
 - e. Scoliosis (adolescence); lordosis of upper spine

Congenital Fiber Type Disproportion 4

1. Myosin light chain 2 that maps to chromosome 12q24; recessive
 - a. Allelic disorders
 - i. Hypertrophic cardiac myopathy 10 (CMH10)
 - ii. Dilated familial cardiomyopathy with type 1 muscle fiber hypotrophy
 - iii. Onset during infancy
 - iv. Generalized hypotonia and weakness
 - v. Facial dysmorphisms:
 1. Tented mouth
 2. Ptosis (some patients)
 - vi. Generalized tremors and clonus
 - vii. Dilated cardiomyopathy

Reducing Body Myopathy

1. FHL1 gene (Four-and-a-half-LIM) that maps to chromosome Xq26.3; sporadic
2. Early onset has a severe clinical course (sporadic inheritance)
3. Late onset (childhood to adult)
4. Onset in the 4th decade
5. Early development is normal
6. Pattern of weakness
 - a. Proximal > distal; asymmetric
 - b. Scapuloperoneal
 - c. PCHA spinal muscle involvement
7. Skeletal abnormalities
 - a. Rigid spine

Hyaline Body Myopathy

1. AD or AR; AD gene (MYH7 that maps to chromosome 14q11.2); encodes cardiac B heavy chain
2. The myopathy is also known as myosin with lysis of type 1 myofibrils and myosin storage myopathy
3. AR; gene has not been defined; maps to chromosome 3p22.2-p21-32
4. Onset in infancy
5. Limb girdle or scapular peroneal pattern; may have distal muscular weakness

H-IBM3/Myosin Storage Myopathy

1. AD; gene is myosin heavy chain type 11 or (MYH2) that maps to chromosome 17p13.1
2. Arthrogryposis
3. Ophthalmoparesis
4. Adult onset of proximal muscle weakness and myalgia

Cap Myopathy

1. AD; B-Tropomyosin 2 gene (TPM2) that maps to chromosome 9p13.3
 - a. Congenital or childhood onset
 - b. Weakness of proximal and distal muscles
 - c. The face and respiratory muscles are involved
 - d. Facial dysmorphism
 - i. Long and narrow
 - ii. High arched palate

Zebra Body Myopathy

1. X-Actin gene (ACTA1) that maps to chromosome 1q42.13
2. Onset at birth
3. Weakness that is proximal, distal and axial that can be asymmetric
4. Some patients have greater arm than leg weakness
5. Normal tendon reflexes
6. Static course; some patients have improved

Tubular Aggregate Myopathy

1. Type 1
 - a. AD; mutation in the STIM 1 gene that maps to chromosome 11p15
 - b. Mutations in the STIM 1 gene also causes Stormorken syndrome
 - i. Tubular aggregate myopathy
 - ii. Platelet dysfunction
 - iii. Thrombocytopenia
 - iv. Asplenia
 - v. Congenital meiosis
 - vi. Ichthyosis
 - vii. Stroke-like episodes
2. Type 1 clinical features
 - a. Childhood or early adult onset
 - b. Limb girdle weakness
3. Type 2 Tubular Aggregate Myopathy
 - a. AD; caused by mutation in the ORAI 1 gene that maps to chromosome 12q24
 - b. Onset in infancy
 - c. Congenital myasthenia
 - d. Fatigable weakness
4. Type 3 Tubular Aggregate Myopathy
 - a. Sporadic; gene not defined
 - b. Excessive induced cramps, pain and stiffness

Metabolic Muscle Disease

Differential Diagnosis of Carbohydrate Muscle Metabolism

General Characteristics

1. Type I (glucose 6 phosphatase deficiency) and type VI (liver phosphorylase deficiency) only involve the liver

2. Type II (lysosomal X-glucosidase), type V (phosphatase deficiency), type VII (phosphofructokinase deficiency), type X (phosphoglycerate mutase) and type XI (lactate dehydrogenase) primarily cause muscle disease
 3. Types III, IV, XI, XII, XIII and IV may involve both the liver and muscle
 4. Type II (acid X1, 4 glucosidase)
 - a. Infant
 - i. Hypertonia and generalized weakness
 - ii. Fibrillating tongue
 - iii. Congestive heart failure
 - b. Adult
 - i. Proximal > distal muscle weakness
 - ii. Ventilatory muscle involvement with respiratory failure
 5. Type III (Cori-Forbes disease)
 - a. Debrancher (amylo-1,6-glucosidase deficiency)
 - b. Infancy
 - i. Hypotonia and generalized weakness
 - c. Childhood/adult onset
 - i. Adult onset 3rd to 4th decade
 - ii. 50% weakness of distal extremity muscles (peroneal and calf)
 - iii. Pseudohypertrophy of proximal muscles
 - iv. Ventilatory involvement
 - v. Cardiomyopathy
 - vi. Spasticity, dementia, incontinence (late)
 6. Type IV (Andersen disease)
 - a. Branching enzyme deficiency (amylo-(1,4 to 1,6) transglycosylase)
 - b. Infantile onset
 - i. Hepatomegaly, liver disease
 - ii. Muscle weakness, hypotonia, atrophy and contractures
 - c. Childhood/adult onset
 - i. Proximal or distal weakness
 - ii. An adult form presents as polyglucosan disease with upper and lower motor neuron signs and symptoms
 - d. A subgroup with muscle weakness, atrophy and cardiomyopathy
 7. Type V (McArdle's disease)
 - a. Myophosphorylase deficiency
 - b. Infantile onset
 - i. Rare weakness
 - c. Childhood/adult onset
 - i. Exertional muscle pain and cramps (intense exercise)
 - ii. Second wind phenomenon
 - iii. Myoglobinuria in the second or third decade
 - iv. Rare proximal muscle weakness and atrophy
 8. Type VII (Tarui disease) PFK
 - a. Phosphofructokinase deficiency
 - b. Exercise intolerance, muscle pain, contractures and relief with rest
 - c. No warm-up phenomenon
 - d. Low incidence of myoglobinuria
 - e. Rarely hemolytic anemia without myopathy
 - f. Subgroup in adulthood presents with proximal or a scapulo-peroneal pattern of weakness
 - g. Infant presentation can occur with generalized weakness and cardiomyopathy
 9. Type VIII (PBK)
 - a. Phosphorylase b kinase deficiency
 - b. Infancy and childhood
 - i. May present with mild weakness and delay in milestones
 - c. Adult presentation
 - i. Exercise intolerance with cramps and myoglobinuria
 - ii. 50% of patients develop proximal or distal weakness
 10. Type IX (PGK)
 - a. Phosphoglycerate kinase deficiency
 - b. Childhood
 - i. Male children may present with hemolytic anemia, cognitive deficits and seizure
 - c. Adulthood
 - i. Exercise intolerance, cramps and recurrent myoglobinuria
 - ii. Slowly progressive proximal myopathy
 11. Type X (PGAM)
 - a. Phosphoglycerate mutase deficiency
 - b. May present in childhood or early adulthood
 - i. Exercise intolerance, cramps and recurrent myoglobinuria
 12. Type XI
 - a. Lactate dehydrogenase deficiency
 - b. Childhood – adult onset
 - i. Exercise intolerance, cramps and recurrent myoglobinuria
 - ii. Normal muscle strength
 - iii. Erythematous scaly skin lesions
 - iv. Uterine stiffness that may require Cesarean section
 13. Type XII
 - a. Aldolase A deficiency
 - b. Infancy-childhood (one patient)
 - c. Exercise and weakness after febrile illness
 14. TYPE XIII
 - a. Trioisomerase deficiency
 - b. Infantile onset of generalized hypotonia, cognitive deficits, weakness and hemolytic anemia
 15. Type XIV
 - a. β -enolase deficiency (one patients)
 - b. Childhood-adult onset
 - i. Exercise intolerance and myalgia
- Rare Lysosomal Glycogen Storage Myopathies**
- Vascular Cardiomyopathy and Myopathy (Danon Disease)*
1. Patients are normal at birth

2. Childhood development of proximal muscle weakness and cardiomyopathy
3. Men are more severely affected than women but women carriers may manifest signs
4. Men are dramatically more often cognitively impaired than women (60% vs. 6%)
5. Death from CHF or arrhythmia by the 3rd decade

X-Linked Myopathy with Excessive Autophagy (XMEA)

1. May present in infancy or early adulthood
2. Slowly progressive proximal weakness and atrophy
3. No cardiomyopathy or cognitive deficits
4. Respiratory involvement may occur

Differential Diagnosis of Myoadenylate Deaminase Deficiency (MAD)

1. Exertional pain, fatigue and rarely myoglobinuria
2. Onset in late adolescence to middle age
3. Normal neurologic exam
4. Patients may be asymptomatic
5. MAD deficiency may be seen incidentally in:
 - a. ALS
 - b. Spinal muscular atrophy
 - c. Inflammatory myopathy
 - d. Some dystrophies

Differential Diagnosis of Lipid Metabolic Disorders

1. Primary Carnitine Deficiency
 - a. Mutation of the OCTN2 gene on chromosome 5q33.1
 - b. Childhood
 - i. Reye's-like syndrome (vomiting, mental status changes, hypoglycemia, hepatomegaly)
 - ii. Proximal muscle weakness and dilated cardiomyopathy
 - iii. Rhabdomyolysis
 - iv. Respiratory weakness
 - c. Adult
 - i. May worsen with pregnancy or in the post-partum
2. Secondary carnitine deficiency occurs with:
 - a. Respiratory chain defects
 - b. Organic acidurias
 - c. Endocrinopathies
 - d. Renal and hepatic failure
 - e. Toxic effect of medications
 - f. Malnutrition
 - g. Total parenteral nutrition in infants
 - h. Chronic renal dialysis
3. CPT2 deficiency
 - a. AR; CPT2 gene maps to chromosome 1p32
 - b. Onset in the second or third decade
 - c. Muscle pain and myoglobinuria after intense exercise
 - d. Rare cardiomyopathy in infancy or early childhood
4. VLCAD deficiency

- a. Myopathy is caused by mutations in VLCAD gene that maps to chromosome 17p11.2
- b. Childhood:
 - i. Hypertrophy cardiomyopathy
 - ii. Hypoketotic hypoglycemia
 - iii. Dicarboxylic aciduria
- c. Adulthood:
 - i. Similar to CPT with exercise induced myoglobinuria

5. LCAD deficiency
 - a. Mutations in the ACADL gene that maps to chromosome 2q34-q35
 - b. Infancy:
 - i. Failure to thrive
 - ii. Non-ketotic hypoglycemia
 - iii. Cardiomyopathy
 - iv. Hepatomegaly
 - v. Encephalopathy
 - c. Adolescent/adult
 - i. Exercise intolerance, rhabdomyolysis and proximal weakness
6. MCAD deficiency
 - a. Mutation of the MCAD gene that maps to chromosome 1p31
 - b. Rare cardiac or skeletal muscle involvement
 - c. Rhabdomyolysis and encephalopathy have been reported in infancy and adulthood
7. SCAD deficiency
 - a. Mutations in the SCAD gene that maps to chromosome 12q22-qter
 - b. Onset in infancy or early adulthood
 - c. Infants
 - i. May have failure to thrive with episodes of non-ketotic hypoglycemia
 - d. Adults
 - i. Myalgia and exercise intolerance
 - ii. Progressive proximal muscle weakness
 - iii. Facial weakness, ptosis, progressive external ophthalmoplegia
 - iv. Respiratory insufficiency
 - v. Cardiomyopathy
8. Mitochondrial Trifunctional Protein Deficiency
 - a. Mutations in long chain HAD, ETF, ETF-QO
 - b. Chronic progressive proximal muscle weakness
 - c. Cardiomyopathy
 - d. Recurrent rhabdomyolysis
9. Long chain 3-hydroxyacyl-CoA dehydrogenase deficiency (HAD)
 - a. AR; the gene maps to chromosome 2p23
 - b. Presentation in infancy and early childhood is similar to that of Reye's syndrome with high mortality
 - c. Adulthood
 - i. Progressive proximal muscle weakness
 - ii. Recurrent episodes of myoglobinuria

- iii. A subset of patients develop a progressive sensorimotor neuropathy and pigmentary retinopathy
- iv. Mothers of affected fetus may develop the HELLP complication during pregnancy (hemolysis, elevated liver enzymes, low platelets and acute fatty liver)

Differential Diagnosis of Mitochondrial Myopathies

1. Myoclonic Epilepsy and Ragged Red Fibers (MERRF)
 - a. AR; multiple mtDNA deletions; point mutations at nucleotide position 8344 in the tRNA gene MTTK; other tRNA mutations and deletions; POLG and MTND5 mutations can present with a similar phenotype
 - b. Myoclonus
 - c. Generalized seizures (GTC and myoclonic)
 - d. Atoxic
 - e. Cognitive impairment
 - f. Sensorineural hearing loss
 - g. Optic atrophy
 - h. Progressive proximal myopathy
2. Mitochondrial Myopathy Lactic Acidosis and Stroke (MELAS)
 - a. 705 of patients have mtDNA mutation at nucleotide 3243 in the MTTL1 gene that encodes to RNA. Mutations have been described at multiple other nucleotide sites and in genes that encode other tRNAs and other subunits of the respiratory chain
 - b. Proximal muscle weakness
 - c. Stroke-like episodes (that do not respect a vascular distribution)
 - d. Increased lactate levels in the serum and CSF
3. Kearns-Sayre syndrome
 - a. Single large mtDNA deletions (1.3 to 8.8 KB) that involve several tRNA genes
 - b. Onset prior to age 20
 - c. PEO, pigmentary retinopathy and cardiomyopathy are the core clinical features
 - d. Associated features include:
 - i. Short stature
 - ii. Proximal muscle weakness
 - iii. Cognitive impairment
 - iv. Sensorineural hearing loss
 - v. Depressed ventilatory drive
 - vi. Endocrinopathies
 - vii. Sensitive to sedatives and anesthesia
4. Progressive external ophthalmoplegia (PEO)
 - a. PEO sporadic
 - i. Approximately 40–70% with PEO have a single large mtDNA deletion
 - b. PEO Autosomal dominant
 - i. Multiple mtDNA deletions
 - ii. Three genes have been defined
 1. PEO A1
 - a. Due to mutations in POLG (polymerase gamma) that maps to chromosome 15q25
 2. PEO A2
 - a. Mutations in the ANT 1 gene (adenosine nucleotide translocator) that maps to chromosome 4q34-q35
 3. PEO A3
 - a. Mutations in the twinkle gene (C100RF2) that maps to chromosome 10q24
 4. A fourth locus has been identified that maps to chromosome 3q14.1-21.4
 5. Autosomal recessive PEO
 - a. Due to mutations in the POLG gene at chromosome 15q25
 6. Clinical Manifestations
 - a. Ptosis and ophthalmoparesis
 - b. Some patients have proximal muscle weakness
 - c. No systemic manifestations, cardiac conduction defects or pigmentary retinopathy
5. Autosomal recessive cardiomyopathy and ophthalmoplegia
 - a. Multiple mitochondrial DNA deletions
 - b. Childhood onset
 - i. Facial and proximal muscle weakness
 - ii. Severe cardiomyopathy (dilated)
 - iii. Reduced muscle tendon stretching reflexes
6. Mitochondrial DNA depletion syndromes
 - a. Approximately 50% of patients are sporadic
 - b. The more mtDNA depleted the more severe the clinical symptoms
 - c. The syndrome is associated with mutations in thymidine kerase² (TK2) and deoxyguanosine kinase (DGK) gene mutations (these nuclear genes are pivotal in regulation the mitochondrial genome)
 - d. Onset is usually in infancy or early childhood
 - e. Wide clinical spectrum
 - i. Severe fatal infantile form with generalized hypotonia and weakness; associated proximal weakness, ptosis and ophthalmoplegia; subset with neuropathy
 - ii. A more benign form with delayed motor milestones but without renal tubular defect
7. Focal mitochondrial depletion
 - a. No molecular defects of mtDNA have been delineated
 - b. May present in the second decade of life with myalgia, fatigue and myoglobinuria
 - c. Congenital weakness, hypotonia, delayed motor milestones and cognitive deficits may occur
8. Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)
 - a. AR with multiple mtDNA deletions; mutations occur in the thymide phosphorylase gene (ECG1) that maps to chromosome 22q13.2-1ter; rare patients have mutations in the polymerase gamma (POLG) and the tRNA gene (MTTK)

- b. Distal proximal weakness and atrophy
 - c. Stocking and glove sensory loss
 - d. Ptosis and EOM paresis
 - e. Minimal CNS involvement although there is a clear leukoencephalopathy on MRI (rare cognitive impairment occurs)
 - f. Associated clinical features include:
 - i. Pigmentary retinopathy
 - ii. Sensorineural hearing loss
 - iii. Facial weakness
 - iv. Hoarseness and dysarthria
 - v. Gastrointestinal dysmotility
 - g. Onset prior to age 20
9. Leigh syndrome
- a. Great genetic heterogeneity
 - i. Maternal with point mutations of mtDNA in transfer RNA genes:
 1. MTND3
 2. MTND5
 3. MTND6
 4. MTCO3
 5. MTATP6
 - ii. Autosomal recessive Leigh syndrome
 1. No mitochondrial DNA mutations
 2. Gene mutations include:
 - a. NDUFV1
 - b. NDUF51
 - c. NDUF53
 - d. NDUF54
 - e. NDUF57
 - f. NDUF58
 - g. SDHA
 - h. BCS1L
 - i. COX10
 - j. SCO2
 - k. SURF1
 - l. LRPPRC
 - iii. X-linked Leigh syndrome
 1. No mitochondrial DNA mutations
 2. Mutations in the PDHA1 gene (pyruvate dehydrogenase lipoamide) alpha 1; xp22.1
 - iv. Sporadic Leigh
 1. Single large mtDNA deletion
 2. Microdeletions of mtDNA; mTCO3
 - b. Clinical Manifestations of Leigh syndrome
 - i. Onset in infancy or early childhood; rare presentation in adults
 1. Recurrent vomiting
 2. Cognitive deficits
 3. Generalized weakness and hypotonia
 4. Ptosis and ophthalmoparesis
 5. Bulbar symptomatology in infants (poor suck and cry, respiratory failure)
 6. Nystagmus, optic atrophy, ataxia spasticity and peripheral neuropathy
10. Mitochondrial myopathies
- a. Sporadic
 - b. Microdeletions of mtDNA; MTCO 3 gene
 - c. Point mutations of mtDNA; MTCYB, ND4 genes
 - d. Maternal inheritance
 - i. Point mutations of mtDNA; tRNA^{PHE}
 - e. Short stature
 - f. Normal strength but decreased muscle bulk
 - g. May have mild proximal muscle weakness
 - h. Recurrent myoglobinuria may be triggered by alcohol or exercise
 - i. A subset of patients with sensorineural hearing loss
11. Mitochondrial myopathy and sideroblastic anemia
- a. MLAS1 is caused by a homozygous mutation in the PVS1 gene that maps to chromosome 12.q24
 - b. MLAS1 is caused by mutations in the YARS 2 gene that maps to chromosome 12p11
 - c. MLASA3 is caused by a heteroplasmic mutation in the mitochondrially encoded MTATP gene
 - d. Myopathy
 - e. Lactic acidosis
 - f. Sideroblastic anemia
12. Fatal infantile myopathy
- a. AR; mt depletion
 - b. TK2 (thymidinekinase mutation) that maps to chromosome 16q21

Differential Diagnosis of the Myotonic Dystrophies

DM1 is caused by an expansion of unstable cytosine-thymine-guanine (CTG) repeats in the 3' untranslated portion of the myotonin protein kinase (DMPK) gene that maps to chromosome 19q.13.2; AD

1. Onset at any age
2. Distal weakness initially that progresses to proximal muscles
3. Neck flexors are affected early
4. Facial and masticatory weakness and atrophy cause the facial dysmorphism ("hatchet face")
5. Involvement of pharyngeal and lingual muscles
6. Myotonia in both action induced and evoked by percussion of muscle groups (thenar eminence)
7. Cognitive impairment in approximately 50% of adults; neurobehavioral deficits
8. Systemic involvement
 - a. Gastrointestinal (dysmotility and pseudo-obstruction)
 - b. Respiratory muscle involvement (alveolar hypoventilation)
 - c. Probable decreased central respiratory drive
 - d. Posterior Stellate cataracts
 - e. 90% of patients with conduction defects by EKG; increased cardiac sudden death
 - f. Testicular atrophy
 - g. Frontal balding
 - h. Hyperinsulism with glucose tolerance testing

Myotonic Dystrophy Type 2 (DM2) or Proximal Myotonic Myopathy (PROMM)

1. DM2 and PROMM are allelic disorders caused by:
 - a. CCTG repeat expansion in the zinc finger protein of gene (ZNF9) that maps to chromosome 3
 - b. Onset between 20–60 years of age
 - c. Initial symptoms are intermittent stiffness and unilateral or bilateral thigh pain
 - d. Myotonia is evident in proximal, distal and facial muscles; may be exacerbated during pregnancy
 - e. “warm-up” phenomenon; no exacerbation with cold; small group exacerbate with heat
 - f. Episodic pain (neuropathic)
 - g. Slowly progressive proximal and distal weakness (fluctuates)
 - h. Atrophy of proximal muscle (10%) in later life
 - i. Rare calf hypertrophy
 - j. Myoglobinuria
 - k. Anticipation is less in DM2 than DM1; no congenital form
 - l. Cataracts, testicular atrophy, cardiac conduction defects, hypogammaglobulinemia, and glucose intolerance

Differential Diagnosis of Nondystrophic Myotonia and Periodic Paralysis

Chloride Channelopathies

Myotonia Congenita

1. Thomsen disease
 - a. AD; CLCN-1 gene that maps to chromosome 7q35
 - b. Onset in the first decade of life
 - c. Infants have difficulty opening eyes after crying
 - d. Adults:
 - i. Stiffness in the legs initially which progresses to the arms
 - ii. Myotonia in muscles of mastication
 - iii. “Warm-up” phenomenon is present (lessened myotonia with continued muscle contraction)
 - iv. Myotonia increases with cold
 - v. In later life phenotype may be similar to PROMM
 - vi. Percussion myotonia is present
2. Becker’s disease
 - a. AR
 - b. Onset between 4–12 years of age (later than Thomsen’s disease)
 - c. Severity of weakness worse
 - d. Distal weakness may occur following severe episode of myotonia
 - e. Mild fixed proximal weakness of the neck flexor musculature and in the extremities

Sodium Channelopathies

1. Hyperkalemic Periodic Paralysis

- a. AD; mutation in the SENA4A that maps to chromosome 17q13.1–13.3
- b. Three clinical forms:
 - i. Without myotonia
 - ii. With clinical or electrical myotonia
 - iii. In conjunction with paramyotonia congenita (PMC)
 - iv. Cooling triggers weakness in the PMC variant
 - v. Myotonia can be elicited in the eyelids, tongue; percussion. Myotonia can be seen particularly well in the forearm finger extensors
 - vi. Myotonia decreases with continued muscle contraction except with the PMC variant where it is increased with exercise and cold
 - vii. Parasthesias in the muscle occur often before weakness (feeling of swelling)
 - viii. Weakness is really mild and lasts for 20 minutes to 2 hours; rare flaccid paralysis
 - ix. Rare involvement of bulbar musculature
 - x. A brief period of exercise after sustained physical exertion may prevent or postpone weakness
 - xi. Affected muscles can be painful after attacks
 - xii. Eyelid myotonia may be the only sign between attacks
 - xiii. Mild fixed proximal weakness can evolve over time

2. Paramyotonia congenita

- a. Caused by mutations in the SCN4A gene that maps to chromosome 17q13.1–13.3; AD and allelic to potassium-sensitive periodic paralysis
- b. Repeated muscle contracture increases the myotonia as does cold
- c. A subset of patients may develop focal or generalized weakness
- d. Onset within the first decade
- e. Cold induced weakness can last for hours
- f. Rarely weakness can be induced by a potassium load
- g. Myalgias may occur but are not as severe as those that occur with DM2/PROMM

3. Potassium exacerbated myotonia

- a. Caused by mutation in SCN4A
 - i. The myotonia:
 1. Fluctuates
 2. Onset is delayed after exercise
 3. Eyelid paramyotonia
 4. The warm-up myotonia phenomenon occurs in the extremities
 5. Potassium, exercise and cold does not trigger weakness
 6. When the myotonia is severe it can affect EOM and bulbar musculature

4. Myotonia Permanens

- a. Caused by the G1306A mutation of the SCN4A gene that maps to chromosome 17q
- b. Constant muscle stiffness

- c. May affect respiratory muscles severely enough to cause hypoxia
- d. There is no episodic weakness or cold exacerbation
- 5. Acetazolamide responsive myotonia
 - a. Caused by mutations in the SCN4A gene that maps to chromosome 17
 - b. Onset in childhood that worsens by early adulthood
 - c. The myotonia is most severe in the hands and face
 - d. Myotonia is exacerbated by potassium, fasting and exercise
 - e. Stiffness and pain may be relieved by carbohydrates
 - f. There is both action and percussion myotonia
 - g. Strength is normal
 - h. There may be paradoxical myotonia of the eyelids
- 6. Facial hypokalemic periodic paralysis type 2
 - a. A subset of hypoKPP is caused by mutations in the SCN4A gene; most hypoKPP is caused by mutation in the voltage-gated calcium channel X-1 subunit gene (CACL1A3)
 - b. In the SCN4A hypoKPP:
 - i. Age of onset is earlier
 - ii. Attacks are similar to those that occur in hypoKPP1 but no fixed muscle weakness develops as it does with hypoKPP1
 - iii. Acetazolamide may exacerbate weakness
- i. The last affected muscles are the first to recover
- j. Frequency of attacks is very variable
- k. After age 30, the frequency of attacks diminish
 - l. Proximal muscles may gradually develop fixed weakness that is seen more in the legs than arms
- m. Attacks may be heralded by heavy sensation in the lower back; thighs and calves
- n. Exercise may block an impending attack in some instances
- 2. Secondary hypokalemic paralysis
 - a. Urinary and gastrointestinal potassium loss may cause proximal muscle weakness
 - b. Onset is usually after the age of 30
 - c. No family history of periodic weakness
 - d. If severe, the hypokalemia may cause a necrotizing myopathy
 - e. Weakness improves with correction of the hypokalemia
- 3. Thyrotoxic periodic paralysis
 - a. Most often occurs in Asian patients
 - b. Similar to hypokalemic periodic paralysis
 - c. More common in men than women
 - d. Beta-blockers may be helpful whereas acetazolamide is not
 - e. Correction of the hyperthyroidism stops the attacks

Calcium Channelopathies

- 1. Hypokalemic periodic paralysis type 1 (HypoKPP1)
 - a. HypoKPP1 is caused by mutations in the CACN1A3 gene that maps to chromosome 1q31-32 (in 70% of patients)
 - b. Onset is within the first two decades of life
 - c. They have no clinical or electrophysiological myotonia or paramyotonia
 - d. Episodic weakness is triggered by:
 - i. Exercise followed by rest or sleep
 - ii. High carbohydrate meals
 - iii. High sodium intake
 - iv. Emotional stress
 - v. Alcohol
 - vi. Viral illness
 - vii. Menstruation
 - viii. Sleep deprivation
 - ix. Beta agonists
 - x. Insulin
 - e. Attacks may be mild with focal weakness that can occur at any time of day but most often are seen in the morning
 - f. Severe attacks cause generalized flaccid weakness that usually spare facial, respiratory musculature and the sphincters
 - g. Muscle is unexcitable during attacks of profound weakness
 - h. Weakness usually lost > for hours to a day but residual weakness may persist for several days

Differential Diagnosis of Rarer Causes of Periodic Paralysis

- 1. Andersen-Tawil syndrome (ATS)
 - a. Approximately 2/3 of patients have mutations or small deletions in the KCNJ2 gene (AST1) that maps to chromosome 17q24; AD
 - b. Periodic paralysis
 - c. Ventricular arrhythmia with long QT interval
 - d. Developmental deficits
 - e. Episodic weakness that occurs spontaneously or after exercise and then rest
 - f. Onset is during the first or second decade
 - g. Attacks may last from hours to days with wide frequency variations
 - h. Patients may develop fixed proximal weakness
 - i. No myotonia or paramyotonia
 - j. Severe ventricular arrhythmias
 - k. Developmental anomalies include:
 - i. Scoliosis
 - ii. Short stature
 - iii. Hypertelorism
 - iv. Cleft palate
 - v. Mandibular hypoplasia
- 2. KCNE3 mutations that map to chromosome 11q13.4
 - a. Attacks of weakness associated with low serum potassium in some patients

Differential Diagnosis of Rare Channelopathies

- 1. Central core disease with malignant hyperthermia

- a. Mutations in the ryanodine receptor gene (RYR) that maps to chromosome 19q13.1
2. Malignant hyperthermia
 - a. MHS1
3. Mutation in the RYR gene that maps to chromosome 19q13.1
 - a. MHS2
 - i. Mutations in the RYR gene that maps to chromosome 17q11.2–q24
 1. May be allelic to hyperKPP, PMC and PAM
 - b. MHS3
 - i. Mutations in gene that maps to chromosome 7q21–22
 - c. MHS4
 - i. Gene not identified; maps to chromosome 3q13.1
 - d. MHS5
 - i. Caused by mutation in the dihydropyridine receptor gene that maps to chromosome 1q31 (allelic to hypoKPP1)
 - e. MHS6
 - i. Mutations that map to chromosome 5p
4. Clinical features are severe muscular rigidity (masseter muscles may be first)

Differential Diagnosis of Malignant Hyperthermia

The diagnosis of malignant hyperthermia is relatively straightforward. A volatile anesthetic agent or succinylcholine is used during induction of anesthesia which causes an elevation rather than a slight depression of temperature. Masseter rigidity, tachycardia, acidosis, an increase in end tidal CO₂ and severe acidosis supervenes. Generalized muscle rigidity follows.

Suspicion of malignant hyperthermia should be raised if a family member of the patient has died or had a major complication during uncomplicated anesthesia. An increased resting CK in a patient with an affected family member is also a clue that the patient is at risk. Baseline CK may be normal in patients at risk. The congenital myopathies, muscular dystrophies, phosphorylase deficiency, carnitine palmityl transferase deficiency and periodic paralysis have all been implicated in MH or a MH-like syndrome.

Fever, metabolic acidosis, tachycardia and cardiac arrhythmias

1. Triggers for MHS include:
 - a. Depolarizing muscle relaxants (succinylcholine)
 - b. Inhalational anesthetics (halothane)

Differential Diagnosis of Uncontrolled Metabolic State of Abrupt Onset

1. Rhabdomyolysis
 - a. Anesthetic agents
 - b. Drug-induced
2. Intense physical exercise
3. Acute intermittent porphyria

4. Ketamine induced catatonia
5. Thyroid storm
 - a. Precipitated by surgery
 - b. Anesthesia
6. Agents and illnesses that have produced MH response in humans:
 - a. Ketamine
 - b. Phencyclidine
 - c. Viral infections
 - d. Lymphoma
 - e. MAO inhibitors
 - f. Tricyclic antidepressants

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Chapter 10

Brainstem and Cranial Nerves

The Regulation of Breathing

The pattern and depth of breathing is determined by acid/base balance. The central chemoreceptors (CCRs) stimulate breathing and are regulated by the PaCO_2 . Peripheral receptors respond to pH and PaCO_2 that is a feedback servo-control-sensory system that regulates breathing.

The Medullary Respiratory Center

Rhythmic cyclical breathing originates in the medulla. Multiple higher nuclear centers (for voluntary control) as well as systemic pulmonary and aortic receptors and reflexes modify medullary respiratory drive.

The Dorsal Respiratory Group (DRG)

The DRG is located in the dorsomedial medulla and is composed of cells in the solitary tract nucleus. The DRG generates the respiratory rhythm and the initiation of respiration. Its afferent input is from the apneustic center of the lower pons and part of the solitary tract neurons that are recipients of chemoreceptive and mechanical receptors from the carotid sinus, carotid body, aorta, and the lungs. The DRG is inhibited by the pneumotaxic center of the upper pons.

Inspiration is initiated from the firing of DRG cells of the solitary tract nucleus in concert with cells of the ventral respiratory group. The output from the medulla to the diaphragm and somatic muscles of respiration is caused by the phrenic and intercostal nerves. The thoracic cavity expands and a negative pressure is achieved that expands the lungs with air. The inspiratory cells are inhibited by mechanical and chemoreceptive reflexes, the inspiratory muscles relax, and inspiration ceases. In normal conditions, the DRG produces a respiratory rate of 12 to 16 breaths/minute. Inspiration lasts approximately 2 seconds and expiration approximately 3 seconds.

The ventral respiratory group (VRG) is a column of neurons that are located in the ventrolateral medulla and extend from the caudal facial nucleus to the obex (about 400 μm).

The VRG is composed of four cell groups:

1. Rostral nucleus retrofacialis
2. Caudal nucleus retroambiguus
3. Nucleus para-ambiguus
4. The pre-Bötzinger complex

The VRG contains both inspiratory and expiratory neurons.

Function of the VRG includes:

1. A component of the initiation of inspiration
2. Para-ambiguus fires during inspiration

3. Nucleus retrofacialis is active during expiration
4. The VRG controls inspiration and expiration during exercise
5. The pre-Bötzinger complex is posited to be the central respiratory rhythm pattern generator from pacemakers' cells that initiate spontaneous breathing

These brainstem respiratory neurons are interconnected and function in concert with respiratory related sensory afferent receptors from the carotid body and sinus, the lungs and aortic arch to effect autonomic and adaptive changes in breathing from environmental stimuli

1. The brainstem respiratory circuits are compartmentalized within the medulla and pons. Neural groups in the brainstem and forebrain innervate brainstem respiratory compartments and include afferences from:
 - a. Serotonergic and catecholaminergic neurons
 - b. Neurons in the periaqueductal gray (PAG)
 - c. The hypothalamus, amygdala, and cerebral cortex
2. The dorsal respiratory group of neuron (DRG) fire bursts of action potentials is independent of afferent input in a fixed phase relationship with breathing:
 - a. In experimental preparation approximately 60% of DRG neurons project monosynaptic excitatory afferents to the phrenic nerve nucleus. There are less extensive projections to C1–C2 motor neurons of the spinal cord (inspiratory neurons) that are the origin of propriospinal projections to interneurons of the phrenic and thoracic motor neurons that innervate intercostal musculature. Vagally myelinated afferent fibers from the lungs and airways activate slowly adapting receptors (SARs) that initiate Hering-Breuer reflexes in which lung inflation terminates an ongoing inspiration. SARs release glutamate in second order nucleus tractus solitarius (NTS) relay neurons (pump cells) that in turn project to central rhythm and pattern neurons in the ventral respiratory chain and pons. Pump cells are primarily GABA-ergic
3. The ventral respiratory column:
 - a. The ventral respiratory column (VRC) is located in the ventral lateral medulla along its entire length
 - b. The generation of the respiratory rhythm is the result of circuit interactions in its rostral half. Bulbosplinal neurons in the caudal half of VRC transmit the generated rhythm but modify the amplitude of respiratory motor output
4. Rostral and caudal divisions of the ventral respiratory group have different functions:
 - a. In the caudal half of the medulla:
 - i. Neurons have been identified as excitatory. These neurons are glutamatergic and project to the cervical motor neurons that comprise the phrenic nerve that innervates the diaphragm as well as to the inspiratory motor neurons of the thoracic cord. The caudal VRC neurons also innervate expiratory neurons of the abdomen and thoracic spinal cord

The Rostral VRG (Ventral Respiratory Group)

1. The Bötzing Complex (BötC):
 - a. Comprises an aggregate of neurons that are located immediately caudal to the facial nucleus and project to the NTS. Neurons of the complex provide widespread inhibitory projections within the VRG that include both inspiratory and expiratory neurons
 - b. Expiratory neurons in the BötC receive SAR afferents (receptors from the lung and airway)
 - c. The BötC mediates the expiratory lengthening of the Hering-Breuer reflex
2. The pre-Bötzing Complex (pre-BötC):
 - a. The pre-Bötzing complex is located between the BötC and rVRG neurons
 - b. Its neurons discharge with greatest frequency between the expiratory and inspiratory phases of the respiratory cycle
 - c. It is essential for respiratory rhythm generation
3. The Retrotrapezoid Nucleus (RTN):
 - a. The Retrotrapezoid nucleus is located along the ventral surface of the pons slightly below the facial nucleus and extending caudally beneath the BötC
 - b. RTN neurons are central chemoreceptors that increase their firing rate in response to a decreased pH. They provide an extensive excitatory projection (glutamatergic) to neurons of the VRG
 - c. RTN neurons also integrate central and peripheral chemoreceptor afferents. Second order neurons that receive peripheral chemosensory afferents that are located in the caudal commissural NTS also project to the RTN
4. The Parafacial Respiratory Group (pFRG):
 - a. The pFRG are located beneath the caudal end of the facial nucleus that extends caudally beneath the BötC
 - b. The function of this aggregate of neurons is controversial. It has been suggested that circuits of the pFRG form the expiratory rhythm generator that is coupled by reciprocal inhibition to the inspiratory generator of the pre-BötC
5. Pontine Respiratory Areas:
 - a. The VRG extends rostrally into the lateral pons:
 - i. Respiratory neurons are intermingled between the motor nucleus V and principal sensory V that comprises the paratrigeminal area
 - ii. Dorsally from the paratrigeminal area, respiratory neurons extend into the Kölliker-Fuse nucleus that merges with parabrachial areas medially
 - iii. Tracing studies reveal that the greatest number of positive respiratory neurons is in the Kölliker-Fuse nucleus and the ventrolateral parabrachial complex
 - iv. The functional role of the respiratory neurons of the ventrolateral pons has not been completely defined. It has been suggested that they are important in the shaping of the hypoxic ventilatory response
6. The Pontine Respiratory Group (PBr):
 - a. Neurons of the PBr complex (respiratory neurons) and those of the Kölliker-Fuse nucleus are the primary constituents of the pontine respiratory group
 - b. This group of neurons contains:
 - i. Phasic inspiratory and expiratory neurons
 - ii. Tonically active neurons that are modulated by the respiratory cycle which in neurons increase their firing with arousal and pain
 - iii. The Kölliker-Fuse (KF) nucleus projects to:
 1. Ventral Respiratory Complex (VRC)
 2. Respiratory areas of the NTS (most heavily to the ventrolateral areas)
 3. Spinal projections to the motor neurons that comprise the phrenic nerve and bulbospinal neurons of the rostral ventral respiratory group (rVRG)
 4. Respiratory neurons of the ventrolateral medulla and spinal cord
7. The neuroanatomical and chemical anatomy of respiration is extremely complex. There are interacting circuits at almost all levels. In outline form:
 - a. The pre-BötC complex initiates inspiration that is facilitated and maintained by neurons in the dorsal medulla and the rostral component of the ventral respiratory complex (VRC) of the pons
 - b. Hering-Breuer reflexes are elicited by myelinated fibers of the IXth and Xth nerves that project to the nucleus tractus solitarius to decrease inspiration in the face of the inflated lungs utilizing slow adapting receptors (SARs)
 - c. The retromedial trapezoid/parabrachial complex is the initiator for expiration (RTN/pFRG)
 - d. The retrotrapezoid body nucleus (RTN) is the central chemosensory nucleus that adjusts the rate and shape of respiration in conjunction with pH and other chemical stimuli
 - e. The A5 cell group in the ventrolateral pons contains glutamatergic and noradrenergic neurons that modulate cardiovascular and respiratory functions. It projects to the medullary and cardiorespiratory centers as well as the sympathetic premotor neurons of the intermediolateral column of the spinal cord
 - f. The Kölliker-Fuse nucleus:
 - i. Is part of the off-switch for inspiration
 - ii. Important as a determinant of breathing rate
 - iii. Controls airway potency during the respiratory cycle
 - iv. Important for the phase transition between inspiration and expiration
 - g. The pons receives extensive projections from the mid-brain, limbic system and forebrain. It is a supramedullary control center for breathing
8. Almost all pathologies that affect the brainstem interfere with some aspect of respiratory control:

- a. Mutations in the PHOS-2 gene causes congenital hypoventilation syndrome
- b. Some evidence that SIDS (Sudden Infant Death Syndrome) is due to deficient medullary pontine serotonergic interaction
- c. The Kölliker-Fuse area may be involved in neurodegenerative diseases. Tauopathy shifts the post-laryngeal constrictive activity towards inspiration that cause glottal constriction during inspiration during sleep that may be a component of obstructive sleep apnea
- d. Demented patients have severe tauopathy in the Kölliker-Fuse area
- e. There are strong projections from the carotid body afferents to the KF complex. It has been suggested that this is a component of the adaptation of central or peripheral arterial chemoreception and that is critical for homeostasis. The KF area demonstrates increased activity during hypoxia, hypercapnia, or carotid sinus stimulation
- f. The lateral PB complex receives strong nociceptive projections that mediate cardiorespiratory functions that include apnea/tachypnea, tachycardia/bradycardia, and blood pressure during painful stimuli
- g. Achondroplasia and other cervical spinal cord anomalies may be associated with Ondine's curse, the failure of automatic breathing during sleep

The Neurogenic Regulation of Short Term Blood Pressure

The short-term control of blood pressure is mediated by vasoceptors, the most sensitive of which are in the carotid sinuses and aortic arch. Carotid sinus baroreceptor axons are within the glossopharyngeal nerve while those from the aortic arch travel with the vagus nerve to synapse within the nucleus tractus solitarius (NTS). NTS neurons project glutamatergic excitatory fibers to the caudal ventrolateral medulla (CVLM). Inhibitory CVLM projections which are GABAergic inhibit the rostral ventrolateral medulla (RVLM). This nucleus (RVLM) is a major brainstem regulator of the sympathetic nervous system by its projections (glutamatergic) to sympathetic intermediolateral column neurons of the spinal cord. Baroreceptors are mechanical stretch receptors and when activated by increased blood pressure, project to the NTS which in turn activates the CVLM that inhibits the rostral ventrolateral medulla (RVLM). This circuit decreases sympathetic activity which decreases blood pressure. There is less activation of pain receptors with a drop in blood pressure and thus less inhibition of RVLM and greater sympathetic tone.

The parasympathetic outflow to the heart is maintained from baroreceptor activation and their projections to the sinoatrial and atrioventricular nodes from the nucleus tractus solitarius and the dorsal vagal nucleus.

Baroreceptors are stretch-sensitive mechanoreceptors that are active to some degree at normal resting blood pressure

although a subgroup activates only after a pressure stretch threshold is exceeded. Cardiovascular reflexes are mediated by high pressure and that can be observed in beat-to-beat changes of heart rate. The nucleus tractus solitarius coordinates these cardiovagal, cardiosympathetic and vasosympathetic reflexes. The arterial baroreceptors discharge when the blood volume affected by the ventricle distends the ventricular wall that modifies heart rate and vascular smooth muscle tone. These rapid modifications cause beat-to-beat blood vessel variability.

The role of the sympathetic nervous system is the maintenance of blood pressure and the regulation of blood flow for seconds to minutes via the arterial baroreflex. Cardiac sympathetic innervation of the SA node increases the slope of diastolic depolarization during the SA node action potential which increases heart rate. Sympathetic innervation of the myocardium increases myocardial contractility and thus stroke volume. Peripheral arterial sympathetic stimulation causes vasoconstriction through norepinephrine and neuropeptide activation of α -adrenergic receptors.

Increases in afferent input from vasoconstriction through norepinephrine and neuropeptide activation causes a decrease in sympathetic outflow which in conjunction with parasympathetic innervation of the SA node decreases heart rate. A drop in blood pressure causes vasoconstriction, an increase in stroke volume and increased heart rate.

As with breathing, brainstem pathologies interfere with short-term cardiovascular control of blood pressure.

The Brainstem and Arousal

Consciousness is dependent upon the action of the ascending reticular activating system (ARAS). It is composed of several neuronal circuits that originate primarily in the reticular formation of the brainstem which relay in the intralaminar nuclei of the thalamus which in turn projects to the cerebral cortex.

Brainstem nuclei of the system include:

1. The locus cereleus
2. Dorsal and median raphe nuclei
3. Pendunculopontine nucleus
4. The parabrachial nucleus

Other components of the system are non-specific thalamic nuclei, the hypothalamus (orexin neurons in the lateral hypothalamus), and the basal forebrain.

In general, the specific connections of the ARAS nuclei are important for arousal while those of the thalamic nuclei modulate arousal.

Hypothalamic orexin is excitatory to the entire ARAS including the midline and intralaminar thalamic nuclei. Orexin causes a slow depolarization mediated by a cation current in cholinergic lateral dorsal tegmental/pendunculopontine nuclei as well as the serotonergic dorsal raphe neurons. The orexin current of significant high frequency input generates Ca^{2+} dependent oscillations that peak in the theta to alpha frequency range (4–14 Hz) that extended to 100 Hz

(gamma activity is 30–60 Hz). The waking state shifts ECG power to higher frequencies that include synchronized periods (epochs) of intracortical gamma activity. The ARAS and the lateral dorsal tegumental (LDT), pedunculopontine (PPT) and serotonergic dorsal raphe neurons are pivotal in the shift of EEG activity to high frequencies associated with wakefulness and cognitive function. Some neurons in the system may be gamma wave generators because they produce high threshold Ca^{2+} dependent oscillators at gamma frequencies.

Lesions of these diffuse brainstem circuits form a broad spectrum of pathologies that affect decreased arousal, wakefulness, and cognitive function.

Cranial Nerves

General Characteristics

1. The olfactory nerve penetrates the cribriform plate of the ethmoid bone to synapse in the olfactory bulbs
2. Axons of mitral and tufted cells form the olfactory tract
3. The olfactory tract divides into a medial and lateral olfactory stria
4. The lateral stria project to the piriform lobe of the temporal cortex (the primary olfactory cortex)
5. There are projections to the amygdala, septal nuclei and the hypothalamus

Clinical Manifestations

1. Anosmia
2. Parosmia:
 - a. Perversion of smell
3. Disturbance of complex olfactory function:
 - a. Detection is preserved to a greater degree than discrimination
 - b. Olfactory hallucinations

Neuropathology

1. Trauma:
 - a. Fracture of the cribriform plate of the ethmoid bone
 - b. Closed head injury without fracture (tear of the olfactory nerve filaments)
2. Tumors
3. Syndromic anosmia
4. Systemic disease
5. Degenerative diseases
6. Abscess of the frontal lobe
7. Mucocele of the frontal sinus
8. Post-viral infection
9. Siderosis (Fe^{++} deposition on the nerve from recurrent cerebral bleeding from AVMs, aneurysms and cavernous hemangiomas)
10. Nasal inflammatory disease:
 - a. Allergic rhinitis
 - b. Chronic rhinosinusitis

Clinical Manifestations

1. Olfactory testing that includes:

- a. Odor threshold
 - b. Odor discrimination
 - c. Odor identification
2. Cranial MRI
 3. Blood tests for B12 deficiency
 4. Gonadotrophins and sex hormones in amenorrheic young women
 5. EEG if olfactory hallucinations are prominent

Differential Diagnosis of Anosmia

1. Trauma:
 - a. Fracture of the cribriform plate and basilar skull fracture
 - b. Closed head injury without fracture
2. Tumor:
 - a. Olfactory groove meningioma (Foster-Kennedy syndrome):
 - i. Ipsilateral anosmia
 - ii. Ipsilateral optic atrophy
 - iii. Contralateral papilledema
 - b. Differential diagnosis of Foster-Kennedy syndrome:
 - i. Mucocele
 - ii. Subdural hematoma (subfrontal)
 - iii. Esthesioblastoma:
 1. Tumor of the olfactory epithelium
 2. Frontal lobe behavioral changes
 3. CSF leak through the nostril
 4. May present with a seizure
 - c. Glioma of the frontal lobe
 - d. Pituitary adenoma with frontal suprasellar extension
 - e. Carcinomatosis of the meninges
 - f. Osteoma of the sphenoid or frontal bone
3. Syndromic anosmia:
 - a. Walker-Warburg syndrome
 - b. Kallmann syndrome (ovarian dysgenesis)
 - c. Hencken's syndrome (post-viral)
 - d. Foster-Kennedy syndrome
 - e. Pseudo Foster-Kennedy:
 - i. Papilledema of the spared eye in a patient with prior optic atrophy in the contralateral eye
 - ii. Gyrus rectus pressure
 - f. Machado-Joseph disease (SCA3)
 - g. Turner syndrome
 - h. Down syndrome
4. Parosmia and cacosmia:
 - a. Head trauma
 - b. Psychiatric disease
5. Olfactory hallucinations:
 - a. Primary olfactory cortical injury (piriform cortex of the temporal lobe)
 - b. Direct disruption of the olfactory pathway
 - c. Unilateral paroxysmal olfactory hallucination (paroxysmal dysosmia); irritation of the olfactory bulb or nerve
 - d. Complex partial seizure of the temporal lobe

- e. Hyperosmia occurs with migraine headache and hyperemesis gravidarum
- f. Hyposmia and parosmia:
 - i. Associated with hypogeusia (diminished and perverted taste)
- 6. Neurodegenerative Diseases:
 - a. Alzheimer's disease
 - b. Parkinson's disease
 - c. Spinocerebellar degeneration (Machado-Joseph disease)
 - d. Huntington's disease
- 7. Allergic Rhinitis
- 8. Infections:
 - a. Herpes simplex (meningoencephalitis)
 - b. HIV
 - c. Hansen disease
- 9. Liver disease:
 - a. Acute viral hepatitis
 - b. Cirrhosis
- 10. Nasal obstruction:
 - a. Adenoid hypertrophy
 - b. Large inferior turbinates
 - c. Polyposis
 - d. Sjögren's syndrome
- 11. Uremia (dialyses)
- 12. Iatrogenic:
 - a. Ethmoidectomy
 - b. Orbitofrontal surgeries
 - c. Rhinoplasty
 - d. Submucous resection of the nasal septum
 - e. X-RT therapy
 - f. Laryngectomy
- 13. Endocrine disorders:
 - a. Adrenal insufficiency
 - b. Diabetes mellitus
 - c. Hypothyroidism
 - d. Pseudohypoparathyroidism
- 14. Detection of odor > discriminative ability:
 - a. Korsakoff's syndrome
 - b. Thalamic lesions
 - c. Prefrontal lesions
 - d. Alzheimer's disease
 - e. Parkinson's disease
 - f. Huntington's disease
- iv. Medial chiasm lesion – decreased visual acuity bilaterally
- v. Lateral chiasmatic lesions decrease acuity in the ipsilateral eye
- vi. Visual acuity remains intact if the macular fovea fibers are intact
- 2. Retrochiasmatic bilateral lesions decrease visual acuity equally in both eyes:
 - a. Impaired contrast sensitivity, more subtle defects than loss of visual acuity that occurs with macular and optic nerve dysfunction
- 3. Color Perception:
 - a. Decreased in areas of the visual field (VF) deficit
 - b. Desaturation of red in lesions of the visual pathways
 - c. Retinal photoreceptor damage affects the perception of blue
 - d. Color loss occurs with macular dysfunction (macular projections may also be affected by optic nerve and chiasmatic lesions)
 - e. Color vision loss usually parallels VA loss:
 - i. Optic neuritis color loss > VA (visual acuity) defects; in optic neuritis there is chromatic sensitivity loss and decreased luminance sensitivity
 - f. Impairment of color perception may occur from posterior VF deficits
 - g. Bilateral lesions of the anteromedial occipital lobe cause color blindness
- 4. Visual Field Defects (Retinal):
 - a. General Characteristics:
 - i. Macular lesions cause central defects
 - ii. Retinal lesions cause inverted deficits:
 - 1. Superior lesion produces an inferior deficit
 - 2. Lateral retinal lesion causes a medial visual field deficit
 - 3. Centrocecal scotoma:
 - a. Extends from central vision to the blind spot
 - b. Macula and components of the papillomacular bundle
 - 4. Nasal field peripheral nerve fiber deficit:
 - a. Arcuate shape
 - 5. Small deep retinal lesions:
 - a. Discrete defects localized to the point of lesion:
 - i. The fiber layer is spared
 - 6. Large deep retinal lesions:
 - a. Superficial fiber layer is affected
 - b. Fan shaped arcuate defect, the tip of the fan is toward the lesion with the base fanning peripherally toward the nasal horizontal meridian
 - 7. Nerve fiber bundle defects (retinal):
 - a. Most common with lesions of the optic nerve head
 - b. Tip of the defect reaches the blind spot

Cranial Nerve II

General Characteristics

- 1. Visual Acuity:
 - a. Visual discrimination of fine details of high contrast
 - b. Macular functions or its projections
 - c. Impaired by:
 - i. Changes in the shape of the globe
 - ii. Refractory characteristics of the vitreous
 - iii. Compressive and non-compressive lesions of the optic nerve

8. Defects from lesions of nasal retinal fibers (subserve the temporal field lateral to the blind spot) are sectoric. The nasal retinal fibers are straight rather than arcuate
9. Ring VF defects (retinal):
 - a. There is preserved vision centrally with preserved vision central and peripheral to the scotoma. Most often, the center coincides with the fovea
 - b. A unilateral pericentral scotoma is macular
 - c. Fusion of superior and inferior arcuate defects causes the ring scotoma
 - d. The horizontal step of the ring is a mismatch of the superior or inferior arcuate defect
 - e. Nerve fiber bundle defects:
 - i. A visual field deficit in which part of the burden (scotoma) corresponds with the course of the retinal nerve fiber layer
5. Central Visual Field Defects:
 - a. Hemianopia:
 - i. A visual field defect that involves one-half of the visual field (both eyes are involved)
 - ii. There is a sharp cut off in the vertical and horizontal meridians
 - b. Unilateral visual inattention:
 - i. Most often occurs with parieto-occipital lesions
 - ii. There is no deficit with unilateral visual field testing; if stimuli are placed in both right and left hemifields simultaneously, the patient fails to see the object in the field opposite the lesion
 - c. Vertical hemianopia can be nasal or temporal
 - d. Altitudinal defects are superior or inferior
 - e. Bilateral homonymous defects are similarly located in both visual fields. They are congruent if their shape is superimposable, if not they are incongruous
 - f. Riddoch phenomenon:
 - i. The patient can appreciate a moving object within a dense VF deficit but can't see the object if it is stationary
 - ii. Dissociation between a kinetic and static stimulus:
 1. Possible non-striated vision via the superior colliculus – pulvinar prestriate cortex
 2. Occipital lobe > optic tract > chiasm
6. Pupillary Light Reflex:
 - a. Some optic nerve fibers leave the visual sensory pathway prior to the lateral geniculate body to synapse in the pretectal region of the dorsal midbrain
 - b. Direct stimulation should elicit a brisk symmetrical constriction if it does not there is often a retinal or optic nerve lesion
 - c. Shining the light in the unaffected eye constricts both pupils; if swinging the light to the affected eye that then elicits dilation to direct light has been attributed to a defect in the ipsilesional retina or the optic nerve

- d. The affected pupillary response is most likely a defect in midbrain neurons that control the reflex ("slippage of the light reflex")
- e. Rarely, this phenomenon may be demonstrated with an optic tract lesion which is known as a Behr's pupil. The light has to be focused (slit lamp) on the affected retinal photo receptors (in the territory of the field loss from the optic tract lesion)
- f. The lateral geniculate body (LGB), optic radiation and cortical lesions do not affect the pupillary light reflex

Ophthalmoscopic Observations

1. Optic atrophy:
 - a. Sharp disc margins
 - b. Loss of the lamina cribrosa (of the optic cup)
 - c. Decreased ratio of the cup of the optic nerve head to the disc margin
 - d. Sharpness of the margin, particularly on its temporal side
 - e. Decreased visual acuity
 - f. Loss of disc capillaries (Less than 14)
 - g. Thinness of the retinal arteries
2. Glaucoma:
 - a. Deepening of the optic cup
 - b. Nasalization of the optic cup:
 - i. Present by the time of decreased visual acuity or arcuate Bjerrum (step) scotoma appear
3. Papilledema order of occurrence of signs:
 - a. Fat veins
 - b. Loss of venous pulsations
 - c. Hyperemic disc (dilation of the capillaries of the disc surface)
 - d. Protrusion of the lamina cribrosa
 - e. Loss of the disc margin: superior prior to inferior; the last is the temporal margin; the nasal margin is always slightly blurred
 - f. Slit hemorrhages off the disc margin
 - g. Retinal and choroidal folds
4. Optociliary shunts and veins:
 - a. Appear at the disc margin or on the disc
 - b. Increased pressure in the optic canal or intracranially
 - c. Anastomosis between the central retinal vein and the peripapillary choroidal venous system
 - d. Differential diagnosis:
 - i. Optic nerve sheath meningioma of Schwalbe
 - ii. Optic nerve glioma
 - iii. Neonatal hydrocephalus
 - iv. Pseudotumor cerebri
 - v. Drusen of the optic disc (pseudopapilledema)
 - vi. Glaucomatous atrophy
 - vii. Chronic atrophic papillitis
 - viii. Central retinal vein occlusion
 - ix. Arachnoid cyst
 - x. Neurofibromatosis
 - xi. Optic nerve coloboma
 - xii. Arteriosclerosis
 - xiii. Hematoma of the disc

Color Perception

General Characteristics

1. Color perception may be decreased in an area of a visual field deficit when vision for a white target is preserved
2. Desaturation for red is often caused by lesions of the visual pathways
3. Color vision loss usually parallels visual acuity loss with ischemic lesions; an exception is in optic neuritis where color vision may be much more affected; in optic neuritis chromatic sensitivity is much worse than luminance sensitivity
4. Patients with nystagmus usually have normal color vision:
 - a. Color vision does not depend on foveation or a well-focused retinal image
5. Visual acuity is usually normal with acquired achromatopsia due to cortical lesions
6. Congenital color vision defects:
 - a. More common in men than in women
 - b. Defects are primarily of red and green
7. Acquired color vision defects:
 - a. Blue-purple or blue-green hues
8. Patients with primary optic nerve disease:
 - a. Difficulties with red and green hues
9. Primary retinochoroidal diseases:
 - a. Blue discrimination defects between blue and yellow
10. Bright light color phenomenon:
 - a. Reveals color processing defects
 - b. Shining a bright light into the patient's eye usually induces a succession of colors; usually decreased with acquired dyschromatopsia
11. Lesions of the posterior visual pathways:
 - a. Decreased color perception
 - b. Bilateral anteromedial occipital lobe lesions may have color blindness with normal visual acuity

Anatomy of the Visual System

General Characteristics

1. The rods and cones are located deep in the retina in the retinal pigment epithelium
2. They project via bipolar and horizontal connecting amacrine cells to the more superficially placed ganglion cells which in turn relay primarily in the lateral geniculate body with a concomitant projection to the superior colliculus
3. The rod pigment is a glycoprotein, rhodopsin, that is stimulated by light within the visible wavelength of 400–800 nm. The rods are most dense in the fundus of the globe and are absent in the macula and optic disc
4. There are three types of cones that are activated primarily by red, green or blue light
5. There are seven million cones. Approximately 100,000 are concentrated in the macular region at the center of which is the fovea which measures 35 mm yet has no vessels or

neural elements other than tightly packed cones. It is the area that has the greatest visual discrimination. This is an area that has direct access to light

6. There are 1.2 million ganglion cells whose receptive fields become smaller in the posterior area of the globe. Cones in this area synapse one to one with ganglion cells. In the periphery of the globe there is extensive overlap between receptive fields of cones and ganglion cells. Thus peripheral vision may be spared with some ganglion disorders
7. There are two major classes of ganglion cells, M- and P-cells. They project to different layers of the lateral geniculate body which in turn projects to the visual cortex
8. M-cells are approximately 10% of ganglion cells and subserve spatial location of the target. They convey depth perception (stereopsis), do not detect color and have high contrast sensitivity:
 - a. They project to the magnocellular neurons of layer one and two of the LGD that in turn projects to 4C alpha neurons of visual area 17 of the occipital cortex. There are further projections to 4 beta area 17 neurons and then to the MT middle temporal gyrus of the temporal lobe
 - b. The macula is 90% P-cells which determine target identification and are characterized by:
 - i. High spatial resolution
 - ii. Color vision
 - iii. Low contrast sensitivity
 - iv. Also are in the peripheral retina
 - v. Project to parvocellular neurons in layers 3, 4, 5 and 6 of the LGD; they project to 4C beta neurons in layers 2 and 3 of cortical area 17. These neurons in turn project to cortical area 18 which projects and synapses with visual area V3 and V4
 - vi. M- and P-cells may be differentially affected
 - vii. Ganglion cell axons constitute the innermost retinal layer that is separated from the vitreous by a thin basement membrane
 - viii. Ganglion cells closest to the disc project their axons through the entire nerve fiber layers; the more peripherally located ganglion cell axons are deeper in the nerve fiber layer. Nasal fibers (located nasally to the optic disc) and those from the nasal side of the macula (the papillomacular bundle) run directly to the disc; the remaining fibers have a superior and inferior accurate projection to the disc
 - ix. Axons from the temporal side ganglion cells (vertical line through the fovea) project to the ipsilateral LGD whereas those from the nasal side run in the optic chiasm (contralaterally)
 - x. Macular neurons are a vertical strip of 1 degree of the fovea and project bilaterally to the LGD

Visual Field Defects*General Characteristics*

1. The central 20–30 degrees of vision are very important as few disorders affect the peripheral fields alone. The exceptions to this rule are:
 - a. Tapetoretinal degenerations
 - b. Retinal detachments
 - c. Anterior visual cortex lesions
2. Ametropia:
 - a. A condition in which an optic defect involves an error of refraction that is most often seen with astigmatism, hyperopia or myopia as well as presbyopia and must be accounted for when testing visual fields:
 - i. Uncorrected astigmatism may cause depression of the upper temporal quadrant (does not respect the vertical meridian) thus differentiating it from chiasmatic lesion; it also spans central fixation
 - ii. Spherical ametropia:
 1. Generalized field depression
 2. Rarely causes an upper temporal depression that may be found under the blind spot (blurring of the blind spot) due to local ametropia from abnormal retinal curvature
 - iii. Angioscotomata:
 1. Due to superficial retinal vessels and the blind spot are physiological scotoma
 - iv. Absolute defects involving the outer limits of the visual fields are known as contractures while depressions are smoothly tapering but not absolute visual field deficits

Specific Visual Field Deficits

1. A central defect of vision is most often from lesions of the macula and its ganglion cells and their axonal projections
2. A centrocecal defect:
 - a. Affects the macular area and the papillomacular bundle
 - b. A scotoma between the point of fixation and the blind spot
3. Nerve fiber bundle defect:
 - a. At least part of the border of the VF defect is coincident with the course of the retinal nerve fiber layer
4. Peripheral nerve fiber bundle in the nasal field:
 - a. If there is an arcuate shape of the lesion it is in the retina or optic nerve
5. Differential diagnosis of arcuate visual field deficits include:
 - a. Glaucoma
 - b. Anterior ischemic optic neuropathy
 - c. Drusen of the disc
 - d. Congenital optic pits
6. Small deep retinal lesions:
 - a. Discrete defect (dependent on the projection zone of the affected ganglion cells)

7. Retinal lesions that affect the superficial fiber layer cause a fan shaped arcuate lesion with its tip pointing to the lesion with the fan facing peripherally and toward the nasal horizontal median (arcuate shaped)
8. Nerve fiber bundle defects:
 - a. Most commonly occur with lesions of the optic nerve head
 - b. Tip of the defect reaches the blind spot
 - c. Differential diagnosis:
 - i. Branch retinal artery or vein occlusion
 - ii. Juxtapapillary inflammation
9. Defects in the temporal field (from nasal fibers that see the temporal field but project directly to the disc) cause sector defects
10. Defects of the temporal field:
 - a. Do not respect the horizontal meridian because neither the blood supply nor nasal retinal fibers are arranged along a horizontal raphe
11. Enlargement of the blind spot:
 - a. Any process that enlarges the disc head by swelling or deposition of material (drusen or hematomas)

Monocular Altitudinal VF Defects

1. Monocular altitudinal defects often have macular sparing
 - a. Central retinal artery territory occlusions cause the defect
 - i. Macular sparing may occur from blood supply derived from the cilioretinal artery
 - b. Anterior ischemic optic neuropathy
 - i. Involves the anterior component of the optic nerve
2. Secondary to ischemia of the posterior ciliary arteries
3. The defect is usually inferior
4. Differential diagnosis of altitudinal VF deficits include:
 - a. Choroiditis
 - b. Choroidal coloboma
 - c. Retinal detachment
 - d. Glaucoma
 - e. Optic nerve hypoplasia
 - f. Chronic atrophic papilledema
 - g. Drusen
 - h. Optic nerve trauma
 - i. Masses that affect the optic nerve and chiasm
5. Differential diagnosis of bilateral altitudinal VF deficits:
 - a. Bilateral ischemic lesions of the retina or optic nerves
 - b. Bilateral occipital lobe lesions
 - c. Prechiasmatic lesion:
 - i. Compresses the optic nerve inferiorly
 - ii. Superior altitudinal defects
 - d. Inferior compression of the optic nerves:
 - i. The nerves are compressed at the intracranial end of the optic canals:
 1. Produces bilateral inferior altitudinal defects
 - e. Bilateral lesions of the medial aspects of the lateral geniculate bodies (LGD)
 - i. Cause bilateral inferior altitudinal deficits

- f. Incomplete altitudinal VF deficits:
 - i. More common with retinal lesions:
 - 1. The nerve fiber layer only respects the horizontal meridian in the nasal VF
- g. Occipital pole lesions:
 - i. Altitudinal VF defects spare macular vision:
 - 1. Due to dual blood supply to the occipital pole (branch from the MCA or well as PCA supply)

Bilateral Ring VF Deficits

- 1. Most often are caused by retinal disorders but can occur from bilateral occipital lobe disorders
 - a. Occipital lesions are associated with a vertical step between the two halves of the ring

Chiasmatic Visual Field Deficits

- 1. General characteristics:
 - a. The ratio of crossed to uncrossed fibers in the chiasm is 53:47
 - b. Dorsal and ventral uncrossed fibers are lateral in the chiasm and project into the ipsilateral optic tract
 - c. Dorsal extramacular crossing fibers:
 - i. Decussate posteriorly in the chiasm
 - ii. Project in the dorsomedial contralateral optic tract
 - d. Crossing macular fibers:
 - i. Central and posterior chiasm
 - e. Inferonasal retinal fibers
 - i. Comprise peripheral fibers and make Von Willebrand's loop
- 2. Chiasmatic syndromes:
 - a. Anterior chiasm:
 - i. Central defect in one field with a superior defect in the contralateral VF
 - ii. The lesion is at the anterior angle of the chiasm that involves the ipsilateral optic nerve and the inferonasal retinal crossing fibers of Von Willebrand's knee (a junctional scotoma)
 - iii. Differential diagnosis of junctional scotomas
 - 1. Pituitary tumors
 - 2. Suprasellar meningioma
 - 3. Supracallosal aneurysm
 - 4. Craniopharyngioma
 - 5. Glioma
 - 6. Demyelinating disease (loss of neuro optica)
 - 7. Pachymeningitis
 - 8. Trauma
 - b. Body of the chiasm:
 - i. Bitemporal heteronymous VF defects:
 - 1. The defects may be peripheral, central or a combination of the two
 - 2. They may or may not split the macula
 - 3. They may be quadrantic or hemianopic
 - 4. Visual acuity is usually normal
 - 5. The optic discs may be normal or pale
 - c. The posterior chiasm syndrome:

- i. Bitemporal heteronymous scotoma
- ii. The peripheral VFs are intact; the defect is central
- iii. Normal visual acuity and optic discs

Binasal Hemianopsias

General Characteristics

- 1. Asymmetric
- 2. Do not respect the vertical meridian
- 3. Differential diagnosis
 - a. Usually due to bilateral intraocular disease of the retina or optic nerve
 - i. Chronic papilledema
 - ii. Schemic optic neuropathy
 - iii. Optic nerve drusen
 - iv. Sector retinitis pigmentosa
 - v. Compression of the lateral chiasm
 - vi. Hydrocephalus with IIIrd ventricular enlargement
 - vii. Empty sella syndrome
 - viii. Dural CSF leak

Homonymous Hemianopsia

General Characteristics

- 1. Causative lesions are in: 1. the optic tract, 2. LGD, 3. occipital lobe
- 2. Homonymous defects affecting the optic tract and LGD are incongruous
- 3. The more posterior the lesion, the greater the degree of congruity in the two VF (the fibers from the LGD are more closely packed and all are more likely to be lesioned)
- 4. Tumors produce sloping defects while vascular lesions produce sharp delineated VF deficits
- 5. Optic tract lesions:
 - a. Macular fibers are dorsolateral; peripheral fibers from the upper retina are dorsomedial and peripheral fibers from the lower retina are ventrolateral
 - b. Complete lesions of the optic tract cause:
 - i. Complete macular splitting, homonymous hemianopia with retained visual acuity
- 6. Most optic tract lesions are incomplete and cause an incongruous VF deficit
- 7. May be associated with a relative afferent pupillary defect in the eye with the temporal field deficit (contralateral to the lesion)
- 8. May be associated with a concomitant IIIrd nerve injury
- 9. Chronic optic tract lesions may cause bilateral optic atrophy with a wedge or band pallor in the contralateral eye and generalized pallor in the ipsilateral eye
- 10. Differential diagnosis of optic tract lesions:
 - a. Glioma
 - b. Meningioma
 - c. Craniopharyngioma
 - d. Pituitary adenoma
 - e. Ectopic pinealoma

- f. Abscess
 - g. Aneurysms
 - h. Metastases
 - i. AVM
 - j. Demyelinating disease
 - k. Iatrogenic surgical procedures
11. Lateral geniculate body
- a. Anatomy:
 - i. Axons that originate from ganglion cells above the fovea synapse medially while those from ganglion cell below the fovea synapse laterally
 - ii. Macular fibers synapse centrally
 - b. Post-geniculate fibers
 - i. With the optic radiations the superior retinal fibers are located in the superior component of the radiation and synapse above the calcarine fissure
 - ii. Upper VF fibers originate from the medial LGD and course through the parietal lobe
 - iii. Lower fibers that have originated in the lateral LGD comprise Von Willebrand's loop in the temporal lobe
 - iv. Clinical manifestation of LGD lesions:
 - 1. Complete macular splitting homonymous hemianopia
 - 2. Hemianopic optic atrophy (transsynaptic degeneration) may occur
 - 3. Occlusion of the anterior choroidal artery causes:
 - a. Homonymous defect in the upper and lower quadrants with sparing of a horizontal sector (quadruple sectoranopia) due to the anatomical organization of the LGD. Vertical columns within the LGD represent horizontal parallel portions of the retina
 - 4. Occlusion of the posterior lateral choroidal artery
 - a. Perfuse the central component of LGD
 - b. Cause a horizontal homonymous sector defect which may also be seen with optic radiation or rarely from occipital cortex lesions in the area of the calcarine fissure, temporo-occipital function or parieto-pero-occipital areas
 - 5. Differential diagnosis of LGD lesions:
 - a. Infarction (most common)
 - b. Arteriovenous malformations
 - c. Trauma
 - d. Mass lesions (tumors)
 - e. Demyelinating disease
 - f. Methanol poisoning

Superior Homonymous Quadrantic VF Defects

- 1. Large lesions of the inferior bank of the calcarine fissure; small lesions cause scotoma
- 2. Temporal loop of the optic radiations (Von Willebrand's knee)
- 3. Deep parietal lesions affect the dorsal component of the optic radiations, which produce inferior quadrantic defects
- 4. Quadrantic defects are most often due to optic radiation lesions

Lesions of the Striate Cortex

- 1. Anterior lesions:
 - a. Lesions are usually adjacent to the parieto-occipital fissure
 - b. Involve the monocular temporal crescent of the contralateral visual field
- 2. Posterior lesions:
 - a. Located in the posterior 50–60 percent of the striate cortex that includes the occipital pole which affects macular vision
- 3. Intermediate lesions
 - a. Are located between the anterior and posterior areas and affect 10 to 60 degrees of vision in the contralateral hemifield
- 4. Differential diagnosis of unilateral occipital lobe disorders include:
 - a. Infarction from disease of the posterior cerebral artery
 - b. Venous infarction
 - c. Intracranial hemorrhage
 - d. AVM and fistulas
 - e. Tumor
 - f. Abscess
 - g. Trauma

Bilateral Occipital Lobe Infarction

- 1. May cause unilateral homonymous scotoma
- 2. Usually have some macular sparing (ring scotoma) that respect the vertical meridian
- 3. Bilateral altitudinal defects
- 4. Bilateral homonymous hemianopia may cause cortical blindness or Anton's syndrome from:
 - a. Embolus to the top of the basilar artery that affects both PCAs
 - b. Serial PCA stroke
 - c. Anoxic insults
 - d. Complications of cerebral angiography
 - e. Migraine
 - f. Tentorial herniation (PCA is occluded under the tentorium)
 - g. Anton's syndrome occurs if there is cortical blindness and includes:
 - i. Denial of blindness
 - ii. Normal pupillary light reflex
 - iii. May have a small portion of the peripheral VF spared and thus patients can navigate around large objects
 - iv. Emotional aberrations (usually early euphoria)

Differential Points from Changes in Visual Perception

1. Lesions of the anterior optic pathways
 - a. Patients complain of:
 - i. Difficulty reading
 - ii. Dimness of vision
 - iii. Altitudinal deficiency:
 1. A downward shade over the eye
 2. Looking over the horizon
2. Vertical hemianopic defects:
 - a. Bumping into objects on the blind side
 - b. Unable to see half of a page
3. Metamorphopsia:
 - a. Objects appear misshapen
 - b. Micropsia (objects appear too small)
 - i. The photoreceptor cells are separated by edema (macular edema)
 - ii. Micropsia may also be seen with chiasm lesions
 - iii. Retinal photoreceptors are too tightly packed
 - iv. Metamorphopsia may occur from complex partial seizures that emanate from posterior temporal or occipital lobe
4. Irregular metamorphopsia:
 - a. Retinal photoreceptors are not evenly spaced
5. Distorted visual perception may occur with migraine or focal seizures
6. Hemimicropsia:
 - a. Decreased size of objects when placed in one hemi-field
 - i. Lesions have been documented in area 18, 19 and the underlying white matter
7. Optic neuritis:
 - a. Movement phosphenes (flashes of light when moving the eyes in the dark)
 - b. Putatively arises from the optic nerve (spontaneous discharge of optic nerve fibers or when they are stimulated by movement)
8. Dazzle:
 - a. Painless intolerance of the eyes to bright light
 - b. Peripheral causes of dazzle include:
 - i. Albinism
 - ii. Cone degeneration
 - iii. Achromatopsia
 - iv. Corneal, lenticular and vitreous opacities
 - c. Central causes of dazzle include:
 - i. Lesions of the optic nerve, chiasm thalamus, occipitotemporal junction and rarely the brainstem
9. Chiasmatic lesions:
 - a. Respect the midline vertical meridian
 - b. Patients may lose central vision with convergence as the bitemporal VF deficits merge
 - c. Image displacement:
 - i. Occurs in the face of normal extraocular muscle function
 1. Small ocular muscle imbalance is compensated by binocular fixation when the VF are full; with

a VF deficit they became manifest (with bitemporal VF defects)

2. Horizontal or vertical deviation of the images from either eye (hemifield slide phenomenon)
10. Moving visual deficit:
 - a. Caused by bilateral temporo-occipital lesions
 - b. The lesions affect the upper components of the occipital gyri and adjacent middle temporal gyrus:
 - i. Patients have difficulty in perceiving motion stimuli
 - ii. Moving stimuli induce an unpleasant feeling

Vascular Supply of the Visual Pathways

1. The retina is supplied by the central retinal artery (CRA) that branches from the ophthalmic artery 5–15 mm in the optic canal:
 - a. The CRA pierces the nerve and divides into superior and inferior branches at the optic disc
 - b. The macula may be supplied by the cilioretinal artery that branches into superior or inferior divisions
 - c. The ophthalmic artery gives off several posterior ciliary arteries that supply the optic disc, outer layers of the retina and the choroid
 - d. In a small percentage of patients the macula and the papillomacular bundle is supplied by the cilioretinal artery that derives from the posterior ciliary arteries; this supply may spare central vision after CRA occlusion
 - e. Posterior ciliary arteries are involved by vasculitis; CRA ischemia is usually from microthrombi, emboli, migraine and hypercoagulable states
 - f. CRA and posterior ciliary artery occlusion cause altitudinal VF deficits
2. The chiasm:
 - a. The proximal optic chiasm is supplied by the ophthalmic carotid and anterior cerebral arteries
 - b. The anterior communicating artery (ACoA) supplies the dorsum
 - c. The inferior chiasm is supplied by:
 - i. Carotid
 - ii. PCOM
 - iii. PCA
 - d. Optic tract is supplied by:
 - i. PCOM
 - ii. PCA
 - iii. Anterior choroidal artery
 - e. Lateral geniculate body (LGD) is supplied by:
 - i. Anterior choroidal artery (laterally)
 - ii. Lateral posterior choroidal artery (medially)
 - f. The optic radiations are supplied by:
 - i. Upper portion (MCA)
 - ii. Lower portion (PCA)
3. Occipital pole anastomosis occurs between the:
 - a. Angular or posterior temporal arteries (MCA branches)
 - b. Calcarine branch PCA

Cranial Nerve II

General Characteristics

1. Intraocular portion of the nerve
 - a. The optic nerve head is 1 mm long; the areas where ganglion cell axons become myelinated
2. Intraorbital portion:
 - a. Is S-shaped and 25 mm in length; the shape allows mobility of the nerve
 - b. The nerve is surrounded by fat in the cone which is formed by the ocular muscles. The ophthalmic artery, the ciliary ganglion and the extraocular muscle nerves are closely approximated to the optic nerve in this area
3. The intracisternal portion of CN II
 - a. This component of the nerve is approximately 9 mm long. The optic canal is oriented postero-superomedially at 45 degrees to the sagittal and horizontal planes
 - b. Sympathetic nerve fibers and the ophthalmic artery also occupy the canal
4. The intracranial portion of CN II
 - a. This component of the nerve varies from 4–16 mm in length depending on whether the optic chiasm is pre- or post-fixed (relationship to the sella turcica). This portion of the nerve bridges the area between the proximal opening of the optic canal and the optic chiasm. The nerve lies above the carotid artery as the vessel exits the cavernous sinus and gives off the ophthalmic artery
 - b. The nerve overlies the sphenoid sinus and the sella turcica when it is post-fixed (posteriorly placed in regard to the sella)
 - c. The horizontal portion of the anterior cerebral artery overlies the nerve superiorly
 - d. The chiasm is below the suprachiasmatic recess
 - e. The lamina terminalis and the anterior communicating artery are above the chiasm

Clinical Manifestations

1. The clinical features of optic neuropathy include:
 - a. Decreased visual acuity
 - b. Decreased color vision
 - c. Central visual field deficit
 - d. Ipsilateral relative afferent pupillary defect in unilateral bilateral asymmetric patient
 - e. Light-near dissociation of the pupils in bilateral and symmetrically affected patients (better constriction with convergence than to direct light)
 - f. Optic disc edema or atrophy; the disc is often normal with retrobulbar disorders (central scotoma is present; the patient sees “nothing” and so does the physician)

Neuropathology

1. Anterior ischemic optic neuropathy (AION)
2. Optic neuritis (ON)
3. The above are the most often cause but there is a very wide clinical group of disorders that affect the nerve (discussed under differential diagnosis)

Laboratory Evaluation

1. Ophthalmoscopic evaluation is excellent for retinal disease and multiple systemic and intracranial disorders
2. OCT (ocular computed tomography) for evaluation of the nerve head
3. Electroretinography (retinal diseases)
4. MRI:
 - a. Specifically of the optic nerves and central nervous system (excellent for all pathologies but demyelinating diseases in particular)
5. Evaluation of visual acuity, contrast sensitivity, color perception and visual fields
6. Laboratory Evaluation:
 - a. Aquaporin 4 antibody titer (Devic’s disease)
 - b. Autoimmune antibodies

Differential Diagnosis of CN II Disorders

Vascular Disorders

1. Anterior ischemic optic neuropathy:
 - a. General characteristics:
 - i. The most frequent cause of a swollen disc in a patient older than 50 years of age
 - ii. Usually is seen in the sixth to eighth decade
 - b. Clinical manifestations (non-arteritic):
 - i. Acute or subacute loss of vision
 - ii. Painless
 - iii. Altitudinal defect (inferior > superior)
 - iv. Small cup to disc ratio in the contralateral eye
 - v. Swollen optic disc:
 1. Pale
 2. Peripapillary flame shaped hemorrhages
 3. Visual loss is often permanent with subsequent optic atrophy
 - c. Clinical manifestations of arteritic AION:
 - i. Affects older patients
 - ii. Associated with amaurosis fugax in 10% of patients
 - iii. Greater visual loss
 - iv. Association with headache, jaw claudication and polymyalgia rheumatic
 - v. Elevated sedimentation rate and C-reactive protein
 - vi. Response to steroids
2. Central retinal artery emboli:
 - a. General characteristics:
 - i. Source:
 1. Burst carotid plaques
 2. Arch of the aorta
 3. Heart valves
 4. Rarely air, nitrogen or tumor emboli
 - b. Clinical manifestations:
 - i. Altitudinal visual field defect (a “shade” coming down over my eye)
 - ii. Painless
 - iii. Birefringent yellow cholesterol plaques; appear larger than the occluded vessel (Hollenhorst plaque)

- iv. The episode generally lasts 1–2 minutes; the embolus leaves the branch point of the arteries and moves peripherally
- c. Neuropathology:
 - i. Rarer sources of emboli (other than cholesterol from a burst plaque):
 1. White emboli:
 - a. Platelet fibrin
 - b. Heart valve is the usual origin
 2. Fat emboli:
 - a. Lung bone fracture
 3. Air emboli:
 - a. ENT and neurosurgical procedures in which the patient is sitting
 - b. Open heart procedures
 - ii. Ischemia of the chiasm and cranial nerve II from surgery:
 1. A-COM aneurysm clipping:
 - a. Disruption of dorsal chiasmatic blood flow
 - b. Ophthalmic artery surgery for aneurysm repair:
 - i. Disruption of the blood supply to the optic nerve
 - c. P-COM artery aneurysm surgery:
 - i. Disruption of the ventral chiasmatic blood supply
 - iii. Watershed ischemia of the optic nerve head:
 1. Decreased perfusion between the central retinal artery from the ophthalmic artery and the posterior ciliary arteries from the ophthalmic artery branches
 2. Vasculitic processes
 3. Distal field ischemia
 4. Central scotoma
 - iv. Delayed effects of X-RT:
 1. X-RT affects the vascular endothelium
 2. Delayed ischemia from proliferative endarteritis
 3. 1–5 years post-X-RT; ischemia due to decreased blood supply from the vasovasorum of the optic nerve and chiasm or from involvement of the carotid, ophthalmic or posterior ciliary vessels
 - ii. Sequential infarction (rare)
3. Ischemic disc swelling:
 - a. Marked or recurrent systemic blood loss (G.I. tract)
 - b. May be delayed for days to weeks
 - c. May occur with bypass surgery (coronary)
4. Uremic optic neuropathy:
 - a. Possibly ischemic
 - b. Disc swelling may occur but most often the disc is pale
 - c. Occurs with severe renal disease (uremic state)
 - d. Bilateral visual loss
 - e. Complicating features of this process include:
 - i. Increased CSF pressure
 - ii. Consecutive episodes of ischemic optic neuropathy
 - iii. Possibly a complication of hemodialysis
5. Carotid artery disease
6. Atrial fibrillation (emboli to the posterior ciliary arteries)
7. Coronary bypass surgery (hypotension)
8. Cardiac catheterization (emboli)
8. Eclampsia (vasoconstriction)
10. Platelet induced hypercoagulability

Tumors of the Orbit

General Characteristics

1. Tumors of the orbit cause visual loss that is associated with:
 - a. Optic disc swelling with consequent atrophy
 - b. Optociliary shunt vessels, a pale white disc and visual loss comprise the Hoyt-Spencer sign that is characteristic of compressive optic nerve lesions such as optic nerve dural meningiomas (meningioma of Schwalbe)
 - c. Diplopia and restriction of extraocular muscle movement
 - d. Proptosis which is protrusion of the optic globe. This may also occur with:
 - i. Thyroid ophthalmopathy
 - ii. Pseudotumor of the orbit
 - iii. Tumor of the middle cranial fossa:
 1. Due to pressure on the veins of the cavernous sinus that leads to intraorbital venous congestion
- iv. Intermittent proptosis occurs with an orbital venous angioma and is induced with any form of valsalva maneuver (strains, bends, coughs) or if the jugular vein is compressed:
 1. During an episode:
 - a. The eye may become tense and painful
 - b. The pupil may dilate
 - c. Bradycardia and syncope may develop (oculocardiac syndrome)
- e. Pulsation of the globe:
 - i. Occurs with congenital absence of the sphenoid bone associated with NFI (chromosome 17)

Differential Diagnosis of Rare Causes of Ischemic Optic Neuropathy

1. Cataract surgery:
 - a. Occurs 4–15 months post-operatively
 - b. Sudden visual loss
 - c. Disc infarction may occur with both retrobulbar or general anesthesia
 - d. The second eye may be involved if previously operated
2. Ischemic optic neuropathy in young patients:
 - a. Cluster headache and migraine:
 - i. Unilateral or bilateral disc infarction (rare)

- ii. Orbitocranial encephalocoele with neurofibromatosis
- iii. Orbital AV malformations
- iv. Venous varices
- v. Transmission of CSF pulsations by defects in the orbital wall
- f. Exophthalmos:
 - i. The most common cause is Grave's disease; most often it is unilateral
- g. Pseudoexophthalmos is caused by:
 - i. An enlarged globe from:
 - 1. Myopia
 - 2. Buphthalmos
 - 3. Congenital cystic eye
 - ii. Shallow or asymmetric bony orbits
 - iii. Contralateral enophthalmos makes the normal appear exophthalmic:
 - 1. Scirrhou breast metastasis
 - 2. Orbital floor fracture
 - 3. Congenital orbital bony defects
- h. Enophthalmos:
 - i. May be caused by:
 - 1. Scirrhou breast carcinoma
 - 2. Carcinoma of the GI tract, lungs or prostate
 - 3. The enophthalmos is due to fibrosis induced by the tumor with posterior traction and tethering of the globe or destruction of the orbital wall
 - ii. Other causes of enophthalmos include:
 - 1. Senile orbital fat atrophy
 - 2. Parry-Romberg disease:
 - a. Facial hemiatrophy
 - 3. Facial osteomyelitis
 - 4. Spontaneous enophthalmos and ptosis:
 - a. Putatively associated with unilateral chronic maxillary sinusitis or hypoplasia in association with orbital floor resorption
 - i. Chemosis and eyelid edema
 - j. Gaze-evoked amaurosis:
 - i. Loss of vision when the globe is placed in an eccentric position
 - ii. Most commonly observed with cavernous hemangiomas and optic nerve sheath meningiomas
 - iii. The differential diagnosis of gaze-evoked amaurosis also includes:
 - 1. Orbital osteoma
 - 2. Glioma of the optic nerve
 - 3. Medial rectus granular cell myoblastoma
 - 4. Venous varix
 - 5. Pseudotumor cerebri
 - 6. Orbital trauma
 - 7. Orbital metastases
 - iv. The putative mechanism for gaze-evoked amaurosis is decreased blood flow to the retina or optic nerve from compression of the central retinal artery. Alternatively, positional change may directly compress the optic nerve

- k. Facial pain:
 - i. Branches of the trigeminal nerve traverse the orbit. The ophthalmic division branches are most often affected
 - ii. The lacrimal, supraorbital and supratrochlear nerves are affected by diseases of the orbital roof; the zygomatic and infraorbital nerves are affected by disorders of the orbital floor
 - iii. Disease of the orbital apex and superior orbital fissure may affect several periorbital dermatomes
 - iv. Corneal hypesthesia may occur with any disease of the orbit that compresses VI
 - v. If the orbital floor is eroded the maxillary division of cranial nerve V may be affected

Patterns of Involvement with Orbital Metastatic Tumors

- 1. Infiltrative:
 - a. Restriction of motility
 - b. Ptosis
 - c. Enophthalmos
 - d. Firm orbit
- 2. Mass effect:
 - a. Proptosis
 - b. Displacement of the globe
 - c. Palpable orbital mass
- 3. Inflammatory:
 - a. Pain
 - b. Chemosis, erythema
 - c. Periorbital swelling
- 4. Functional:
 - a. Ocular motility deficit; out of proportion to orbital involvement
- 5. Asymptomatic
- 6. Direct metastasis to orbital muscle occurs with carcinoma of the breast and malignant melanoma

Tumors of Cranial Nerve II

General Characteristics

- 1. Optic disc swelling with orbital lesions
- 2. Direct metastasis to the orbit with compression of the optic nerve
- 3. Compression by dural attachment or subdural (optic dura) infiltration
- 4. Meningeal involvement of the optic nerve dura

Clinical Manifestations

- 1. Optic disc swelling
- 2. Proptosis may be minimal or absent
- 3. Fundoscopic changes induced by retrobulbar mass lesions:
 - a. Compression of the posterior wall of the globe:
 - i. Choroidal retinal striae

- b. Compression of the equator of the globe:
 - i. Diffuse retinal flattening
- c. Dilatation and tortuosity of the veins as a consequence of high orbital pressure
- d. Papilledema early with later optic atrophy
- e. Decreased visual acuity
- f. Decreased contrast light sensitivity
- g. Color perception poor (desaturation; red often appears brownish)
- h. VF (visual field) deficits:
 - i. Central scotoma
 - ii. Arcuate defects
- i. Relative pupillary afferent defect (Marcus Gunn phenomenon)

Neuropathology

1. Lymphoma:
 - a. Most often in the inferior and anterior orbit
 - b. Superior rectus muscle may be preferentially involved
 - c. Displacement of the globe > exophthalmos
 - d. The optic nerve is affected by compression
2. Chloroma:
 - a. Associated with both myelogenous and lymphatic leukemia
 - b. Greenish mass
 - c. Affects the base of the skull but has a predilection for the orbit
 - d. May be bilateral
 - e. Hemorrhage into the lids and orbit is common
3. Malignant melanoma:
 - a. Primary malignant melanoma is rare (origin is in the choroid pigment epithelium)
 - b. Recurrence after enucleation does occur
 - c. Brownish mass
 - d. Extrusion of an implant or poor retention of a prosthesis from a recurrence is common
4. Rhabdomyosarcoma:
 - a. Exophthalmos may be a presenting sign
 - b. Associated with tuberous sclerosis
 - c. Eye displacement is out and down > forward; mass occupies the upper nasal orbit
 - d. Progresses rapidly without pain
 - e. Ptosis occurs in 2/3rds of patients
 - f. 10% of patients have a nosebleed and orbital pain
 - g. Frequent conjunctival chemosis and congestion
 - h. Retinal venous congestion and striae; rare disc edema
5. Retinoblastoma:
 - a. Almost always a childhood illness
 - b. 25% are bilateral
 - c. Origin is intraocular; grows along the optic nerve
 - d. May grow through the sclera to form an orbital mass
 - e. Endophytum (endophytic) vs. exophytum (exophytic) type:
 - i. Endophytum type:
 1. Inner retinal layers
 - ii. Exophytum type:
 1. Outer retinal layers
 2. May grow through central optic pathways
 3. Necrosis and calcification in the orbit
 4. May present with leukocoria (white pupil)
- f. Sarcoma of the orbit:
 - i. Specific types:
 1. Rhabdomyosarcoma
 2. Osteosarcoma
 3. Chondrosarcoma
 4. Myxosarcoma
 5. Fibrosarcoma
 - ii. The tumors may be primary, metastatic or involve the orbit by extension
 - iii. Approximately 2% present with proptosis
 - iv. Leiomyosarcoma:
 1. Usually arise in the uterus, GI tract or the genitourinary system
 2. Originates from the smooth muscle of blood vessels
 3. Grows rapidly and metastasizes
 - v. Fibrosarcoma:
 1. Rare in the orbit
 2. Extends locally rather than metastasizes
 - vi. Chondrosarcoma:
 1. Arise from bone primarily
 2. Orbital tumors arise from bone
 3. Usually affect the orbit by extension (from the greater wing of the sphenoid)
 - vii. Osteosarcoma:
 1. Associated with fibrous dysplasia
 - viii. Liposarcoma:
 1. 20% of malignant tumors of soft tissue
 2. Extremely rare in the orbit
 - ix. Malignant granular cell myoblastoma:
 1. Average age of onset is between 20–30 years of age
 2. Metastases or recurrence may be delayed
 3. Bone formation may occur within the tumor
 - x. Primary orbital melanoma:
 1. The majority of orbital melanotic tumors are extensions of choroidal melanoma
 2. Possible association with the nevus of Ota
 - xi. Post-irradiation orbital tumor:
 1. Sarcoma may occur following XRT of a retinoblastoma
 2. Delayed development (4–25 years following therapy)
 3. Other induced tumors include: 1. fibrosarcoma and 2. mesenchymal tumors
 4. The tumors occur in the areas that were irradiated
 5. The mass is frequently at the orbital margin

g. Lacrimal Gland Tumors:

i. Mixed tumor:

1. Benign or malignant
2. 50% are epithelial tumors of the lacrimal gland
3. Myxomatous stroma and epithelial elements
4. Benign mixed tumors:
 - a. Most common type of epithelial tumor of the lacrimal gland
 - b. Encapsulated
 - c. May recur and invade bone

ii. Adenoid cystic carcinoma:

1. The lacrimal gland > frequency than the salivary gland
2. 50% of the epithelial tumors of the lacrimal gland are carcinomas (adenocystic is the most common)
3. Occurs in adulthood
4. Presents as a lump in the upper outer orbit
5. Exophthalmos is slight or late
6. May have early disc edema
7. Decreased vision due to pressure on the optic nerve
8. May invade bone and cause pain

Intraocular Metastatic Tumors*General Characteristics*

1. Primarily affect the posterior choroid
2. Left side is involved > right; more direct course of the carotid artery
3. There are twenty short posterior ciliary arteries; seven anterior ciliary arteries and two long posterior ciliary arteries. Metastases are more likely to go to the short posterior ciliary arteries
4. Occurs in less than 1% of primary malignant intraocular tumors
5. Tumor emboli metastasize to the uveal tract while infectious emboli go to the retina (smaller than metastatic tissue; the infectious material traverses the central retinal artery)
6. Uveal metastases females > males
7. In 25% of patients, metastases are bilateral
8. Breast carcinoma > 50% of uveal metastasis
9. Lung metastases have a higher incidence of iris and ciliary body metastasis
10. Prostate metastasizes to the orbit > uveal tract
11. Neuroblastoma occurs after the age of 20 in 13% of patients
12. GI tract tumors account for approximately 7% of intraocular metastases
13. Rare primary tumors that metastasize to the orbit are:
 1. thyroid, 2. liver, 3. ovary, 4. pancreas, 5. kidney, 6. uterus, 7. bladder, 8. parotid or 9. testicle

Clinical Manifestations

1. Choroidal:

- a. Usually are located temporal to the disc and near the macula
 - b. Visual impairment with a rapidly progressive course (involvement of the macula), retinal detachment that causes a central scotoma
 - c. Rarely painful
 - d. Extraocular muscle extension is rare; involvement of the retina is rare except by detachment
2. Anterior uveal metastasis:
 - a. There may be no visual loss
 - b. Single or multiple metastases
 - c. Discrete nodules are in the iris and ciliary bodies
 3. Metastasis to the retina:
 - a. Rarely occurs
 - b. Does occur in a setting of widespread metastases
 - c. Painless loss of vision
 4. Adnexal metastasis:
 - a. Rare
 5. Metastasis to the optic nerve:
 - a. Extremely rare
 - b. May involve the nerve or the nerve sheath
 - c. Progressive loss of vision

Neuropathology

1. Orbital metastases are less common than tumors that extend from the paranasal sinuses
2. Tumor emboli metastasize to the uveal tract
3. Specific neuropathology dependent on the type of tumor

Laboratory Evaluation

1. Complete ophthalmologic evaluation
2. CT and MRI of the orbit
3. Visual evoked potentials
4. Metastatic and primary tumor diagnostic workup

Orbital Cysts*General Characteristics*

1. Most often are congenital and include:
 - a. Dermoid
 - b. Teratoid
 - c. Meningocele
 - d. Encephalocele

Clinical Manifestations

1. Increased intraorbital pressure with compression of the optic nerve
2. Central scotoma; rarely arcuate deficits in the VF (visual field)

Neuropathology

1. Parasitic:
 - a. Hydatid
 - b. Cysticercosis
2. Epidermoid:

- a. Present at puberty
- b. Located most frequently at the upper and outer quadrant of the orbit; rarely seen near the lacrimal gland or deep in the orbit
3. Dermoid:
 - a. The cysts may have multiple diverticulae
 - b. Involve the choroid
 - c. Most commonly located at the limbus of the globe or the upper outer quadrant of the orbit
 - d. Associated with coloboma of the lid and aniridia
 - e. Inflammatory reactions occur around cysts that have perforated
 - f. Deep dermoids compress the optic nerve
 - g. Primary cholesteatoma of the orbit can only be differentiated from a dermoid histologically
 - h. Dermoids may span the orbit
4. Orbital bone cysts:
 - a. The cysts contain channels with thin or thick septa
 - b. Usually located in the orbital roof
 - c. Blood may be present in the cyst
5. Cystic orbital teratoma
6. Congenital cystic eyeball
7. Orbital encephalocele
8. Meningocele

Laboratory Evaluation

1. Complete ophthalmoscopic evaluation
2. CT and MRI of the orbit
3. VEP (visual evoked potentials)

Differential Diagnosis of Tumors Affecting the IInd Cranial Nerve and/or the Orbit

1. Meningioma of Schwalbe (optic nerve sheath; perioptic meningioma)
2. Sphenoid wing meningioma
3. Lymphoma
4. Rhabdomyosarcoma
5. Leukemia (particularly CLL)
6. Chloroma (plasma cell tumor)
7. Optic nerve glioma (neurofibromatosis type I; chromosome 17)
8. Ganglioneuroma
9. Hemangioma of the orbit
10. Hypereosinophilia (involves CN II directly) toxic proteins are released that damage the nerve
11. Carcinomatosis of the meninges (lung > breast > GI tract > melanoma)
12. Dermoid
13. Epidermoid

Masses of the Optic Disc

General Characteristics

1. Papilledema must be distinguished from pseudopapilledema

Clinical Manifestations

1. Pseudopapilledema:
 - a. An absent central cup with a small disc diameter
 - b. Vessels originate from the central apex of the disc
 - c. Anomalous vessel branching
 - d. Increased number of disc vessels
 - e. Venous pulsations are present
 - f. Irregular disc margins with abnormalities of the peripapillary retinal pigment epithelium
 - g. Absence of superficial capillary telangiectasia
 - h. No hemorrhage
 - i. No cotton wool spots

Neuropathology

1. Drusen are usually clearly seen but may be small and buried in the disc head
2. Anomalies that may simulate papilledema:
 - a. Hyperopic discs
 - b. Tilted discs
3. Gliotic dysplasia
4. Fibrillary astrocytoma (NFI)
5. Glial remnants of the hyaloid vasculature (their membranes or gray nodules attached to the disc)
6. Capillary and cavernous hemangioma
7. Racemose malformation (Wyburn-Mason disease)
8. Melanocytoma
9. Sarcoid granuloma
10. Leukemic infiltrate
11. Metastatic carcinoma

Vascular Masses of the Orbit

General Characteristics

1. Usually present in children
2. Plateau of growth by adulthood

Clinical Manifestations

1. Compression of the optic nerve
2. Central and arcuate scotoma
3. Venous congestion of the retina
4. Several involve the lids, conjunctiva, and facial structures

Neuropathology

1. Orbital lymphangioma:
 - a. Benign slowly progressive tumor
 - b. Most often in children
 - c. Approximately 50% of patients have involvement of the lids, conjunctiva, face and palate
 - d. Involves both the lymph and vascular systems
 - e. Resembles a cavernous hemangioma (the spaces within the tumor contain lymph rather than blood)
 - f. Hemorrhage into the tumor occurs frequently
2. Hemangioma:
 - a. Approximately 23% of orbital tumors
 - b. Cavernous hemangiomas:

- i. Epithelium lined spaces
- ii. The tumors are long and encapsulated
- c. Racemose form:
 - i. Completely formed blood vessels; veins predominate
 - ii. Isolated masses of blood vessels that may pulsate
 - iii. They may have A-V aneurysms in the retina
 - iv. The tumors occur within the muscle core
 - v. Proptosis is straightforward without deviation of the globe
 - vi. Engorgement of retinal vessels, disc edema, loss of vision
 - vii. Occasional ocular bruit may be heard with ocular pulsation
 - viii. Intermittent exophthalmos
- 3. Hemangioliomyoma:
 - a. Composed of thick walled vessels
 - b. Contain smooth muscle
 - c. An encapsulated tumor
- 4. Hemangioendothelioma:
 - a. Originates from endothelial cells
 - b. Contains anastomosing vascular channels
 - c. May be malignant and can metastasize
 - d. May occur in soft tissue
- 5. Hemangiopericytoma:
 - a. Proliferating cell is the pericyte
 - b. Potentially malignant
 - c. May invade the bone and erode into the cranial cavity

Optic Neuritis

General Characteristics

1. An inflammatory or autoimmune disease that affects the optic nerve
2. More common in females than males and usually affects patients between 20 to 50 years of age

Clinical Manifestations

1. Loss of vision that progresses over hours to days
2. Visual loss is often most severe by the end of the first week
3. The disc is normal in approximately 2/3rds of patients and swollen in approximately 1/3
4. If the process is retrobulbar, there is pain induced or exacerbated by eye movement. It is usually periorbital or may be projected to the forehead
5. There is decreased visual acuity most frequently in the central 20° of vision with associated:
 - a. Decreased brightness
 - b. Hue desaturation; color vision may be more affected than visual acuity
 - c. An afferent pupillary response (Marcus Gunn pupil)
 - d. Arcuate and altitudinal defects may be seen
6. Vision usually starts to improve by the second to third week and if the demyelinated segment is short may return to normal by six weeks. There is a correlation of length of

the optic nerve lesion in demyelinating disease and visual deficit. The lesion may be more severe and initially bilateral with Devic's disease (aquaporin 4 antibodies). Multiple sclerosis presents overwhelmingly with unilateral disease (Devic's may be simultaneously bilateral)

7. Uhthoff's phenomenon may be seen:
 - a. Decreased vision with increased temperature (failure of conduction of partially demyelinated fibers with increased temperature)
 - b. Failure of vision with bright light suggests decreased photoreceptor replenishment that may occur with severe carotid stenosis

Neuropathology

1. Demyelination of the optic nerve is the primary pathology of CN II in multiple sclerosis
2. Aquaporin antibody disease affects the astrocytic foot processes of blood vessels throughout the optic nerve and for long segments of the spinal cord (at least 3 vertebral segments) as well as some periventricular areas
3. Autoimmune processes that may affect the optic nerve include:
 - a. Demyelinating disease (MS) [multiple sclerosis]
 - b. Acute disseminated encephalomyelitis (ADEM)
 - c. AIDP/CIDP (rare)
 - d. Post-viral infections
 - e. Devic's disease (NMD)
 - f. Paraneoplastic disorders
4. Specific viral infections:
 - a. Measles
 - b. Mumps
 - c. Herpes zoster
 - d. HIV
 - e. Any viral encephalitis
5. Contiguous inflammation:
 - a. Orbital disease
 - b. Sinusitis
 - c. Meningeal disorders
6. Deep fungal infection:
 - a. Cryptococcosis:
 - i. The fungus surrounds the nerve under the dural sheath
 - b. Aspergillus
 - c. Mucormycosis (destroys the contents of the orbit most often in severely immunosuppressed patients)
7. Syphilis
8. Sarcoid:
 - a. Compression of the nerve from infiltration of the meninges
9. IgG pachymeningitis (dural hypertrophy with nerve compression)
10. Intraocular inflammation:
 - a. Serous retinopathy
 - b. Neuroretinitis
11. Carcinomatosis of the meninges

Laboratory Evaluation

1. Complete ophthalmoscopic examination
2. CT (if there is sinus disease or bony orbital involvement)
3. MRI of the head and orbit
4. Appropriate serum and CSF evaluation for autoimmune disorders, infectious agents, paraneoplastic antibodies, aquaporin-4 antibodies
5. OCT particularly in demyelinating disease

Toxic and Nutritional Optic Neuropathies*General Characteristics*

1. Toxic and nutritional neuropathies are most often seen in malnourished and addicted patients in the Western world
2. In general, famine, introduction of new drugs, nutritional deficiencies, and toxic exposures cause large-scale outbreaks of cranial nerve II involvement

Clinical Manifestations

1. Present with a slowly progressive loss of central vision
2. No pain or photopsias
3. Associated paresthesias, ataxia and sensorineural hearing loss occur with general nutritional deficiencies; if found in equatorial countries they have been termed "tropical amblyopias"
4. Bilateral decrease of visual acuity (VA 20/200) or minimal 20/25. VA loss is usually symmetrical
5. Loss of color vision may be worse than visual acuity; early patients may present with isolated color vision deficiency
6. Centrocecal scotoma:
 - a. Initially nasal to the blind spot and extends to the point of fixation on both sides of the vertical meridian. There is a bridge between the scotoma of the blind spot and at the point of fixation
7. Loss of red color perception
8. Relative afferent pupillary defect brightness is normal
9. May demonstrate nerve fiber layer loss in the papillomacular bundle; there may be swelling in the arcuate bundles; mildly pale temporal disc late in the disease course

Neuropathology

1. Ethambutol:
 - a. Primarily used for pulmonary tuberculosis
 - b. Toxic neuropathy (CN II) occurs in approximately 5% of patients
 - c. Severe dyschromatopsia, central or cecocentral scotoma
 - d. Mitochondrial dysfunction:
 - i. Ethambutol chelates copper which is required for cytochrome C oxidase activity
2. Disulfiram:
 - a. A chelating agent
 - b. Similar clinical manifestations as ethambutol
3. Linezolid:
 - a. An oxazolidinone antimicrobial drug utilized against gram-positive infections

- b. Causes a reversible optic neuropathy
- c. Putatively inhibits mitochondrial protein synthesis
- d. Usually the optic neuropathy is apparent after 3 months of continued use
4. Isoniazid:
 - a. Utilized for tbc (tuberculosis) treatment
 - b. Severe bilateral optic disc swelling
 - c. Bitemporal hemianopic scotomas
5. Tacrolimus:
 - a. A cytotoxic T-cell suppressor primarily used in transplant medicine
 - b. Only a few reported patients; one with a rapid onset similar to ischemic optic neuropathy
6. Amiodarone:
 - a. Primarily utilized to treat ventricular arrhythmias
 - b. Similar presentation as isoniazid and a more rapid course than ethambutol
 - c. Disc swelling; severe visual field deficits similar to anterior ischemic optic neuropathy
7. Phosphodiesterase-5 inhibitors (sildenafil, tadalafil and vardenafil):
 - a. Treatment of erectile dysfunction
 - b. Clinically similar to non-arteritic anterior ischemic optic neuropathy
8. Methanol:
 - a. Methanol most often accompanies illegally brewed alcohol taken orally after being filtered:
 - i. Causes a severe metabolic acidosis from its toxic metabolite formalin which is metabolized to formaldehyde
 - ii. Vision loss occurs within hours
 - iii. A characteristic hyperemic and swollen disc
 - iv. Decreased pupillary light reflex portends a poor prognosis
9. Ethylene glycol:
 - a. Antifreeze; usually ingested in a suicide attempt
 - b. May cause blindness with a similar course to methanol
10. Cuban optic neuropathy:
 - a. Epidemic optic neuropathy occurred between 1992–1993
 - b. The neuropathy of CN II was associated with weight loss and deficiency of vitamins and protein (vitamin B12 and folate)
 - c. Swelling of the nerve fiber layer in the arcuate bundles; thinning of the nerve fiber layer approximate to the papillomacular bundle
11. Cassava root neuropathy:
 - a. Seen in epidemic proportions during the Nigerian civil war
 - b. Cassava root and leaf diet in starving patients
 - c. Associated with sensorineural hearing loss and sensory ataxia
 - d. Putative cyanide toxicity that is found primarily in the cassava root
12. Jamaican optic neuropathy:

- a. Affects young adults
- b. May be seen in all of the Caribbean islands
- c. Rapidly progressive visual loss
- d. Bilateral optic atrophy
- e. Visual acuity may be reduced to 20/200 with dense central scotoma
- f. A putative mitochondrial disorder
- 13. Tobacco-alcohol amblyopia:
 - a. Probable dietary deficiency of B-complex vitamins
 - b. Elderly patients
 - c. Some patients have been found to have concomitant B12 deficiency
 - d. Bilateral symmetric centrocecal scotoma (between the blind spot and the point of fixation)
 - e. No nerve fiber deficit
 - f. VA 20/200 is typical
 - g. The defect may extend across the vertical meridian
 - h. Rare hemorrhages are seen on or off the disc (splinter variety); rare disc swelling
 - i. Cyanide in tobacco and free radicals may impair mitochondrial metabolism
- 14. Tamoxifen:
 - a. Reported to cause bilateral optic neuropathy
- 15. Tumor necrosis factor α inhibitors (golimumab):
 - a. TNF α inhibitors are now increasingly being utilized for Crohn's disease, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis and uveitis:
 - i. Anterior optic neuropathy may occur with influx; mab
 - ii. Retrobulbar neuritis
 - iii. Sudden onset of visual loss during treatment
- 16. Nutritional optic neuropathy:
 - a. Insufficient dietary intake primarily of vitamin B12 or folic acid in a setting of:
 - i. Unbalanced diet
 - ii. Malnutrition
 - iii. Chronic alcoholism and drug abuse
 - iv. Severe anemia
 - v. Bariatric surgery
- 17. Decreased retinal ganglion layer thickness and volume is demonstrated by optical coherence tomography

Hereditary Optic Neuropathies

- 1. Hereditary Optic Nerve disease:
 - a. Leber hereditary optic neuropathy (ADOA) and autosomal-dominant optic atrophy are the two most common inherited optic neuropathies
 - b. Both have selective loss of retinal ganglion cells (RGCs) and early involvement of the papillomacular bundle
 - c. Inherited optic neuropathies are seen in 1 in 10,000 individuals

Leber's Hereditary Optic Neuropathy (LHON)

General Characteristics

- 1. LHON is caused by multiple genes encoded by the mitochondrial genome
- 2. Drugs/Toxins
 - a. Ethambutol (green cones are affected)
 - b. Chloromycetin
 - c. Streptomycin
 - d. Isoniazid
 - e. Chlorpropamide
 - f. Digitalis
 - g. Chloroquine (macular lesion)
 - h. Placidyl
 - i. Antabuse
 - j. Heavy metals
 - k. Methanol (optic nerve destruction; hemorrhagic papilledema)
 - l. Halogenated hydroxyquinolones: subacute myeloptic neuropathy (SMON)
 - m. Toluene (glue sniffing)
 - n. D-penicillamine
 - o. Intracarotid BCNU (glioma treatment)
 - p. Amiodarone
 - q. Hexachlorophene
 - r. 5-fluorouracil

Clinical Manifestations

- 1. Disease onset is usually an acute loss of central vision which is bilateral in 25% of patients; if unilateral the contralateral eye is affected within eight weeks (invariably within 1 year)
- 2. Patients become symptomatic in the second and third decade of life
- 3. Central or centrocecal scotoma
- 4. Decreased color vision
- 5. Pupillary light reflex is not affected as severely as the extent of visual loss
- 6. Funduscopic evaluation:
 - a. Tortuosity of the central retinal vessels
 - b. Swelling of the nerve fiber layer
 - c. Circumpapillary telangiectatic microangiopathy
 - d. 90% of patients have normal discs
 - e. At approximately six weeks optic nerve pallor is more marked temporally
 - f. Pathologic cupping of the disc occurs with extensive axonal loss within the papillomacular bundle in long standing patients
 - g. Extraocular manifestations include:
 - i. Psychiatric disorders
 - ii. Spastic dystonia
 - iii. Encephalopathy

Neuropathology

- 1. The majority of patients with LHON (90–95%) have one of three primary mtDNA point mutations

- Visual loss occurs if the mutational load exceeds 60% which is required to cause a bioenergetic defect

Laboratory Evaluation

- Complete ophthalmological evaluation
- OCT (ocular coherence tomography):
 - RGC loss and early involvement of the maculopapillary bundle
- All three primary LHON mutations have been shown to involve complex 1 subunits which decrease oxidative phosphorylation and ATP synthesis

Autosomal Dominant Optic Atrophy

General Characteristics

- Affects approximately 1 in 35,000 individuals (North of England)

Clinical Manifestations

- Insidious visual loss that starts within the first two decades of life
- A milder phenotype than LHON with approximately 25% of patients visually asymptomatic
- There is marked inter- and intrafamilial variability in the rate of disease progression
- Most patients have generalized dyschromatopsia; approximately 10% have pure tritanopia (blue-yellow color blindness)
- Involvement of the papillomacular bundle causes central, centrocecal and paracentral scotomata
- The pupillary light reflex is relatively preserved
- Funduscopy evaluation:
 - Optic disc pallor may be diffuse and involve the entire neuroretinal rim or demonstrate a temporal wedge
 - Approximately 1/3 of patients have normal discs
 - Peripapillary atrophy
 - Enlarged cup-to-disc ratio (greater than .5)
- Associated neurologic manifestations include:
 - Bilateral sensorineural deafness that begins in late childhood and early adulthood (occurs in approximately 2/3rds of patients)
 - Ataxia
 - Myopathy
 - Peripheral neuropathy
 - Chronic progressive extraocular ophthalmoplegia
 - OPA1 mutations have been identified in patients with spastic paraplegia and in individuals with a multiple sclerosis-like disorder

Neuropathology

- Approximately 50–60% of patients with AD optic atrophy have mutations in the OPA1 gene located at chromosome 3q29:
 - The majority of OPA1 mutations cause premature termination codons; approximately 30% of patients have missense mutations

- OPA1 is a transmembrane protein that is located within the mitochondrial inner membrane
- Pathologic hallmark of OPA1 mutations is mitochondrial network fragmentation with isolated dysmorphic aberrant balloon-like enlargements, disorganized cristae and paracrystalline inclusion bodies
- Cytochrome c molecules lose their sequestration within tight cristae junctions, leach into the cytosol and activate apoptotic cascades
- OPA1 is a component of oxidative phosphorylation regulation through its interaction with respiratory chain complexes

Laboratory Evaluation

- Complete ophthalmologic evaluation
- Genetic testing
- Ocular coherence tomography
- Visual evoked potentials
- MRI:
 - Particularly useful in patients with extraocular manifestations

Hereditary Motor and Sensory Neuropathy type VI

General Characteristic

- HMSN-VI is a subtype of Charcot-Marie-Tooth (CMT) disease

Clinical Manifestations

- Childhood onset
- Severe peripheral neuropathy
- Severe visual loss that starts in late childhood
- A subgroup of patients has had return of vision later in life

Neuropathology

- Mutations in the MFN1 and MFN2 genes:
 - Encode outer mitochondrial membrane proteins with GTPase domains
 - The MFN1,2 and OPA1 proteins function synergistically in mitochondrial fusion
 - MFN2 is involved in regulating the expression of nuclear-encoded respiratory chain subunits

Laboratory Evaluation

- EMG:
 - Severe peripheral neuropathy
- Ophthalmoscopic evaluation
- Direct genetic testing

Spastic Paraparesis (EPGF7)

General Characteristics

- Prevalence in 3–10/100,000 patients in the general population
- The uncomplicated form causes slowly progressive spastic paraparesis
- Complicated forms have additional neurologic deficits
- SPGF7 that maps to chromosome 16q24,3 is an AR HSP that has prominent optic atrophy in some patients

Clinical Manifestations

1. Variability in the spectrum of clinical features that include:
 - a. Bilateral optic atrophy
 - b. Spastic paraparesis
 - c. Peripheral neuropathy
 - d. Cognitive dysfunction

Neuropathology

1. Muscle biopsy (2 patients):
 - a. Ragged red fibers and COX-negative fibers
 - b. Electron microscopy:
 - i. Abnormal mitochondria that contain paracrystalline inclusions
2. Defect in complex I activity and impaired oxidative phosphorylation
3. There is interaction between the defective paraplegin protein and OPA1 proteins that are associated with mitochondrial network fusion

Laboratory Evaluation

1. Genetic testing
2. Ophthalmic evaluation
3. MRI of the spinal cord
4. Muscle biopsy

Friedreich's Ataxia*General Characteristics*

1. Autosomal recessive
2. The mutation is in the FXN gene that maps to chromosome 9q13-q21.1:
 - a. There is a pathologic expansion of the ⁹GAA trinucleotide repeat in FXN that encodes the protein frataxin

Clinical Manifestations

1. Onset is usually the second decade
2. Progressive gait ataxia
3. Scoliosis and pes cavus
4. Distal limb weakness
5. Dorsal column deficits
6. Dysarthria
7. Hypertrophic cardiomyopathy
8. Optic nerve dysfunction

Neuropathology

1. Diffuse and progressive atrophy of the retinal nerve fiber layer loss without papillomacular bundle involvement (in distinction to LHON and OPA1)
2. Frataxin is located in the inner mitochondrial membrane and functions in the assembly of iron-sulfur clusters that are essential for the respiratory chain
3. In addition to defects in oxidative phosphorylation, there is intramitochondrial accumulation of iron. Frataxin has antioxidant properties and its deficiency has been suggested as a cause of reactive oxygen species damage in the disorder

Laboratory Evaluation

1. Genetic testing
2. Ophthalmologic evaluation
3. Echocardiogram and EKG
4. MRI of the brain

Autosomal Recessive Non-Syndromic Optic Atrophy*General Characteristics*

1. Mutations of the TMEM 26 A gene that maps to chromosome 11q14.1-q21:
 - a. Encodes a transmembrane mitochondrial protein which is located in the retinal ganglion cell layer and the optic nerve head
 - b. Gene function is unknown but no mitochondrial network fragmentation or mtDNA depletion has been found

Clinical Manifestations (Simple Recessive)

1. Optic Atrophy:
 - a. Severe visual impairment with optic atrophy
 - b. Associated with nerve deficit in a subgroup
2. Complicated (recessive) disorders:
 - a. Behr's syndrome:
 - i. Optic atrophy
 - ii. Mild cognitive impairment
 - iii. Spasticity
 - iv. Ataxia
 - b. Onset by nine years of age
 - c. Temporal disc pallor
 - d. Strabismus occurs in 2/3rds of patients

Neuropathology

1. Atrophy in the optic nerves, LGB (lateral geniculate body) visual radiation and the striate cortex

Laboratory Evaluation

1. Ophthalmological evaluation
2. Visual evoked response
3. OCT
4. MRI of the brain

Recessive Optic Atrophy and Juvenile Diabetes (Wolfram Syndrome)*General Characteristics*

1. The Wolfram syndrome is caused by mutations in the WFSI gene that maps to 4p16.1

Clinical Manifestations

1. Optic atrophy with severe visual loss (20/200)
2. Insulin-dependent diabetes mellitus
3. Diabetes insipidus
4. Deafness
5. Cognitive and psychiatric disorders
6. Some patients have had ataxia, nystagmus, ptosis, seizures and short stature

Neuropathology

1. Smaller than control intracranial volume that primarily affects gray and white matter in the brainstem, cerebellum and optic radiations
2. Pattern of deficits suggests that the disorder affects brain development as well as later neurodegeneration

Laboratory Evaluation

1. Genetic testing for the WFSI gene
2. MRI of the brain
3. Ophthalmologic evaluation
4. Serum abnormalities for both diabetes mellitus and lipids
5. Increased CSF protein

Mitochondrial Protein-Import Disorders***Mohr-Tranebjaerg Syndrome****General Characteristics*

1. The Mohr-Tranebjaerg or deafness-dystonia-optic neuropathy (DDON) syndrome is caused by mutations in the TIMM8A gene that maps to Xq22

Clinical Manifestations

1. Sensorineural deafness
2. Dystonia and ataxia in late childhood
3. Visual loss with optic atrophy with onset at approximately 20 years of age
4. Cognitive deficits and psychiatric disorders by age 50

Neuropathology

1. Visual loss is secondary to retinal ganglion cell loss
2. The TIMM13 protein is a 70 KDa hetero-oligomeric complex that is located in the mitochondrial intermembrane space:
 - a. In conjunction with TIMM8A (another mitochondrial membrane translocase), facilitates the import and insertion of inner mitochondrial proteins
3. Decreased complex I–IV mitochondrial chain activity

Laboratory Evaluation

1. Genetic testing
2. MRI of the brain
3. Hearing evaluation

Dilated Cardiomyopathy with Ataxia (DCMA)*General Characteristics*

1. DCMA also known as 3-methyl glutaric aciduria type Vis caused by mutations in the DNA JC19 gene that maps to chromosome 3q26.33
2. The encoded protein is within mitochondria
3. It is an autosomal recessive disorder of Hutterite patients of the Northern United States and Canada

Clinical Manifestations

1. Growth failure
2. Early onset cardiomyopathy
3. Optic atrophy in a subset of patients
4. Cerebellar ataxia
5. Muscle weakness
6. Genital abnormalities in males

Neuropathology

1. The encoded protein localizes to the mitochondrial inner membrane and is putative translocase that functions to import proteins into the mitochondrial matrix

Laboratory Evaluation

1. Ophthalmologic evaluation
2. Microcytic anemia
3. Excretion of 3-methylglutaconic acid

Optic Atrophy in Mitochondrial Encephalomyopathies

The optic neuropathy in the clonic mitochondrial syndromes listed is a secondary feature that is overshadowed by the more significant associated deficits:

1. MELAS
2. MERRF
3. Kearns-Sayre syndrome
4. Maternally inherited Leigh syndrome
5. MNGIE

Glaucoma from OPTN Mutations*General Characteristics*

1. Primary open angle glaucoma may be caused by mutations in 4 genes:
 - a. Optineurin (OPTN)
 - b. Myocilin (MYOC)
 - c. CYP1B1
 - d. WDR 36
2. OPTN mutations are detected in approximately 17% of families with normal tension glaucoma and are causative of 2% of sporadic patients
3. It has been suggested that the OPTN variant (PM98K) may be a risk factor for glaucoma
4. The optineurin gene maps to chromosome 10p13
5. The protein optineurin interacts with Huntington (HTT) transcription factor IIIA and RAB8
6. Phosphorylation of it may be associated with its action as an autophagy receptor

Clinical Manifestations

1. Associated with primary open angle glaucoma
2. One gene mutation has been associated with normal tension glaucoma
3. Associated with autosomal recessive amyotrophic lateral sclerosis

Neuropathology

1. OPTN is a pleiotropic protein and one of its functions is to protect against oxidative stress which is accomplished by regulating NF- κ B:
 - a. Upregulation of NF- κ B inhibits cytochrome-c oxidase and cytochrome b mRNA which decreases ATP production
 - b. OPTN also colocalizes in the Golgi apparatus that suggests a role in protein membrane trafficking and vesicular transport
 - c. Mitochondrial dysfunction of RGCs

Laboratory Evaluation

1. Complete ophthalmologic evaluation
2. OCT
3. Detailed visual field testing

Idiopathic Intracranial Hypertension*General Characteristics*

1. Definition:
 - a. Raised intracranial pressure
 - b. Papilledema
 - c. No clinical or radiological structural lesions noted
 - d. Normal CSF (the exception is increased pressure)
2. Associated neurological signs and symptoms:
 - a. Increased size of the blind spot
 - b. VIth nerve palsy (due to generalized increased intracranial pressure; the nerve is trapped in Dorello's canal under the petroclinoid ligament)
 - c. Tinnitus (may be pulsatile)
 - d. Visual obscuration (variable pressure on the chiasm from the suprachiasmatic recess)
 - e. Severe headaches

Clinical Manifestations

1. Female preponderance (teen years through the fifth decade); most often patients have an increased BMI
2. Twenty percent of the disorder occurs in men
3. Visual field defects:
 - a. The most common feature is an enlarged blind spot
 - b. Arcuate nerve bundle defects (within the central 80% of vision)
 - c. The defects are usually along the horizontal meridian

Neuropathology

1. Visual acuity loss occurs from both outer retinal changes (often reversible) or optic neuropathy

Laboratory Evaluation

1. MRI:
 - a. Empty sella syndrome
 - b. Transverse sinus stenosis (some patients)

- c. Flattening of the posterior globe
- d. Optic disc protrusion
- e. Increased perioptic nerve CSF space

Differential Diagnosis of Idiopathic Intracranial Hypertension (Pseudotumor Cerebri)

1. Congenital defects:
 - a. Aqueductal stenosis:
 - i. Forked aqueduct
 - ii. Small multichannel aqueduct
 - iii. Congenitally small aqueduct (less than 3 mm)
 - b. Syringomyelia
 - c. Chronic sepsis (obliteration of the Pacchionian granulations)
- d. Drugs:
 - i. Amiodarone
 - ii. Tetracycline
 - iii. Nalidixic acid
 - iv. Steroid withdrawal
 - v. Birth control pills
 - vi. Lithium
 - vii. Hypervitaminosis A and D
- e. Venous thrombosis:
 - i. Venous anomalies of sinuses:
 1. Lateral sinuses (otitic hydrocephalus)
 2. Transverse sinuses
 3. Sagittal sinus (usually the superior > inferior)
 4. Hypercoagulable state
- f. Hypothyroidism
- g. Pernicious anemia
- h. Iron deficiency anemia
- i. Addison's disease
- j. SLE
- k. Polythemia vera
- l. Hypothalamic pituitary dysfunction:
 - i. Stein-Leventhal syndrome

Differential Diagnosis of Unusual Cause of Optic Nerve Disease

1. Orbital complications of sinus disease:
 - a. Frontal sinusitis:
 - i. Microcode:
 1. Orbital mass
 2. Exophthalmos
 3. Naso-orbital hyperostosis
 - ii. Encrypted empyema:
 1. Upper inner angle of the orbit
 2. Swelling and ptosis of the lids
 3. Orbital osteoperiostitis
 4. Diffuse orbital suppuration and abscess
2. Maxillary sinusitis:
 - a. Osteoperiostitis
 - b. Early optic nerve involvement
 - c. Lacrimal apparatus destruction

- d. Iritis, iridocyclitis, neuroretinitis
3. Ethmoidal sinusitis:
 - a. Associated mucocele in young patients
 - b. Suppuration
 - c. Osteoperiostitis
4. Sphenoidal sinusitis:
 - a. Associated with cavernous sinus thrombosis
 - b. Orbital abscess
 - c. Optic neuritis (inflammatory)
 - d. Associated ocular nerve palsies; the VIth nerve is most frequently involved
5. Thyroid ophthalmopathy:
 - a. The most common cause of unilateral exophthalmos
 - b. Often preceded by exophthalmos without ocular globe deviation
 - c. Orbital edema
 - d. Inflammation and fibrosis of extraocular muscles
 - e. Insertions of the muscles are not involved
 - f. Inferior rectus more severely affected (controversial) > medial recti > superior recti > oblique muscles
 - g. Vertical diplopia may occur from asymmetric involvement of the inferior or superior recti is a common early presentation
 - h. Abduction may cause extortion of the globe (due to involvement of the inferior oblique muscle)
 - i. Orbital congestion
 - j. Upper lid retraction (Dalrymple's sign)
 - k. Lid lag on down gaze (Von Graefe's sign)
 - l. Infrequent blinking (Stellwag's sign)
 - m. Convergent weakness (Moebius' sign)
 - n. Optic nerve compression with central scotoma (due to severe orbital compression by swollen muscles at the orbital apex)
6. Paget's disease:
 - a. Overgrowth of bone that compresses the orbital canal
7. Fibrous dysplasia of bone:
 - a. Compression of optic canal
8. Osteopetrosis:
 - a. Compression of the optic canal
9. Increased intracranial pressure:
 - a. Suprachiasmatic recess pressure compresses the chiasma (transient visual obscurations)
 - b. Venous congestion of the cavernous sinus with secondary orbital venous congestion
10. Idiopathic pachymeningitis
11. Paraneoplastic involvement
12. Traumatic optic nerve injury:
 - a. Orbital and facial fractures:
 - i. Penetrating orbital lesions
 - ii. Blunt trauma to the eye:
 1. Putative contusion of retrobulbar axons
 2. Hemorrhage of the nerve or the nerve sheath
 - iii. Loss of vision during orbital surgery:
 1. Post-operative orbital hemorrhage
2. Direct optic nerve injury
3. Repair of orbital floor fracture
4. After rhinoplasty
5. Blepharoplasty (orbital hemorrhage)
6. Neurosurgical procedures (face down):
 - a. Malposition of the headrest tamponades the globe
 - b. Retinal choroidal infarction
- iv. Optic nerve tethered to the bone:
 1. Areas of injury:
 - a. Orbital opening of the canal
 - b. Canal (12 mm)
 - c. Intracranial entrance of the canal is compressed with head trauma
 2. Anterior frontal impact (rapid acceleration):
 - a. Falls, windshield trauma, frontal head trauma
 - b. Instantaneous severe visual loss
13. Radiation injury of the optic nerve:
 - a. Usually secondary to X-RT of a pituitary tumor, paranasal malignancy or temporal lobe glioma
 - b. Radiation necrosis:
 - i. Proliferative endarteritis of the vasa vasorum (endothelial cells)
 - ii. Fibrinoid arterial necrosis
 - iii. Necrosis of retrolaminar nerve
 - iv. Delayed visual loss with optic atrophy
14. Thermal burns:
 - a. Delayed optic neuropathy
 - b. Bilateral involvement
 - c. Early visual loss due to diffuse cerebral edema or hypoxia
15. Infection of the optic nerve:
 - a. Syphilis:
 - i. Neuroretinitis
 - ii. Papillitis
 - iii. Perineuritis
 - b. A manifestation of second stage disease
 - c. Reoccurrence (particularly in AIDS patients)
 - d. Slowly progressive atrophy (Stage III)
 - e. Retrobulbar neuritis
 - f. Neuroretinitis in secondary syphilis:
 - i. Clouding of the central retina
 - ii. Hemorrhages
 - iii. Migration of the pigment epithelium (retinitis pigmentosa; the pigment localizes around blood vessels)
 - iv. Vitreous cellular debris
 - v. Disc swelling
 - vi. Vasculitis
16. Optic neuritis in association with HIV:
 - a. CMV neuroretinitis and papillitis
 - b. Syphilitic optic perineuritis
 - c. Hepatitis B
 - d. HIV:

- i. Bilateral optic neuritis
- e. Lyme's disease
- f. Toxoplasmosis (inflammatory papillitis)
- g. Taxocara canes (inflammatory papillitis)

Differential Diagnosis of the Swollen Disc

1. Congenital causes:
 - a. Anomalous disc:
 - i. Tilted and elevated
 - b. Hyalin bodies
 - c. Gliotic dysplasia:
 - i. Embryonic vascular remnants
2. Intraocular disease:
 - a. Uveitis
 - b. Hypotony
 - c. Vein occlusion
3. Inflammatory:
 - a. Papillitis
 - b. Neuroretinitis
 - c. Papillophlebitis
4. Infiltrative:
 - a. Lymphoma
 - b. Leukemia
5. Reticuloendothelial disease
6. Systemic disease (Fe deficiency, B12):
 - a. Anemia
 - b. Hypoxemia
 - c. Severe hypertension (encephalopathy)
 - d. Acute blood loss
 - e. Uremia
7. Disc Tumors:
 - a. Hemangioma
 - b. Glioma
 - c. Metastatic
 - d. Hamartoma
8. Vascular disease:
 - a. Ischemic optic neuropathy
 - b. Arteritis (giant cell)
 - c. Arteritis associated with collagen vascular disease
9. Juvenile diabetes
10. Proliferative retinopathies
11. Orbital tumors:
 - a. Perioptic meningioma (Schwalbe)
 - b. Glioma
 - c. Sheath tumor (cylindromas)
 - d. Retrobulbar masses
12. Graves's disease
13. Elevated intracranial pressure:
 - a. Mass lesion
 - b. Idiopathic Intracranial Hypertension (IIH)
14. Hypertension encephalopathy

Papilledema Secondary to Increased Intracranial Pressure

1. Increased nerve sheath pressure

2. Optic nerve fibers:
 - a. Compressed by increased CSF pressure in the sub-arachnoid space
 - b. The intraorbital part of the nerve is affected
 - c. Water and protein diffuse into the prelaminar region of the disc
3. Later evaluation of the process:
 - a. Venous obstruction
 - b. Nerve fiber layer hypoxia
 - c. Vascular telangiectasia

Rare Causes of Papilledema

1. Cyanotic congenital heart disease
2. Decreased arterial saturation
3. Polycythemia vera
4. Sleep apnea (CO₂ retention)
5. Syringomyelia without hydrocephalus
6. Spinal cord tumors (increased CSF protein) blocks absorption through the Paccianian granulations
7. AIDP/CIDP (increased CSF protein; cytotoxic antibodies to the nerve)

Different Mechanisms That Cause Papilledema

1. Increased intracranial pressure from mass lesions (direct pressure on the nerves and venous outflow obstruction)
2. Increased CSF production (choroid plexus papilloma)
3. Decreased CSF absorption (obstruction of Paccianian granulations)
4. Obstructive hydrocephalus
5. Increased cerebral blood volume (AVM)
6. Venous outflow obstruction:
 - a. Arteria of venous sinuses
 - b. Obstruction of venous sinuses (inflammatory, hyper-coagulable state with thrombosis)
7. Neck surgery (compression of venous outflow)
8. Jugular vein compression
9. Increased thoracic pressure
10. Chronic unilateral papilledema:
 - a. Nerve sheath tumor
 - b. Intraorbital mass
 - c. Rarely with generalized increased intracranial pressure
 - d. Previous optic atrophy in the contralateral eye (pseudo Foster-Kennedy syndrome; an atrophic disc cannot be swollen)

Clinical Manifestations of Papilledema

1. Infants with open sutures and elderly patients with cortical atrophy do not get papilledema
2. It usually takes days to weeks to develop
3. Papilledema may develop within hours with:
 - a. Severe head trauma (loss of autoregulation)
 - b. SAH (acute obstruction of CSF absorption by blood and protein)
 - c. Intracranial hemorrhage with > than 60–80 ml of blood
4. There is no visual acuity loss

5. There is enlargement of the blind spot
6. There is a normal pupillary light reflex
7. Visual fields are intact
8. Late or long standing papilledema:
 - a. Irregular peripheral VF constriction
 - b. There are nerve fiber bundle defects
 - c. Transient visual obscurations occur and are characterized by:
 - i. Momentary dimming of vision
 - ii. One eye at a time
 - iii. Lasts a few seconds (< than 10–15 seconds)
 - iv. Occurs with postural change or spontaneously
 - v. Clears completely
 - vi. Pressure on the globe may reproduce the obscuration
 - vii. A proposed mechanism is fluctuation of optic disc perfusion
 - viii. Late VF loss has tendency to involve the nasal quadrants; a late sign is:
 1. General visual field constriction
 - ix. Ophthalmoscopic evaluation:
 1. Blurring of the nerve fiber layer: nasal quadrant earlier than:
 - a. Superior > inferior > temporal
 - b. Veins are engorged, dusky and tortuous
 2. Spontaneous pulsations cease:
 - a. They are seen in 80% of normal patients
 - b. Cease at 200 ± 25 mm H₂O
 - c. The optic cup is pushed forward and the lamina cribrosa is indistinct
 - d. Splinter hemorrhages are seen off the disc; they may also be seen with drusen, glaucoma and rarely in the elderly
 - e. In patients with chronic increased pressure intracranially or in the optic canal, optociliary vessels may be prominent. They are anastomotic channels between the central retinal veins and the peripapillary choroidal venous system that bypass the compressed optic nerve venous system
 3. Optociliary shunt vessels may also be seen with:
 - a. Central retinal vein occlusion
 - b. Optic nerve glioma
 - c. Neonatal hydrocephalus
 - d. Idiopathic intracranial hypertension
 - e. Drusen of the optic disc
 - f. Glaucoma
 - g. High myopia
 - h. Chronic atrophic papillitis
 - i. Arachnoid cyst of the optic nerve
 - j. Optic nerve coloboma
 - k. Osteosclerosis
 - x. Nerve fiber layer infarcts:
 1. Cotton wool spots
 - xi. Disc hyperemia (dilation of the superficial capillary bed on the disc)
 - xii. Retinal folds (Patent lines); circumferential retinal microfolds that may extend to the macula
 - xiii. Rare concomitants of severe papilledema:
 1. Choroidal folds
 2. Ischemic infarction of the disc
 3. Infarction of the central retinal artery

The Optic Chiasm

General Characteristics

Anatomy

1. The chiasm is in the suprasellar cistern
2. It forms the floor of the suprachiasmatic recess
3. It lies 8–13 mm above the plane of the clinoid processes
4. The intracranial optic nerve:
 - a. Lies 45 degrees above the horizontal
 - b. $17 (\pm 2.5)$ mm in length
5. The lateral portion of the chiasm is adjacent to the supraclinoid carotid artery
6. The anterior cerebral arteries are dorsal to the optic nerves

Clinical Manifestations

1. Visual acuity may be decreased bilaterally if lesions involve macular fibers medially or posteriorly
2. Decreased acuity in the ipsilateral eye from lateral lesions (uncrossed fibers)
3. Color perception desaturation is common
4. Visual field deficits:
 - a. Junctional scotoma
 - b. Ipsilateral temporal or paracentral defect (anterior chiasm)
 - c. Bitemporal superior heteronymous quadrantanopsia (lesion of the paracentral chiasm; upper crossing fibers are inferior)
 - d. Impaired central vision on convergence
 - e. Hemislide of the visual field with pseudodiplopia (VF defect that has unmasked minor ocular motor imbalance that had been controlled by fixation)
 - f. Marcus Gunn phenomenon with an ipsilateral lesion
 - g. Nerve fiber layer atrophy of straight nasal retinal fibers “bow tie” configuration (crossing fibers)
 - h. Insidious progressive visual loss
 - i. Usually asymmetrical
 - j. Tumors or aneurysms may cause alterations of vision
 - k. Non-paretic diplopia
 - l. Clumsiness with motor functions
 - m. Diminished fusional capacity (non-fixed nasal fields):
 - i. Vertical and horizontal slippage:
 1. Doubling of images
 2. Gaps in a visual image
 3. Steps in the perception of horizontal lines

- n. Extinction of objects beyond the fixation point
- o. Optic nerve atrophy
- p. The vertical meridian is respected in chiasmatic defects
- q. Rare chiasmatic VF deficits:
 - i. Bilateral optic atrophy with central scotomas
 - ii. Posterior chiasm angle defect:
 - 1. Homonymous hemianopsia
 - 2. Depression of the inferior temporal VF near fixation
- r. A pseudochiasmatic VF defect:
 - i. The vertical meridian (isopter defect “8–12”) is involved in true chiasmatic defects
 - ii. Bilateral intrinsic eccentric central or centrocecal scotoma:
 - 1. Intrinsic optic nerve or retinal disease is causative
 - iii. Nasal sector retinal disease (bilateral retinitis pigmentation)
 - iv. Congenitally tilted discs (inferior crescents; nasal fundus ectopia)

Neuropathology

1. Congenital chiasmatic defects:
 - a. Maldevelopment of the optic vesicles:
 - i. Unilateral or bilateral anophthalmos
 - ii. Micro-ophthalmic cysts
 - b. Nerve hypoplasia:
 - i. May occur in isolation
 - ii. Occurs with ocular and forebrain malformations
 - iii. Partial aplasia; micropapilla
 - c. Bilateral optic nerve hypoplasia:
 - i. Associated with forebrain or developmental anomalies
 - d. Septo-optic dysplasia (De Morsier syndrome):
 - i. Short stature
 - ii. Nystagmus
 - iii. Disc hypoplasia
 - iv. Holoprosencephaly
 - v. GH and ADH deficiency
 - vi. Small pituitary
 - vii. Cognitive dysfunction
 - e. Dysplastic disc development:
 - i. Congenital tumor:
 1. Associated with a hypoplastic, truncated, irregularly shaped oval disc
 - f. Coloboma:
 - i. A congenital malformation that enlarges or distorts the nerve head circumference
 - ii. Faulty closure of the embryonic ventral fissure of the optic stalk and cup
 - iii. An enlarged disc that is excavated
 - iv. Retained glial and vascular remnants
 - v. Posterior displaced disc within excavated peripapillary coloboma

- vi. Excavated disc adjacent to retinochoroidal coloboma
- vii. Pits within the optic nerve head
- viii. Rare AD inheritance of colobomas; most are sporadic

Association of Disc Malformations and Forebrain Anomalies

1. Basal encephalocele:
 - a. Pulsating exophthalmos (spheno-orbital encephalocele)
 - b. Hypertelorism with pulsatile nasopharyngeal mass
 - c. Frontonasal mass (frontoethmoidal encephalocele)
2. Coloboma of the disc with hypertelorism or midface abnormality:
 - a. Associated with basal encephalocele
3. Bilateral disc coloboma:
 - a. Bilateral retrobulbar arachnoid cyst
 - b. Dandy-Walker malformation
4. Unilateral coloboma:
 - a. Carotid occlusion
 - b. Moyamoya syndrome with dolichoectasia
 - c. Absent carotid artery
5. Pits of the disc:
 - a. Intrapapillary pearly gray dimples or slits
 - b. Contain glial elements
 - c. Located within the scleral rim of the disc margin
 - d. Single: temporal location > central > inferior > superior or nasal quadrant
 - e. Temporal pits are associated with serous detachment of the macula
6. Diversion (tilted disc) and associated crescents of the optic discs:
 - a. Inferior crescent most frequent (inferior conus; Fuchs coloboma)
 - b. Adjacent retinal sector disorganization of the choroid and pigment epithelium
 - c. Inferior crescents are associated with:
 - i. Myopia
 - ii. Astigmatism
 - iii. Decreased visual acuity
 - iv. Decreased foveal reflex
7. Disc abnormalities are associated with:
 - a. Hypertelorism
 - b. Crouzon syndrome
 - c. Apert syndrome

Neoplasms Affecting the Optic Chiasm

1. Adenoma of the pituitary:
 - a. The most common presentation is in the 4–7th decade; they are uncommon in patients younger than 20 years old
 - b. Non-secretory adenoma:
 - i. Larger than secretory tumors

- ii. Present at 50–60 years of age
 - iii. More frequent in males than females
- c. Visual field deficits:
 - i. Superior bitemporal hemianopia
 - ii. Hemianopic scotoma near the fixation point adjacent to the vertical meridian
 - iii. Asymmetric deficits
 - iv. The eye with the greater deficit may demonstrate loss of visual acuity (papillomacular bundle fibers are affected)
 - v. Posteriorly located adenomas that may extend into the optic tract cause:
 - 1. An incongruous hemianopia
 - 2. Decreased central visions (of the ipsilateral eye)
 - 3. Optic atrophy
 - 4. Rarely: a β -ferrum arcuate scotoma is demonstrated
- 2. Prolactinoma:
 - a. The most common pituitary tumor
 - b. Females > males
 - c. Microadenomas (<10 mm in size)
 - d. Amenorrhea and galactorrhea
 - e. Males:
 - i. Decreased libido
 - ii. Impotence
 - iii. Gynecomastia
- 3. Suprasellar optic tumors:
 - a. Irritate the pituitary stalk (stalk effects increases the prolactin level)
 - b. Disrupt fiber tracts in the hypothalamus
 - c. Cause hyperprolactinemia
- 4. Pituitary apoplexy:
 - a. Acute change in the volume of a pituitary adenoma causes necrosis, edema or infarction of the pituitary:
 - i. Sheehan's syndrome:
 - 1. Acute hemorrhage during pregnancy (extremely rare in developed countries)
 - ii. The mean age of apoplexy is 50 years
 - iii. MRI has demonstrated that in a large percentage of glands that have hemorrhaged are asymptomatic
 - b. Differential diagnosis of pituitary apoplexy:
 - i. Large adenomas
 - ii. Pregnancy
 - iii. Coagulation defects
 - iv. X-RT
 - v. Trauma
 - vi. Adrenalectomy
 - c. Clinical manifestations:
 - i. Acute severe retro-orbital or infrabrow pain
 - ii. Rapid expansion into the cavernous sinus with unilateral or bilateral partial ophthalmoplegia
 - iii. Asymptomatic ophthalmoplegia
 - iv. Epistaxis or CSF rhinorrhea (from erosion into the sphenoid sinus)
 - v. Pseudomeningitis
 - vi. Decreased mental status or stupor is rare
 - vii. Late effects are panhypopituitarism
 - viii. If there is upward expansion:
 - 1. There is visual loss without ophthalmoplegia
 - 2. Downward expansion:
 - a. Ophthalmoplegia without visual loss
- 5. Perichiasmal or optic nerve compression by meningioma:
 - a. Characteristic locations:
 - i. Posterior perioptic foramina
 - ii. Medial sphenoid ridge
 - iii. Tuberculum sellae
 - iv. Olfactory groove (posterior extension)
 - v. Planum sphenoidale (posterior extension)
 - b. Clinical manifestations:
 - i. Slowly progressive monocular visual loss
 - ii. VF deficits:
 - 1. Markedly asymmetric; an extensive defect develops ipsilaterally prior to contralateral deficits
 - iii. More frequent in middle-aged women
 - iv. Enlargement of the meningioma during pregnancy
 - v. Infrabrow or frontal headache occurs with suprasellar meningiomas
 - vi. Onset of visual loss (unilateral) to bilateral visual deficits is (1–8 years)
 - vii. Periorbital eye pain that is exacerbated by movement is more common with optic neuritis
- 6. Craniopharyngioma:
 - a. The origin of the tumor is from vestigial epidermoid remnants of Rathke's pouch; scattered cell rests in the infundibulohypophyseal area
 - b. Calcification occurs in the tumor in 80% of children
 - c. There is a bimodal incidence:
 - i. The first two decades and again between 50–70 years of age
 - d. Accounts for 2 to 4% of intracranial tumors
 - e. In adults, 20% of the tumors are suprasellar; 15% are intrasellar
 - f. Clinical manifestations:
 - i. Visual deterioration
 - ii. Endocrine deficits:
 - 1. D1 (diabetes insipidus)
 - 2. Amenorrhea/galactorrhea
 - 3. Hypopituitarism
 - iii. VF deficit:
 - 1. Asymmetric bitemporal hemianopia (inferior quadrants)
 - 2. If there is optic tract extension:
 - a. Incongruous homonymous defect with decreased visual acuity
 - iv. The chiasm and optic nerve may be infiltrated and thickened
 - v. The optic canal may be enlarged
- 7. Optic and hypothalamic glioma:
 - a. Onset is usually during middle age

- b. Rapid severe unilateral visual loss; may be bilateral with chiasmatic extension
- c. Invasive malignant astrocytoma that may metastasize
- d. Death within months to two years
- 8. Chiasmatic glioma:
 - a. More common than is the orbital type
 - b. Unilateral or bilateral visual loss
 - c. More aggressive growth of chiasmatic gliomas in adults
 - d. Primary malignant glioblastoma of visual pathways is rare in adults:
 - i. Age of onset is 40–50 years of age
 - ii. Monocular loss of vision early if it has an optic nerve origin
 - iii. Retro-orbital pain
 - iv. Disc edema
 - v. There may be 5 to 6 weeks of progressive visual loss that causes bilateral blindness
 - vi. Death is usually within 2 years
- 9. Dysgerminoma:
 - a. Origin is from cell rests of the anterior floor of the IIIrd ventricle
 - b. Suprasellar location
 - c. Histological resemblance to a typical pineal teratoma
 - d. Clinical manifestations:
 - 1. Chiasmatic VF deficit
 - 2. May have concomitant anterior optic pathway involvement
 - 3. Diabetes insipidus in 80% of patients
 - 4. Partial hypopituitarism
 - 5. The age of onset is the first or second decade
 - 6. Growth retardation
 - 7. Most often an insidious visual loss

Arachnoidal and Epithelial Cysts

- 1. Serous cavity lined by neuroepithelium
- 2. Suprasellar cysts may arise in the floor of the IIIrd ventricle
- 3. Cysts of the sella turcica:
 - a. Cysts of the Rathke's pouch
 - b. Epithelial cysts
 - c. Colloid cysts
 - d. Clinical manifestations
 - i. May extend into the chiasmatic cistern
 - ii. Chiasmatic VF deficits
 - iii. Pituitary dysfunction
- e. Arachnoid cysts
 - i. 70% occur at the base of the skull
 - ii. Temporal fossa (29%) > posterior fossa (21%) > parasellar region (18%)
 - iii. Clinical manifestations
 - 1. A large percentage is asymptomatic
 - 2. Headache (50%)
 - 3. Blurred vision (40%)
 - 4. Seizures (40%; temporal lobe cysts)

- 5. Diplopia (15%)
- 6. Rarely, optic nerve sheath cysts are associated (disc swelling)

Suprasellar Aneurysm

- 1. Supra-arachnoid carotid aneurysm
 - a. Greater than 25 mm (giant aneurysm)
 - b. Women in the 5th to 6th decade
 - c. Compresses both the optic nerve and the chiasm
 - d. Clinical manifestations
 - i. Severe visual loss of the ipsilateral eye
 - ii. The aneurysm arises below the ipsilateral optic nerve and compresses it; it expands anteriorly and superiorly
 - iii. Most often there is an insidious progression of visual loss
 - iv. If the chiasm is prefixed there may be VF tract deficit

Multiple Sclerosis

- 1. Chiasmatic defects are much rarer than those of the optic nerve
- 2. VF deficits
 - a. Junctional scotoma (decreased acuity of the ipsilateral eye; temporal crescent contralaterally)
 - b. Bitemporal defects

Metastatic Disease of the Optic Nerves and the Chiasm

- 1. Rapid unilateral or bilateral visual loss
- 2. Usually there is no disc swelling
- 3. Hematogenous spread through CSF spaces
- 4. Most often associated with rapid sequential multiple cranial nerve palsies
- 5. Malignant lymphoma grows through the perivascular spaces and may also cause segmental demyelination
- 6. Chronic lymphocytic leukemia involves the chiasm
- 7. Metastases to the pituitary gland (breast cancer) may secondarily grow into the chiasm and may be associated with diabetes insipidus
 - a. Seeding of the posterior > anterior lobe
 - b. Associated diplopia

Sphenoidal Mucocele

- 1. Mucocele of the posterior ethmoid and sphenoid paranasal sinus:
 - a. Chronic headache (may project to the top of the head)
 - b. Varying ophthalmoplegia from involvement of the orbital apex
 - c. Visual loss (central) with various peripheral chiasmatic defects

Trauma

- 1. Visual loss after closed head trauma:

- a. Neuropraxia, contusion or laceration of the optic nerve to fixed points of the entry into and exit from the optic canal
- b. Immediate visual loss
2. Chiasmatic traumatic syndrome
 - a. Much less common than optic nerve lesions
 - b. Visual field deficits
 - i. Complete monocular blindness with contralateral temporal deficits (functional type)
 - ii. Bitemporal arcuate scotomas
3. Associated neurologic deficits:
 - a. Transient diabetes insipidus
 - b. Anosmia and associated defects of CN III, IV, VII and VIII
 - c. CSF rhinorrhea and otorrhea
 - d. Carotid – cavernous fistula
 - e. Carotid pseudoaneurysm
 - f. Delayed onset of meningitis
 - g. Mechanics of chiasmatic injury:
 - i. Sagittal tearing of the chiasm from sphenoidal fractures
 - ii. Thrombosis or shearing of the carotid artery blood supply to the chiasm
 - iii. Contusion or hemorrhage of the chiasm itself

Complications of X-RT

1. Radiation necrosis occurs approximately 8–12 months after treatment
2. The radionecrosis is greater in the anterior visual system than the chiasm
3. Rapidly progressive visual loss in one eye; decreased vision in the second eye follows after a short interval
4. There is a relentless progression to a severe deficit
5. Visual field deficits
 - a. Central scotoma or nerve fiber bundle defects
 - b. Chiasmatic defects
 - c. Optic tract defects
6. Chiasmatic defects are associated with pituitary X-RT
7. Optic atrophy occurs two to three months after visual loss
8. Doses clearly associated with radionecrosis (5000 cGY): complications may occur with daily fractional doses of 200 to 220 cGY treatments
 - a. The pathology is a proliferative endarteritis of small blood vessels with anoxia

Hydrocephalus

1. Pressure of the anterior aspect of the IIIrd ventricle (suprachiasmatic recess) on the chiasm that produces a neuropractic injury
2. Bitemporal VF deficit
3. Progressive optic atrophy from pressure of the nerve against the bones of the sella turcica or the carotid body

Chiasmatic Pathology with Pregnancy

1. Increase of suprasellar meningioma growth during the 2nd and 3rd trimester

2. Optic neuritis is more common after delivery (usually 6–8 weeks)
3. Lymphocytic adenohypophysitis:
 - a. Occurs often concomitantly with pregnancy
 - b. Diffuse lymphocytic infiltration of the pituitary gland
 - c. Immune-mediated
 - d. Apparently exclusive to women

The Empty Sella Syndrome

1. There is an extension of the subarachnoid space through the diaphragm sella
2. Defects in the diaphragm sella that are greater than 5 mm occur in 40% of the general population
3. There is a normal volume of the sella; glandular pituitary tissue is compressed against its posterior wall
4. The empty sella is associated with:
 - a. Arachnoid cysts
 - b. Infarction of the pituitary gland
 - c. Idiopathic intracranial hypertension
 - d. Pituitary surgery
 - e. X-RT
 - f. Pituitary apoplexy
 - g. Clinical manifestations
 - i. Chiasmal herniation into the sella
 - ii. Visual defects due to adhesions of the optic nerves and the chiasm that lead to diplopia and micropsia
 - iii. The syndrome is more common in obese women between 20–70 years of age (mean is 50 years of age)
 - iv. Headache is usually frontal or bitemporal
 - v. Rarely there is pituitary dysfunction (growth hormone, thyroid decreased secretion; increased prolactin)
 - vi. Occasional CSF rhinorrhea
 - vii. Blurred vision, diplopia and micropsia are rare visual complaints

Devic's Disease

1. Bilateral optic neuritis that may extend into the chiasm
2. At least 3 vertebral body segment spinal cord immune-mediated inflammation
3. The demonstration of aquaporin antibodies in the serum

Infectious Meningitis

1. Chiasmatic arachnoid inflammation (possibly infectious)
2. CMV of the optic nerve and chiasm as well as the retina (necrotizing)
3. Cryptococcus (extension from the optic nerve subdural infection)
4. Pseudomonas aeruginosa
5. EBV (direct infection)
6. Staphylococcus (hematogenous)
7. Streptococcal pneumonia (hematogenous)
8. HIV (direct infection)

Optochiasmatic Arachnoiditis

1. Associated with meningovascular syphilis
2. Polyarteritis
3. Cystic adhesive fibrous arachnoidal thickening with lymphocytes

Sarcoidosis

1. Involves the posterior hypothalamus
2. Pituitary
3. Optic nerve sheath
4. Chiasm
 - a. May cause chiasmic VF defects

Laboratory Evaluation

1. Specific serum markers that identify autoimmune, infectious or specific entities (aquaporin antibodies)
2. Ophthalmologic evaluation
3. MRI for intracranial processes
4. CT scan for sinus pathology
5. OCT for genetic abnormalities

Cranial Nerve III**General Characteristics***Anatomical Features*

1. The third nerve nuclear complex is located in the midbrain at the level of the superior colliculus; it extends rostrocaudally for approximately 5 mm
2. The complex is anatomically organized such that:
 - a. Dorsal neurons of the lateral nucleus innervate the inferior rectus; intermediate neurons of the lateral nucleus innervate the inferior oblique and its ventral neurons the medial rectus muscle
 - b. The central caudal nucleus innervates the levator muscles of both eyes
 - c. There is both ipsilateral and contralateral innervation of the superior rectus muscle
3. The Edinger-Westphal nucleus overlies the dorsal rostral portion of the oculomotor complex
 - a. The anteromedian nucleus and EW nucleus supply pre-ganglionic parasympathetic axons to the ciliary ganglion
 - b. Post-ganglionic sympathetic fibers reach the eye by way of short ciliary nerves
 - c. Approximately 3–3.5% of ocular parasympathetic axons supply the iris sphincter while greater than 90% supply the ciliary muscle and mediate pupillary constriction with ocular convergence (accommodation)
 - d. Pressure sensitive axons for pupillary constriction occupy the dorsomedial margin of the IIIrd nerve by some counts while it is postulated by others that they are spread equally throughout the nerve

4. Within the IIIrd nerve fibers to each muscle are organized with:
 - a. The pupillomotor fibers most medially
 - b. From medial to lateral – the IR, MR, SR and inferior oblique (most lateral)
 - c. The levator fibers are dorsal to the IR and MR
 - d. Fibers for accommodation course with pupillomotor fibers in the nerve
 - e. Clinically several syndromes can be identified from the various lesions that affect the nerve from its origin in the midbrain to the orbit. They include:
 - i. A nuclear IIIrd nerve
 - ii. Fascicular IIIrd nerve
 - iii. Cavernous IIIrd nerve syndrome
 - iv. Involvement of the IIIrd nerve in the superior orbital fissure
 - v. In the orbit
5. The IIIrd nerve separates into two divisions within the anterior cavernous sinus or the orbit:
 - a. The superior division innervates the superior rectus and the levator of the lids
 - b. The inferior division innervates the medial rectus, the inferior rectus, the inferior oblique; parasympathetic fibers to the pupil course with the branch to the inferior oblique muscle
6. The blood supply to the IIIrd nerve:
 - a. Small arteries from the posterior cerebral and basilar arteries supply the IIIrd nerve complex
 - b. A branch of the meningohypophyseal trunk (origin is in the inferior cavernous sinus)
 - c. Recurrent branches from the ophthalmic artery to the orbital branches of the nerve

Clinical Manifestations

1. Diplopia in the field of gaze of the affected component muscle of the IIIrd nerve complex
2. Associated neurological deficits at the level of IIIrd nerve involvement
3. Complete IIIrd nerve palsy (peripheral) of the eye is abducted and down with a dilated unresponsive pupil
4. Pupillary involvement of the IIIrd nerve:
 - a. Internal carotid artery disease
 - i. Fibromuscular dysplasia, dissection, carotodynia, ischemia of the carotid (atherosclerosis or arteritis) all may cause sympathetic paresis. The internal carotid artery branches of the vasovorum supply the internal branch of the sympathetic innervation of the eye
 - ii. Complete Horner's syndrome
 1. Myosis
 2. Ptosis (sympathetic innervation of the tarsal muscles of the upper and lower lid; the upper lid droops to cover the upper iris while the lower lid rises)

3. Decreased sweating of the face (if the common carotid bifurcation and/or the external carotid branch is affected)
4. Apparent enophthalmos; decreased sympathetic innervation of Mueller's muscle behind the globe
5. Iris ischemia that causes a large pupil in severe carotid disease (<10%) of patients
6. Argyll Robertson pupil
 - a. Secondary to syphilis; a pretectal lesion
 - b. Six components:
 1. Small (approximately 1 mm)
 2. Irregular
 3. Does not respond to light
 4. Responds to accommodation
 5. No response to ciliospinal reflex
 6. No response to mydriatics
5. Behr's pupil:
 - a. Slightly dilated
 - b. Ipsilateral to an optic tract lesion
6. Holmes-Adie pupil:
 - a. Responds sluggishly to light and accommodation
 - b. May be unilateral
 - c. More common in young women
 - d. Associated with absent ankle jerks: occasionally loss of knee deep tendon reflexes
 - e. A component of a generalized small fiber neuropathy
7. Wernicke's pupil
 - a. Slit lamp is directed at the area of the retina that subserves the VF deficit from a stroke
 - b. Slower contraction of the contralateral pupil
8. Elliptical pupil (cat's eye pupil)
 - a. Pretectal lesion
 - b. Usually seen after severe head trauma
9. Oval pupil (tadpole pupil)
 - a. Diabetes mellitus
 - b. Syphilis
 - c. Herniation or other compressions of the third nerve
10. Light-near dissociation:
 - a. Diabetes mellitus
 - b. Amyloid
 - c. Syphilis
 - d. Rarely from pressure in the IIIrd nerve nuclear complex or the pretectal area
 - e. Anisocoria
 - i. 25% of the population
 - ii. Equally reactive to light and convergence
11. Leukocoria (white pupil)
 - a. Glioma
 - b. Retrocentral fibroplasia
 - c. Nematode enophthalmos
 - d. Massive retinal fibrosis
 - e. Retinoblastoma
 - f. Metastatic retinitis
 - g. Retinal dysplasia

- h. Coats' disease
 - i. Disease of young men
 - ii. Onset in the second to third decade
 - iii. Unilateral
 - iv. Massive macular exudative retinitis

Neuropathology

1. Vascular IIIrd nerve syndromes:
 - a. Nuclear IIIrd nerve syndrome:
 - i. The interpeduncular branch of the P1 division of the PCA is most often involved from an embolus or atherosclerosis
 - ii. Clinical manifestations include:
 1. Bilateral ptosis
 2. Bilateral pupillary dilatation
 3. Bilateral superior rectus palsy
2. Fascicular IIIrd nerve syndrome:
 - a. Weber's syndrome:
 - i. Ipsilateral IIIrd nerve lesion may or may not be pupil sparing that is accompanied by a contralateral hemiparesis
 - ii. The patient usually has no alteration in mental status
3. Benedict's syndrome:
 - a. Ipsilateral IIIrd nerve palsy with a contralateral movement disorder of the extremities
 - b. No mental status alterations
4. Claude's syndrome:
 - a. Ipsilateral IIIrd nerve palsy with a contralateral cerebellar outflow tremor
5. Subdural hematoma:
 - a. Ipsilateral IIIrd nerve palsy
 - b. The pupil is dilated, poorly responsive to light and may be oval in shape
 - c. Severe headache associated with lethargy (develops over hours to days)
 - d. Contralateral spastic hemiparesis
6. Cavernous sinus IIIrd nerve lesion:
 - a. Involved concomitantly with the IVth CN, VIth CN, and the first division of V1
7. Orbital IIIrd nerve lesion:
 - a. Concomitantly involved with cranial nerve IVth, VIth and the first division of Vth (at the superior orbital fissure)
 - b. Superior division involvement impairs the SR and the levator palpebrae
 - c. Inferior branch involvement impairs pupillomotor fibers and the innervation of the IR, MR, and inferior oblique muscles
8. Nuclear IIIrd and IVth nerve (Masugi's syndrome):
 - a. Infarction of the posterior lateral choroidal artery from the terminal PCA (P4)
 - b. Simultaneous nuclear IIIrd and IVth nerve paralysis
 - c. Crossed hemisensory deficit

- d. Rare contralateral mild internal capsule deficit
9. Hematoma of the midbrain:
 - a. Lethargy to obtundation (involvement of the periaqueductal gray)
 - b. Impairment of vertical gaze
 - c. Large 3–5 mm pupils that react sluggishly to light
 - d. Quadriplegia (if there is pressure on the cerebral peduncles)
 - e. Nystagmus refractories
 - f. Rarely there is convergent nystagmus
 - g. Hydrocephalus
10. Vascular malformations of the midbrain:
 - a. Cavernous hemangioma
 - b. Capillary telangiectasia (rare; these are usually in the pons or the cerebral cortex)
 - c. Arteriovenous malformation:
 - i. Different clinical manifestations that may involve the IIIrd nerve from size, recurrent bleeding and location
 - ii. Arterial venous malformations occur in association with Wyburn-Mason and Von Hippel-Lindau malformations
 - iii. Cavernous hemangiomas rebleed repeatedly
 - iv. Capillary telangiectasia (often are asymptomatic)
11. IIIrd nerve involvement may also occur from emboli or infarction secondary to “top of the basilar syndrome”
12. Aneurysmal Involvement of the IIIrd Nerve:
 - a. P-COM aneurysms often affect the IIIrd nerve in isolation
 - b. The pupil is often involved early from aneurysmal compression due to pupillomotor motor fiber vulnerability; they are located at the periphery of the dorso-medial part of the nerve or are of pressure sensitive axons that are spread throughout the nerve. The pupil may be spared with aneurysmal disease in a percentage of patients
 - c. Carotid artery aneurysm:
 - i. May involve the ipsilateral IIIrd nerve and cause contralateral face, arm and leg weakness
 - d. Between the posterior cerebral and superior cerebellar artery the IIIrd nerve may be compressed in isolation
 - e. Giant aneurysms at the top of the basilar artery (the IIIrd nerve is involved in the interpeduncular fossa) and is associated with hydrocephalus and contralateral spastic hemiparesis
 - f. IIIrd nerve may be compressed by a ceroid posterior cerebral artery (elongated and tortuous)
 - g. Retro-orbital pain is more severe and prolonged than occurs with a diabetic IIIrd nerve neuropathy
 - h. An intracavernous aneurysm may erode into the sphenoid sinus and present with nose bleed; usually there is VIth CN weakness and first division trigeminal nerve pain
13. Ischemia of the intracavernous internal carotid artery:
 - a. Inferolateral trunk of the ECA (external carotid artery):
 - i. The superior or terminal branch
 - ii. Anteromedial branch of the ILT (inferolateral trunk of the ECA) anastomoses with the distal portion of the internal maxillary artery and the posterior branch anastomoses with the accessory and middle meningeal arteries
 - iii. The IIIrd and IVth nerve are supplied by the superior or tentorial branch of the ILT
 - iv. Cranial nerves IIIrd, IVth, VIth are supplied by the anteromedial branch
 - v. The vascularization of the IIIrd nerve depends on the specific territory supplied by the ILT; the nerve is most often supplied by the superior or tentorial components of the anteromedial branch
 - b. Clinical manifestations of ischemia of the IIIrd nerve from external carotid artery disease:
 - i. Isolated IIIrd nerve palsy
 - ii. IIIrd nerve associated with Vth nerve (sensory component)
 - iii. IIIrd nerve associated with Vth, IVth, and VIth nerve
 - iv. IIIrd and IVth nerve may be involved concomitantly
 - c. In general, ischemia affects the central portion of the nerve

Congenital IIIrd Nerve Disorders

1. Congenital absence of the IIIrd nerve nuclei in association with absence of other cranial nerves
2. Congenital abnormalities of innervation; fascicles of the IIIrd nerve may innervate the VIth nerve
3. In association with Moebius syndrome (facial diplegia and ptosis)

Trauma of the IIIrd Nerve

1. Head trauma (with cerebral edema):
 - a. The IIIrd nerve may be trapped between the posterior cerebral artery and the superior cerebellar artery
 - b. At the tentorial edge
 - c. Damaged in the cavernous sinus
 - d. Disrupted by fractures of the orbital wall
 - e. Compressed by the uncus of the hippocampal gyrus
2. Aberrant regeneration:
 - a. Classic misdirection syndrome:
 - i. Engagement of the IIIrd nerve causes pathological lid retraction
 - ii. There is no up or down movement of the globe (simultaneous innervation of the superior and inferior rectus muscles)
 - iii. Adduction of the eye and pupillary constriction are intact
 - iv. Fully developed misdirection syndrome causes:

1. Minimal retraction of the globe
2. Slight enophthalmos
3. Droop of the upper lid on abduction

Neoplasms of the IIIrd Nerve

1. Account for approximately 20% of IIIrd nerve paralysis
2. Midbrain tumors that involve the intraparenchymal portion of the IIIrd nerve include:
 - a. Glioma
 - b. Medulloblastoma
 - c. Hemangioma
 - d. Metastatic lesions
3. Parinaud's syndrome:
 - a. Compression of the tectal plate (pinealoma)
 - b. Paralysis of upward or downward gaze
 - c. Dissociation vertical and horizontal gaze with optokinetic nystagmus
 - d. Pupillary abnormalities:
 - i. Large poorly reactive 3–4 mm pupils
 - ii. Dissociated light and accommodation pupillary response
 - e. Associated bilateral sensorineural hearing loss
 - f. Failure to converge
 - g. Nystagmus retractorics
 - h. Tumors of the quadrigeminal plate (primarily gliomas) do not produce motility disorders until they extend beyond the tectal plate:
 - i. Mild head trauma may precipitate IIIrd nerve palsy from a parasellar or clival tumor (needs to be ruled out if there is no fracture or the palsy lasts longer than 1–2 months)
 - ii. Pituitary adenoma:
 1. May spread into the cavernous sinus with compression of the IIIrd nerve against the dura at the entrance of the cavernous sinus
 - iii. Pituitary apoplexy (associated with headache, sudden loss of vision, cranial nerve palsy) may have an associated unilateral or bilateral IIIrd nerve palsy; CT and MRI have demonstrated a more benign clinical picture of pituitary apoplexy than was formerly taught (many hemorrhages are asymptomatic)
 - iv. There may be intermittent signs and symptoms with pituitary tumors
4. Nasopharyngeal tumors:
 - a. May affect the IIIrd nerve in the cavernous sinus
 - b. The tumor originates in the fossa of Rosenmüller and extends into the middle cranial fossa through the foramen lacerum or ovale
 - c. Squamous cell carcinoma, lymphoepithelioma and lymphoma may present similarly
5. Sphenoid sinus tumor:
 - a. May produce a cavernous sinus syndrome
6. Intrinsic IIIrd nerve tumors:

- a. Schwannoma
- b. Neurofibroma
- c. Fibroblastic tumors
7. Metastatic Tumors:
 - a. Intracranial metastases constitute approximately 30% of neoplasms that affect the IIIrd nerve
 - b. Nasopharyngeal tumors are the most frequent metastatic tumors (by extension)
 - c. Metastases occur with breast, thyroid, lung, and lymphoid tumors
 - d. The metastases most frequently affect the nerve by direct invasion
 - e. 10–25% of late stage lymphomas invade the CNS; affect the nerve by involvement of the meninges and by direct extension
8. Orbital Tumors:
 - a. Metastatic:
 - i. Breast, lung, melanoma of the choroid, lacrimal gland, lymphosarcoma, lymphoma, leukemia and hypereosinophilic syndrome
 - b. Intraorbital masses:
 - i. Hemangioblastoma of the conus
 - ii. Dermoid
 - iii. Pseudotumor of the orbit
 - iv. Meningioma

Muscle Disease Affecting the IIIrd Nerve

1. Oculopharyngeal dystrophy:
 - a. Middle aged to older patients
 - b. Bilateral ptosis that may be severe
 - c. French Canadian ancestry
2. Myotonic dystrophy:
 - a. Severe ptosis
 - b. AD; chromosome 17
 - c. Multisystem disorder:
 - i. Cardiac arrhythmias
 - ii. Cognitive impairment
 - iii. Glucose intolerance
 - iv. Frontal balding
 - v. Stellate cataracts
 - iv. Small testicles with elevated FSH/LH
3. Mitochondrial Diseases:
 - a. Kearns-Sayre:
 - i. Complete ophthalmoplegia
 - ii. Heart block
 - iii. Syncope
 - b. PEO:
 - i. Associated myopathy
 - ii. Neuropathy
 - c. Late onset mitochondrial myopathy:
 - i. Ptosis
 - ii. Short stature
 - iii. VIIIth nerve involvement
4. Myotubular myopathy:

- a. Primarily bilateral ptosis with minimal proximal weakness
- 5. Thyroid muscle disease (Hoffman's syndrome):
 - a. Inferior rectus muscle may enlarge first
 - b. All muscles become thickened and enlarged
 - c. Elevated long acting thyroid stimulating hormone
 - d. The sclera and tendinous insertions of muscle are not involved (they are in pseudotumor of the orbit)

Neuromuscular Junction Disorders and the IIIrd Nerve

1. Acquired myasthenia gravis:
 - a. Asymmetric ptosis and IIIrd nerve involvement
 - b. The pupil is not clinically involved
 - c. May be associated with pseudointranuclear ophthalmoplegia
 - d. Rapid nystagmus
2. Congenital myasthenia gravis:
 - a. Poor bulbar muscle functions at birth
 - b. Ptosis and cranial nerve involvement
 - c. Floppy infant syndrome
 - d. Most often little or no response to acetylcholinesterases
3. Tetanus:
 - a. IIIrd nerve is involved with pupillary dysfunction
 - b. Systemic muscle involvement
 - c. Opisthotonus in late stages
 - d. Extreme sensitivity to auditory and mechanical stimuli (induces muscle spasms)
4. Botulinum toxin:
 - a. Nausea and vomiting
 - b. Bilateral ptosis
 - c. Bilateral dilated pupils
5. Snake bite (primarily Elapidae species):
 - a. Nausea, vomiting and vertigo rapidly occur after envenomation
 - b. Ptosis
 - c. Diplopia, IIIrd nerve and other cranial nerve involvement
 - d. Estimated 2–3 million deaths world-wide
6. Lambert-Eaton syndrome:
 - a. Most often asymmetrical ptosis
 - b. IIIrd nerve as well as other cranial nerve involvement
 - c. Autonomic involvement (dry mouth)
 - d. "Load in the pants gait"
 - e. Improved strength with exercise
 - f. Loss of reflexes

Collagen Vascular Diseases

In general the arteritic process associated with these disorders affects the vascular supply to the nerve that irrigates the central rather than the peripheral component of the nerve. Most experts state that the pupillomotor fibers are in the peripheral dorsomedial area of the nerve.

1. SLE: affects the IIIrd and VIth nerve most frequently
2. Wegener's granulomatosis:

- a. Affects the Vth nerve most frequently (adjacent to the involved sinus)
- b. The IIIrd and VIth nerves may also be affected
- 3. Tolosa-Hunt:
 - a. Severely painful ophthalmoplegia:
 - i. All eye muscles may be involved in the affected eye (IIIth, IVth and Vth)
 - ii. Vth nerve, IInd and periarterial sympathetic fibers may be involved
 - iii. Painful episodes persist for days to weeks; remission and exacerbations are common
 - iv. Non-specific granulomatous involvement in the cavernous sinus
 - v. Steroid responsive
- 4. Periarthritis nodosa:
 - a. IIIrd nerve involvement is rare
 - b. Usually the peripheral manifestation is that of a mononeuritis multiplex
- 5. Hypereosinophilic syndromes:
 - a. $>20,000$ eosinophils/mm³ for longer than 6 weeks
- 6. Granulomatous angitis

Infections That Involve the IIIrd Nerve

1. Viral infection:
 - a. IIIrd nerve involvement may rarely be seen with:
 - i. St. Louis encephalitis
 - ii. Eastern and Western Equine encephalitis
 - b. In polio and Von Economo encephalitis IIIrd nerve palsy was occasionally reported
 - c. In most viral illnesses the IIIrd nerve palsy occurs 2–3 weeks after the febrile illness
 - d. IIIrd nerve palsy may occur with:
 - i. Hz
 - ii. EBV
 - iii. Pertussis
 - iv. Measles
 - v. Influenza
 - vi. HIV

Bacterial Infection

1. In acute bacterial meningitis the IIIrd and VIth nerve are frequently involved; the deficits may clear with recovery after treatment
2. Perineural inflammation may extend into the nerve substance (most commonly seen with meningococcal, pneumococcus and *Haemophilus influenzae* meningitis)
3. Syphilitic IIIrd nerve involvement occurs with basilar meningitis:
 - a. Pupillomotor and medial rectus fibers are most vulnerable
4. Lyme's disease:
 - a. IIIrd nerve involvement may be the initial manifestation of the disease
5. Tuberculosis:
 - a. Tuberculosis affects the IIIrd nerve:
 - i. The pupillomotor fibers are vulnerable

Fungal Infections

1. Mucor mycosis (genus *Rhizopus*):
 - a. Occurs in severely immunocompromised patients (cancer, anemias, diabetic ketoacidosis, and HIV)
 - b. Origin is from the cranial sinuses
 - c. May concomitantly involve the venous sinuses with consequent thrombosis
 - d. Black palate syndrome (lateral and jugular sinus thrombosis)
 - e. Often with complete unilateral ophthalmoplegia
2. Cryptococcosis:
 - a. Associated with HIV infection
 - b. Cranial nerve II > involvement than III
 - c. Indolent meningitis with headache and dementia

Systemic Diseases

1. Diabetes mellitus:
 - a. Painful or painless ophthalmoplegia:
 - i. May project pain to retro-orbital areas
 - b. Pupil sparing
 - c. Usually the recovery occurs without “misdirected re-innervation”; much more common after traumatic IIIrd nerve injury (aneurysm clipping)
2. Cranial nerve amyloid:
 - a. Primary uveal veil (occurs in the vitreous)
 - b. Associated with meningeal involvement
 - c. Light-near dissociation
3. Hypertrophic pachymeningitis:
 - a. An exuberant overgrowth of the meninges that traps cranial nerves
 - b. Differential diagnosis includes: 1. sarcoid, 2. lymphoma, 3. syphilis, 4. tuberculosis and 5. as a component of the IgG4 syndrome
 - c. Patients are afebrile, do not appear ill and the IIIrd nerve is usually involved
 - d. Pupil sparing
4. Carcinomatosis of the meninges:
 - a. MRI reveals that carcinomatosis of the meninges may be associated with few signs and symptoms; a percentage of patients are asymptomatic
 - b. The IIIrd nerve is commonly involved but not as frequently as Ist, VIth, VIIth and VIIIth
5. Wernicke-Korsakoff syndrome:
 - a. Cranial nerve II and VI are frequently involved bilaterally
 - b. IIIrd may be involved
 - c. Associated with thiamine deficiency
 - d. Encephalopathy, ataxia and neuropathy are associated
 - e. Ophthalmoparesis is less common in black patients
6. Sarcoid:
 - a. Primarily affects the VIIth nerve
 - b. There is meningeal involvement of the IIIrd nerve as well as an arteritic infarction
7. Immune-mediated IIIrd nerve palsy:

- a. Multiple sclerosis:
 - i. The IIIrd nerve is relatively uncommonly involved directly; commonly involved as a component of intranuclear ophthalmoplegia
- b. Miller-Fisher variant of GBS:
 - i. GD1b or GQ1b epitopes
 - ii. Ophthalmoparesis, areflexia, ataxia are concomitant neurological findings
- c. Descending GBS:
 - i. IIIrd, VIth and VIIIth are involved concomitantly
 - ii. Pharyngeal innervated cranial nerves are involved (cervical-brachial pattern)
- d. CIDP:
 - i. There is rarely an associated IIIrd nerve palsy
8. Trauma:
 - a. Orbital fractures injure either the superior or inferior division of the nerve
 - b. The nerve may be injured during uncus herniation or anterior temporal lobectomy during complex partial seizures

Cranial Nerve IV**General Characteristics****Anatomy**

1. The trochlear nerve nucleus lies caudal to the IIIrd nerve complex and dorsal to the medial longitudinal fasciculus and is at the level of the inferior colliculus, ventrolateral to the cerebral aqueduct. It courses posteroinferiorly around the aqueduct to decussate in the anterior medullary velum of the dorsal midbrain. It emerges in the dorsal midline below the inferior colliculus
2. Its cisternal segment traverses the quadrigeminal, ambient, crural and pontomesencephalic cisterns
3. It is closely associated with the under surface of the tentorium (where it is frequently injured by neurosurgical procedures and various traumas)
4. It enters the cavernous sinus below the IIIrd nerve along the lateral side of the clivus below the petroclinoid ligament
5. It lies below the IIIrd nerve in the wall of the cavernous sinus dorsal to the first division of the Vth nerve in a common connective tissue sheath
6. It enters the superior orbital fissure to innervate the contralateral superior oblique muscle

Blood Supply

1. Anastomosis of ascending and descending branches of nutrient subial arteries
2. Superior cerebellar artery branches supply the IVth nerve nuclei
3. The superior division of the intermediolateral trunk of the external carotid artery supplies the nerve in the superior orbital fissure
4. It also is supplied by a branch of the posterior lateral choroidal artery from the PCA

Neuropathology*Vascular Lesions*

1. Nuclear IVth nerve is involved as part of a superior cerebellar artery stroke
2. Masugi's syndrome in which the IIIrd and IVth nerve are infarcted simultaneously with associated ipsilateral ataxia and loss of pain and temperature sensitivity below the clavicle contralaterally (superior cerebellar artery infarction)
3. The IVth nerve nuclei may be involved in isolation from a posterolateral choroidal artery infarction from infarction of the PCA 4 branch; there is concomitant pulvinar involvement

Congenital Defects of the IVth Nerve

1. Unilateral or bilateral absence of the IVth nerve may be seen in association with absence of the IIIrd, VIth and other brainstem nuclei

Trauma

1. Approximately 5% of cranial nerve palsies that follow severe head trauma affect the IVth nerve
2. Approximately 30% of IVth nerve palsies are traumatic; the brainstem is compressed against the lateral edge of the tentorium during herniation
3. The nerve may be damaged in an orbital fracture
4. Surgical procedures that involve the tentorium, injure the nerve and include anterior temporal lobectomy and top of the basilar artery procedures
5. The nerve may be injured by traumatic intracavernous aneurysms

External Carotid Artery Ischemia

1. The lesions involve the ILL of the external carotid artery or its superior branch (usually during the course of embolization treatment of vascular lesions or tumors)
2. Diabetic infarction
3. Arteritic syndromes

Systemic Diseases That Affect the IVth Nerve

1. Cavernous sinus infection and tumor (simultaneous involvement of IIIrd, VIth and the first division of Vth)
2. Superior orbital fissure syndrome
3. Collagen vascular disease with infarction of the blood supply to the nerve from arteritis
4. Diabetes mellitus (small vessel infarction)
5. Wegener's and other necrotizing arthritides
6. Scleroderma

Neuromuscular Junction Diseases

1. Congenital and acquired MG
2. Tetanous
3. Botulinum poisoning
4. Neurotoxic snake envenomation
5. Lambert-Eaton syndrome

Ocular Muscle Diseases

1. PEO
2. Kearns-Sayre syndrome
3. Other mitochondrial diseases
4. Thyroid ophthalmopathy
5. Orbital pseudotumor

Superior Oblique Muscle Myokymia

1. Rapid spontaneous firing of the superior oblique muscle
2. Congenital superior oblique palsy

Neoplasms of the IVth Nerve

1. Tumors that invade the cavernous sinus which include, pituitary adenomas, meningioma and lymphoma
2. Nasopharyngeal cancer
3. Isolated neurinoma or Schwannoma
4. Carcinoma of the sphenoid sinus

Infections of the IVth Nerve

1. Herpes zoster (rare); much more commonly involves Vth and IIIrd nerve
2. EBV, St Louis, Eastern and Western equine viral infections
3. Syphilis
4. Lyme's disease
5. HIV
6. Purulent bacterial infections (meningeal involvement)
7. Rarely involved with polio
8. Mucormycosis

Immune-Mediated Diseases of the IVth Nerve

1. Miller-Fisher syndrome
2. CIDP
3. Descending GBS
4. MS (extremely rare)
5. Brown's superior oblique tendon sheath syndrome

The Vth Cranial Nerve**General Characteristics***Anatomy*

1. The motor nucleus of the Vth nerve is in the mid-pons and lies medial to the main sensory nucleus near the floor of the IVth ventricle
2. After exiting the pons it traverses the posterior fossa to enter a cavity in the dura mater (Meckel's cave) beneath the attachment of the tentorium to the tip of the petrous bone. It leaves the skull through the foramen ovale and joins the mandibular branch of the trigeminal nerve that then becomes the mandibular nerve
3. The mandibular nerve innervates the muscles of mastication which include the masseter, temporalis and the medial and lateral pterygoid muscles. It also innervates the tensor tympani, tensor veli palatini, mylohyoid and the anterior belly of the digastric muscle

4. The sensory portion of the nerve originates in the gasserian ganglion that lies near the apex of the petrous bone in the middle cranial fossa. The sensory fibers from the gasserian ganglion traverse the dorsomedial pons to synapse in the nuclear complex of the sensory trigeminal nerve. A group of sensory fibers that enter the mid-pons descends as the spinal tract of the Vth nerve (the spinal tract of the trigeminal nucleus). The tract descends through the medulla to terminate in the third and fourth segments of the cervical spinal cord. Its continuation is Lissauer's tract. The descending spinal tract synapses with the three components of the nucleus of the trigeminal nerve:
 - a. The pars oralis (located from the mid-pons to the inferior olive)
 - b. The pars interpolaris (extends from the rostral third of the inferior olive to the obex of the IVth ventricle)
 - c. The pars caudalis (extends into the 4th segment of the spinal cord) that is continuous with the dorsal horn of the spinal cord. The pars caudalis is also the termination of cervical root innervations from the pre- and post-auricular nerves
 - d. The ophthalmic divisions of the Vth nerve traverse the most ventral part of the spinal tract to synapse at C2
 - e. Mandibular division fibers are located dorsally in the spinal tract and synapses in the most rostral level of spinal nucleus
 - f. Midline facial representation of the nose and mouth are represented rostrally in the spinal nucleus while lateral aspects of the face terminate more caudally. Intramedullary lesions may cause an "onion skin" sensory loss and perioral numbness from rostral spinal nuclear and tract lesions:
 - i. Ascending fibers of the spinal nucleus carry the modalities of pain, temperature, and light touch from the face and mucous membranes ipsilaterally in the trigeminothalamic tract that synapses in thalamic VPM and the intralaminar nuclei
 - ii. The main sensory nucleus of V, which receives fibers from the Gasserian ganglion, carries tactile and proprioceptive modalities of sensation. The nucleus lies posterolateral to the motor nucleus of V in the lateral pons. Axons travel in the ventral crossed trigeminothalamic tract and the ipsilateral dorsal trigeminothalamic tract to synapse in the thalamic VPM nucleus
 - iii. The mesencephalic trigeminal nucleus is rostral to the main sensory nucleus and extends to the superior colliculus. It carries proprioception from the muscles of mastication
5. The Vth nerve innervates the head, mouth, nasal cavity, and the motor and proprioceptive muscles of mastication
6. Sensation extends to the angle of the jaw, which is innervated by C2, which also innervates the scalp to the bregma and tragus of the ear; the Vth nerve innervates the anterior wall of the external auditory meatus; the anterior portion of the tympanic membrane; the dura of the anterior and middle cranial fossa; the somatic sensation of the tongue and palate
7. The mental nerve, buccal nerve, dural innervations of the anterior and middle cranial fossa are mediated by the VI division (ophthalmic) nerve, which traverses the lateral wall of the cavernous sinus and enters the orbit through the superior orbital fissure
 - a. In the cavernous sinus the ophthalmic division divides into:
 - i. Tentorial, lacrimal, frontal and nasociliary branches
 - ii. The tentorial branch supplies:
 1. The dura of the cavernous sinus
 2. The anterior fossa and sphenoid wing
 3. The petrous ridge and its apex as well as the dura of Meckel's cave
 4. The tentorium of the cerebellum
 5. Posterior falx
 6. Dural venous sinuses
 - iii. The frontal branch divides into a supraorbital component that innervates the medial upper lid and conjunctiva, the frontal sinuses, forehead and scalp (approximately one inch into the hair line); its other component forms the supratrochlear sensory nerve that innervates the medial upper conjunctiva and ventral areas of the forehead and lateral areas of the nose
 - iv. The lacrimal nerve via its palpebral branch innervates the conjunctiva and the area of the lacrimal gland. It also carries postganglionic parasympathetic fibers that effect reflex lacrimation
 - v. The nasociliary nerve divides into nasal nerves and an infraorbital branch:
 1. Nasal nerves innervate the mucosa of the nasal septum, the lateral nasal wall, the inferior and middle turbinates
 2. An external nasal nerve branch innervates the tip of the nose (vesicles may be seen here first with HZ infection)
 3. The infraorbital branch of the nerve subserves the lacrimal sac, the caruncle, conjunctiva and the skin of the medial canthus
 4. Two long ciliary nerves transmit sensory modalities from the cornea, ciliary body and iris and also innervate (sympathetic) the dilator of the pupil
 5. Short ciliary nerves carry sensory fibers from the globe via the ciliary ganglion as well as parasympathetic post-ganglionic fibers, which innervate the constrictor of the pupil and the ciliary muscle. These sensory and pupillary fibers join the nasociliary nerve. These important parasympathetic fibers travel with the inferior division of the IIIrd nerve that innervate the inferior oblique muscle

The Maxillary Division of V (V₂)

The maxillary division exits the inferolateral area of the cavernous sinus to leave the skull via the foramen rotundum and enters the sphenopalatine fossa. It next traverses the infraorbital fissure to enter the orbit. It courses through the infraorbital canal to innervate the face via the infraorbital foramen.

1. This division gives rise to the palatine nerves, middle, posterior and superior alveolar nerves from its sphenopalatine and infraorbital canal portions
 - a. These nerves innervate the upper teeth, maxillary sinus, nasopharynx, soft palate, roof of the mouth and tonsils
 - b. After leaving the infraorbital foramen the division gives off:
 - i. An inferior palpebral branch that innervates the lower lid
 - ii. A nasal branch that innervates the side of the nose
 - iii. A superior labial branch that innervates the upper lip
 - iv. A zygomaticofacial branch that innervates the cheek
 - v. The maxillary division also supplies the dura of the middle cranial fossa from the middle meningeal nerve

Mandibular Division of V

1. The motor root of the trigeminal nerve and the mandibular division join to form the mandibular nerve
2. The mandibular nerve exits the skull through the foramen ovale and traverses the infratemporal fossa
 - a. Motor branches supply the muscles of mastication (eight)
 - b. The lingual nerve innervates the lower gums and papillae of the tongue; the mucous membranes of the anterior 2/3rds of the tongue
 - c. The inferior dental branches innervate the lower gums and teeth
 - d. Mental branches innervate the mucous membrane of the lower lip; the mental nerve may be involved in isolation with scleroderma, sickle cell disease and breast cancer ("the numb chin syndrome")

Neuropathology

Vascular Lesions of Vth nerve

1. Wallenberg's syndrome (infarction of the medial branch of PICA or more commonly the vertebral artery)
2. Pontine ischemia (occlusion of short circumferential arteries)
3. Aberrant branch of AICA that abuts the Vth nerve (a major cause of tic douloureux)
4. AVM of the Gasserian ganglion

5. Ischemia of the inferolateral trunk of the external carotid artery; often involved in association with Vth nerve ischemia or with nerves of the superior orbital fissure
6. Internal carotid artery aneurysm (compression of the trigeminal ganglion and concomitantly the IIIrd nerve)
7. Cavernous sinus aneurysm:
 - a. Primarily affects middle age women
 - b. The VIth nerve is often involved first as it is closest to the carotid artery; its involvement is usually followed by severe pain in V1 and V2
 - c. Often bilateral involvement
 - d. Pain is often the predominant symptom

Idiopathic Trigeminal Neuropathy

1. The diagnosis is tendered after the exclusion of all known entities that affect the Vth nerve
2. Motor function of the nerve is rarely affected
3. Possibly 10% of trigeminal lesions
4. Numbness is most often experienced in V2 and V3. It gradually spreads to adjacent divisions in days to weeks; recovery usually occurs over weeks to months
5. Patients experience a sensation of numbness, swelling, coldness and tingling
6. Pathologic inflammatory process of the Vth nerve ganglion
7. Has been reported with arteritides, rheumatoid arthritis, Sjögren's syndrome, mixed collagen vascular diseases and most commonly with scleroderma

Associated with Systemic Disease

1. Hypothyroidism:
 - a. Mucopolysaccharide deposition in the Gasserian ganglion with the mucopolipidoses
 - b. Rarely presents with severe facial pain
2. Sarcoid:
 - a. Rare Vth nerve involvement
 - b. Involves the dura
3. Wegener's granulomatosis:
 - a. Contiguous involvement of V(2) from inflammation of the maxillary sinus
4. SLE:
 - a. Arteritic involvement of the blood supply to the nerve
5. Sjögren's disease:
 - a. A common cause of Vth nerve involvement from arteritis
6. Periarthritis nodosa
7. Scleroderma:
 - a. Vth nerve involvement may be the presenting symptom
 - b. "Numb chin syndrome" from compression of the Vth nerve in its exit foramen
8. Mixed collagen vascular disease

Tumors of the Vth Nerve

1. Trigeminal neurinoma

- a. 0.2% of intracranial tumors
- b. Occur between 14–67 years of age. They most often occur in middle age; the incidence is equal in both sexes
- c. They arise in the distal portion of the nerve and are probably of Schwann cell origin; they may involve ganglion and rarely may extend through the foramen rotundum or ovale
- d. In general they are 2.5 cm by the time of diagnosis and may undergo malignant transformation
- e. The usual symptoms are numbness or paresthesia in the distribution of the divisions of the nerve; trigeminal neuralgia or painful paresthesia are less common
- f. The tumor may erode the medial part of the floor of the middle fossa or erode the apex of the petrous bone
2. Meningioma:
 - a. Those that affect the Vth nerve arise from the dura of Meckel's cave
 - b. They may spread in plaque along the floor of the middle fossa or along the trigeminal nerve roots into the middle fossa
 - c. Meningiomas may affect V3 more often than trigeminal neuromas
3. Gangliocytoma:
 - a. A rare primary malignant tumor of the ganglion
4. Epidermoids (primary or secondary)
5. Chondroma
6. Chondromyxoma
7. Sarcoma
8. Lymphoma
9. Fibrous xanthoma (fibrous histiocytoma)
10. Hemangioblastoma
11. Malignant Schwannoma (from the trigeminal ganglion or its divisions)
 - a. Numbness or paresthesias in the distribution of the nerve or its branches in 2/3rds of affected patients
 - b. Painful burning and paresthesia in 1/3 of patients
 - c. May erode into the cavernous sinus with involvement of IIIrd, IVth, VIth and V1 involvement with proptosis and visual loss
12. Nasopharyngeal cancer that originates from the fossa of Rosenmüller
13. Maxillary sinus cancer
14. Neural spread of squamous cell cancer of the face
15. Prostate cancer metastasis to Meckel's cave or the petrous apex
 - a. The spread is through the valveless Batson's plexus of paravertebral veins
16. Cholesterol granulomatosis that is benign and is located at the petrous apex
 - a. Striking positive T2-weighted MRI sequences
17. Spread of a salivary gland adenoma
18. Submaxillary gland cylindroma

Congenital Trigeminal Anesthesia

1. May be isolated and is usually bilateral

2. Associated with ectodermal or mesenchymal structural defects
 - a. Goldenhar syndrome
 - b. Abnormalities of the first and second branchial arches, vertebrae and eyes, which include pre-auricular tags, malformed pinnae and epibulbar dermoids
 - c. Associated with Moebius syndrome:
 - i. Congenital facial diplegia and horizontal gaze dysfunction

Trauma

1. Dental treatment
2. Pressure on the mental nerve from dentures (bone resorption)
3. Surgical trauma
4. Head and facial trauma
5. Skull base fracture:
 - a. Trigeminal abducens nerve synkinesis may occur with lesions at the petrous apex
6. Migraine variants:
 - a. Facial paresthesias and numbness are common with both common and classic migraine
 - b. Lower face migraine affects V2 and V3
 - c. Paroxysmal hemifacial pain:
 - i. Multiple attacks of severe pain primarily in the V2 division daily
 - ii. Responsive to indomethacin
 - d. Classic cluster migraine with severe orbital and retro-orbital V1 pain
 - e. Raeder's paratrigeminal neuralgia pain in the V1 distribution with associated photophobia, phonophobia and nausea:
 - i. Type 1 with ptosis and miosis
 - ii. Type 2 with no cranial nerve abnormality
 - f. SUNCT (sudden unilateral neuropathic pain in V1 with conjunctival injection and tearing)
7. Trigeminal Neuralgia:
 - a. In older patients:
 - i. Idiopathic
 - ii. Vascular loop compression of the nerve root entry zone that originates from:
 1. Superior cerebellar artery > AICA > basilar artery
 - b. In younger patients:
 - i. Multiple sclerosis
 - ii. A vascular loop compressing the nerve root entry zone
 - iii. Rare in some spinocerebellar degenerations (Behr's syndrome)
 - c. Clinical presentation of tic douloureux:
 - i. Lancing severe pain
 - ii. Less than 15 seconds in duration
 - iii. More often unilateral; V3 > V2 < 10% in V1
 - iv. No associated motor or sensory signs

- v. There is an absolute refractory VI period following attacks of varying lengths
- d. Triggering events include:
 - i. Light touch in the affected division
 - ii. Chewing, swallowing, and speaking
 - iii. Positional change (if there is arterial compression)
 - iv. Cold
- e. "Tic convulsive":
 - i. Associated with hemifacial spasm; need to r/o (rule out) extracranial lesions of the VIIth nerve
 - ii. Either pain or the paroxysmal movement may occur independently
 - iii. The usual cause is an arterial loop from the superior cerebellar, vertebral or basilar artery that touches the nerve in the cerebellopontine angle
 - iv. Differential diagnosis of pathologies in this location includes:
 - 1. Meningioma
 - 2. Neurofibroma
 - 3. Arteriovenous malformation
 - 4. Cirsoid aneurysm of the vertebral artery
- f. Immune-mediated trigeminal neuralgia:
 - i. Multiple sclerosis:
 - 1. 2% of trigeminal neuralgia patients have MS
 - 2. It may occur bilaterally
 - 3. Triggers that induce attacks are less common in MS
 - 4. The demyelinating plaque is most often in the root entry zone
 - ii. CIDP
 - iii. Idiopathic trigeminal sensory neuropathy
- 8. Infection:
 - a. Syphilitic:
 - i. Lesion may occur from meningeal involvement or a proliferating endarteritis
 - ii. Causes mid-face numbness; rarely a gumma of the mid-pons is causative
 - b. Herpes simplex:
 - i. V₂, V₃ pain following oral outbreaks
 - c. Herpes zoster:
 - i. V₁ infection is often associated with encephalitis (may be asymptomatic but there is a lymphocytic pleocytosis, increased protein in the CSF)
 - ii. Rarely there is clinically evident encephalitis
 - iii. A delayed MCA stroke may occur on the ipsilateral side (7–14 days after the infection). Viral particles have been identified in the vessel wall that have triggered a severe inflammatory response in the affected carotid or MCA
 - d. Gradenigo's syndrome:
 - i. In the past, the major pathology was recurrent purulent middle ear infection
 - ii. There needs to be a pneumatized petrous bone for the infection to spread from the middle ear through the petrous bone
 - iii. The infection causes a petrous apicitis with:
 - 1. Vth and VIth nerve involvement
 - 2. The VIth nerve is involved in Dorello's canal under the petroclinoid ligament
 - 3. This infection occasionally is associated with lateral sinus thrombosis that causes "otitic hydrocephalus"
 - e. Actinomycosis:
 - i. Lung infection with spread through the blood or venous sinuses
 - f. Leprosy
- 9. Toxins and Physical Agents that Affect the Vth Nerve:
 - a. Trichloroethylene (detergent)
 - b. Stilbamidine (used in the treatment of North American blastomycosis)
 - c. Post-radiation therapy
- 10. Structural lesions of the Vth Nerve:
 - a. Meckel's cave arachnoid cyst
 - b. Brainstem syringobulbia
 - c. Brainstem glioma
 - d. Fibrous dysplasia of bone:
 - i. Foraminal stenosis with nerve entrapment
- 11. Unusual Entities that Affect the Vth Nerve:
 - a. Kennedy's disease (motor V)
 - b. ALS (in association with bulbar involvement; patients are unable to close their mouth properly from involvement of the muscles of mastication)
 - c. Spinocerebellar atrophy type 4
 - d. A component (division V₁) of the superior orbital syndrome
 - e. The "numb chin and cheek" syndrome:
 - i. Lesions of the mental nerve from the mandibular (division V₃) most often from scleroderma, breast cancer and sickle cell disease
 - ii. Elderly patients:
 - 1. Impingement of the mental nerve at the mental foramen
 - iii. Inferior alveolar nerve involvement (branch of V₃):
 - 1. Metastasis (lung, breast and nasopharyngeal cancer)
 - 2. Lower lip anesthesia
 - 3. Numb cheek:
 - a. Malar anesthesia

The VIth Cranial Nerve

General Characteristics

- 1. Intraparenchymal anatomy:
 - a. The VIth nerve nucleus is located in the dorsal lower pons; dorsally it is covered by the genu of the VIIth nerve that lies under the floor of the IVth ventricle
 - b. Its motor neurons that effect abduction are intermixed with internuclear neurons that project from the mid-

- line to join the opposite medial longitudinal fasciculus which synapses in the IIIrd nerve
- 2. As the nerve courses along the ventral pons it is crossed by AICA and the interauditory arteries
- 3. It enters the cavernous sinus beneath the petroclinoid ligament (Gruber's ligament) to lie adjacent to the carotid artery

Clinical Manifestations

1. Failure of abduction of the ipsilateral eye in the horizontal plane
2. Abducting nystagmus contralateral to a MLF lesion that causes an internal intranuclear ophthalmoplegia
3. Esotropia of the globe in primary gaze
4. Congenital defects of innervation:
 - a. Unilateral or bilateral, congenital absence of the VIth nerve may be seen in association with abnormalities of CN III; these defects may occur in association with other cranial nerve abnormalities and hypoplasia or aplasia of components of the brainstem
 - b. There may be innervation of the lateral rectus muscle by the IIIrd nerve in the absence of the IVth nerve nucleus
 - c. Congenital absence of the VIth nerve nucleus may also be associated with an ipsilateral horizontal gaze paralysis as there are no interneuronal neurons to activate the contralateral IIIrd nerve adductor neurons by means of the medial longitudinal fasciculus
5. Duane's retraction syndrome:
 - a. Narrowing of the palpebral fissure with adduction and retraction of the globe (rare); the globe rarely moves up with adduction:
 - i. Type I: abduction is limited but adduction is normal
 - ii. Type II: normal abduction but impaired adduction
 - iii. Type III: impairment of both abduction and adduction
 - b. The syndrome is caused by the anomalous innervation of the rectus muscle by the inferior division of the IIIrd nerve
 - c. The syndrome is more common in females than males; it may be unilateral or bilateral
 - d. The left eye is affected more often than the right
 - e. Acquired Duane's syndrome occurs with:
 - i. Pontine glioma
 - ii. Rheumatoid arthritis
 - iii. Trigeminal rhizotomy
 - iv. Post-removal of an orbital cavernous hemangioma
 - f. Moebius syndrome:
 - i. Facial diplegia usually in association with bilateral abducens palsy
 - ii. Convergence strabismus occurs in approximately 50% of patients
 - iii. There is rare ptosis and paralysis of the IIIrd nerve
 - iv. There is no internal ophthalmoplegia
 - v. Rarely there are other associated congenital deformities that include: 1. paralysis and atrophy of the tongue, 2. hearing loss, 3. clubfoot and 4. other skeletal deformities
- g. Congenital horizontal gaze palsy:
 - i. No convergent strabismus
 - ii. No facial diplegia
 - iii. Substituted convergence and cross fixation is used to accomplish lateral gaze
 - iv. Vertical eye movements are spared
- h. Chiari malformation
- i. Basilar impression
- j. Vascular Lesions Affecting the VIth Nerve:
 - i. Penetrating pontine branch artery that causes Ramon syndrome:
 1. Ipsilateral VIth nerve palsy with a contralateral hemiparesis
 - ii. Millard-Gubler syndrome:
 1. Ipsilateral VIth and VIIth nerve palsy
 2. Contralateral hemiparesis
 3. Ipsilateral Vth and Horner's syndrome (rare)
 4. Contralateral spinothalamic (pain and temperature) loss of sensation
 5. Most often caused by a hemorrhage rather than an ischemic lesion
 - iii. Infarction of the inferolateral trunk of the external carotid artery:
 1. Superior division (associated infarction of IIIrd, IVth and VIth in the superior orbital fissure)
 2. Emboli (during ablation of AVM or hemorrhagic tumors that involve the external carotid artery); diabetic small vessel disease
 - iv. Gradenigo's syndrome:
 1. Short circumferential artery occlusion that originates from the basilar artery
 - a. Facial numbness
 - b. Weakness of the masseter, pterygoid, temporalis, anterior digastric mylohyoid and tensor tympani muscles
 - c. Contralateral loss of pain and temperature below the clavicle
 - d. Contralateral hemiparesis
- k. Neoplasms of the VIth nerve:
 - i. Primary tumors:
 1. Pontine glioma
 2. Meningioma
 3. Pinealoma
 4. Hemangioma
 5. Craniopharyngioma
 6. Acoustic neurinoma (late)
 7. Chordoma
 8. Pituitary adenoma (extension into the cavernous sinus)

9. Neuroma
10. Malignant pituitary tumor
11. Cerebellopontine angle tumor
- ii. Secondary tumors:
 1. Carcinomatosis of the meninges
 2. Lymphoma/leukemia
 3. Nasopharyngeal cancer:
 - a. Squamous cell carcinoma
 - b. Lymphoepithelioma
 - c. Lymphosarcoma
 4. Pilocytic adenoma
 5. Breast, thyroid and lung metastasis
- l. Trauma of the VIth nerve:
 - i. Head trauma:
 1. A few patients suffer combined IVth and VIth injury; more commonly the VIth and IIIrd nerves are injured concomitantly
 2. VIth nerve injuries are commonly due to:
 - a. A long course along the basiocciput
 - b. Dural attachment over the clivus
 - c. A 90° bend under the petroclinoid ligament
 - d. A fracture through the temporal bone or the posterior clinoid injures the nerve directly
 - e. Fractures of the orbital wall
 - f. Transient injury of the VIth nerve after maxillary sinus surgery
 - m. Infections that affect the VIth Nerve:
 - i. It rarely occurs in Eastern and Western equine encephalitis, St. Louis encephalitis, bulbar poliomyelitis, HZ, measles, influenza, pertussis and EBV, HIV-CMV
 - ii. Bacterial meningitis:
 1. IIIrd and VIth are affected equally
 2. There is usually partial recovery with treatment
 - iii. Syphilitic meningitis (Stage II):
 1. The nerve is affected at the entry zone
 - iv. Tuberculous meningitis (associated stroke)
 - v. Lyme's disease (common and may be bilateral)
 - vi. Cryptococcosis (IInd nerve often involved concomitantly)
 - vii. Mucormycosis:
 1. Associated immunosuppression and ophthalmoparesis
 - viii. Coccidioidomycosis:
 1. Often associated with lumbosacral vertebral involvement
 2. Erythema nodosum
 - ix. Aspergillosis:
 1. Aggressively invades veins
 2. Immunosuppressed patients
 3. CNS involvement with lung abscesses
 - x. Gradenigo's syndrome (purulent mastoiditis with spread through a pneumatized petrous bone to the petrous apex)
 - xi. Cysticercosis (rare parenchymal lesions)
 - xii. Retropharyngeal infection
 - n. VIth Nerve Palsy Following Procedures:
 - i. Lumbar puncture (neurapractic traction injury)
 - ii. Various lumbar or ventricular shunts (neurapractic injury)
 - iii. Post-myelography
 - iv. Spinal and epidural anesthesia
 - v. Cervical traction
 - vi. Intrathecal glucocorticoid injections
 - vii. Post-radiofrequency rhizotomy for trigeminal neuralgia
 - o. Increased intracranial pressure:
 - i. Idiopathic intracranial hypertension
 - ii. Meningitis
 - iii. Mass lesion
 - iv. Sagittal sinus thrombosis
 - v. Trauma (loss of autoregulation)
 - vi. Subdural and epidural hematoma
 - p. Immune-mediated:
 - i. AIDP
 - ii. CIDP
 - iii. Miller-Fisher variant of GBS (GD1b or GQ1b epitopes)
 - iv. Multiple sclerosis (VIth nerve is more frequent than IIIrd)
 - v. ADEM (acute disseminated encephalomyelitis)
 - vi. Post-vaccinations
 - vii. Tolosa-Hunt (possibly autoimmune)
 - viii. Necrotizing vasculitis
 - ix. Bone marrow transplantation with cyclosporin, tacrolimus, and steroids
 - q. Collagen vascular diseases:
 - i. SLE (IIIrd and VIth nerves are most commonly affected)
 - ii. Periarteritis nodosa
 - iii. Mixed collagen vascular disease (MCVD)
 - iv. Hypereosinophilic syndrome (interleukin driven)
 - v. Wegener's granulomatosis (granulomatosis with polyangiitis)
 - r. Systemic diseases that affect the VIth nerve:
 - i. Wernicke-Korsakoff syndrome (chronic alcoholism, dialysis, emesis gravidarum, severe malnutrition)
 - ii. Diabetes mellitus (IIIrd nerve involvement much more frequent than VIth)
 - iii. Chronic hypertension:
 1. Small lacunar infarct of the nerve in the parenchyma
 2. Isolated VIth nerve palsy in an elderly hypertensive patient
 - iv. Idiopathic intracranial hypertension (thyroid and adrenal insufficiency, acute intermittent porphyria, vitamin A and D excess, and iron deficiency anemia)

- v. Sarcoidosis:
 - 1. Meningeal involvement
 - 2. Arteritic infarction of the nerve
- vi. Thyroid ophthalmopathy
- vii. Cranial arteritis (giant cell); usually the muscle is more involved than the nerve
- viii. Histiocytosis X

Rare Causes of VIth Nerve Palsy

- 1. Persistent primitive trigeminal artery
- 2. PICA and vertebral artery aneurysm
- 3. Capillary hemangioma of Meckel's cave
- 4. Spontaneous CSF leak (ruptured perineural cyst) with intracranial hypotension
- 5. Thrombosis of the inferior petrosal, transverse or sigmoid sinus
- 6. Sphenoid sinus mucocele
- 7. Squamous cell cancer of the pterygopalatine fossa
- 8. Internal carotid artery disorders:
 - a. Dolichoectasia
 - b. Balloon test occlusion (prior to surgery)

Cranial Nerve VII

General Characteristics

- 1. Anatomy:
 - a. The motor division is located in the reticular formation of the caudal pontine tegmentum
 - b. The facial nucleus is composed of four longitudinal subnuclei that supply specific muscle groups:
 - i. The dorsal medial group innervates the auricular and occipital musculature
 - ii. The intermediate group innervates the frontalis and corrugator muscles
 - iii. The ventromedial group innervates the platysma muscle
 - iv. The lateral subnucleus supplies the buccinator and buccolabial muscles
 - v. The orbicularis oculi motor neurons are clustered in the dorsolateral margin of the nucleus
 - vi. Another proposal for facial nuclear group organization proposes that:
 - 1. Lower facial muscles innervating motor neurons are in the lateral component of the nucleus
 - 2. Neurons that innervate the upper facial muscles are in the dorsal part of the nucleus
 - 3. Medial motor neurons innervate the platysma and posterior auricular muscles
 - vii. The intrapontine axons ascend rostrally and dorsally over the VIth nerve nucleus (genu of the facial nerve) and then course ventrolaterally in the pons to exit laterally
 - viii. Corticobulbar fibers provide supranuclear control of facial movement. Their origin is the lower 1/3

of the precentral gyrus and they descend through the corona radiata, the genu of the internal capsule, and the medial cerebral peduncle to the pons. The majority of pontine fibers decussate and synapse in the motor nucleus contralaterally. The ventral nucleus of the VIIth nerve nuclear complex, which innervates the lower 2/3rds of the face, is predominantly innervated by crossed supranuclear fibers. The dorsal nucleus of the motor VIIth nerve complex, which supplies the upper 1/3 of the face, has bilateral supranuclear innervation. The mimetic fibers to the VIIth nerve complex are thought to originate in the basal ganglia and temporal lobe. Their exact path to synapse with the motor nuclear complex has not been established. Thus voluntary and emotional activation of the motor nucleus can be disassociated by specific lesions

- 2. The Nervus Intermedius of Wrisberg:
 - a. The parasympathetic and sensory division of the facial nerve is the nervus intermedius of Wrisberg
 - i. Parasympathetic fibers carried in the nerve have their origin in the superior salivatory nucleus that is located in the pontine tegmentum
 - ii. Fibers that control lacrimation originate in the lacrimal nucleus
 - iii. The parasympathetic fibers reach but do not synapse in the geniculate ganglion. Some preganglionic parasympathetic axons course with the greater petrosal nerve as it projects from the geniculate ganglion to synapse in the pterygopalatine ganglion that innervates the lacrimal gland. Preganglionic parasympathetic fibers join the mixed facial nerve as it courses through the facial canal. After the facial nerve has given off a branch to the stapedius muscle, it gives off the chorda tympani nerve, which exits in the skull through the petrotympanic fissure. It then merges with the lingual nerve and parasympathetic fibers synapse in the submandibular ganglion. Post-ganglionic parasympathetic fibers innervate the submandibular and sublingual glands. The sensory component of the VIIth nerve innervates the external auditory meatus, the mucous membranes of the nasopharynx and nose as well as taste from the anterior 2/3 of the tongue, floor of the mouth and part of the soft palate. The greater petrosal nerve conveys sensation from the mucous membranes of the nasopharynx and palate. The chorda tympani and lingual nerve convey sensory afferent fibers from the anterior 2/3 of the tongue, floor of the mouth and palate. The cell bodies of the sensory afferent input of the VIIth nerve are in the geniculate ganglion
- 3. The Peripheral Course of the VIIth Nerve

- a. The meatal canal segment of the VIIth nerve (7–8 mm)
 - i. The motor division is on the super anterior surface of the VIIth nerve
 - ii. The nervus intermedius is in between the VIIth and VIIIth nerve
 - iii. The VIIth nerve is closely approximated with the vestibular and cochlear division of the VIIIth nerve in this segment
- b. The Labyrinthine Segment of the VIIth Nerve (3–4 mm)
 - i. The nervus intermedius and motor division of the nerve enter the facial canal, course above the labyrinth and synapse in the geniculate ganglion. As noted above the greater superficial petrosal nerve takes origin from the apex of the geniculate ganglion
- c. The Tympanic Segment of the VIIth Nerve (12–13 mm)
 - i. After synapsing in the geniculate ganglion the VIIth nerve courses backward which is medial and below the horizontal semicircular canal
- d. The Mastoid Segment of the VIIth Nerve
 - i. At the level of the posterior middle ear (sinus tympani) the VIIth nerve courses inferiorly and gives off the nerve to the stapedius muscle from its proximal portion. The other major branch of this segment is the chorda tympani. The nerve exits the facial canal through the stylomastoid foramen. This segment gives rise to the posterior auricular nerve that innervates the occipitalis, posterior auricular, transversal, and oblique auricular muscles. Its digastric branch innervates the posterior belly of the digastric muscle, and its stylohyoid branch innervates the stylohyoid muscle. In the parotid gland the VIIth nerve divides into the temporofacial and cervicofacial branches, which supply all facial mimetic muscles or as well as the platysma
- e. The Vascular Supply of the VIIth Nerve
 - i. The intracranial components of the nerve are supplied by the anterior inferior cerebellar artery
 - ii. The intrapetrosal component of the nerve is supplied by both the superficial branch of the middle meningeal and the stylomastoid branch of the posterior auricular artery
 - iii. The extracranial portions of the nerve is supplied by the stylomastoid, posterior auricular, superficial temporal and the transverse facial arteries
- b. Associated VIth nerve ipsilateral weakness
- c. Contralateral hemiparesis
- d. Ipsilateral facial sensory loss (midline or peripheral depending on associated Vth nerve involvement); contralateral sensory loss
3. Cerebellopontine angle:
 - a. Associated VIIIth nerve and often Vth nerve signs and symptoms
4. Meatal level:
 - a. Unilateral (ipsilateral) peripheral VIIth nerve weakness
 - b. Decreased taste of the anterior 2/3 of the tongue (ipsilateral)
 - c. Impaired lacrimation
 - d. Deafness (associated VIIIth nerve involvement)
5. The facial canal distal to the meatal segment but proximal to the stapedial branch:
 - a. The motor nerve and the nerve of Wrisberg are involved
 - b. No deafness
 - c. Ipsilateral VIIth nerve muscle weakness
 - d. If the lesion is proximal to the greater superficial petrosal nerve lacrimation is impaired
 - e. Geniculate ganglion involvement causes eardrum pain
 - f. There is decreased taste in the anterior 2/3 of the tongue
 - g. Hyperacusis
6. Facial canal between the stapedius and chorda tympani
 - a. Peripheral facial paralysis
 - b. Loss of taste on the anterior 2/3 of the tongue
 - c. No hyperacusis
7. Distal facial canal lesions (at the stylomastoid foramen level)
 - a. Peripheral VIIth muscle weakness
 - b. No loss of taste
 - c. No hyperacusis
8. Lesions distal to the stylomastoid foramen:
 - a. Individual facial nerve branches to specific facial muscles
 - b. Differential diagnosis if pathology is at this level includes:
 - i. Inflammation of retromandibular lymph nodes
 - ii. Cylindroma and adenocarcinoma
 - iii. Obstetric forceps
 - iv. Bell's palsy
 - v. Lyme's disease
 - vi. Mycoplasma
 - vii. Post-infections (autoimmune)

Clinical Manifestations

1. Supranuclear lesions
 - a. Weakness of the lower 2/3 of facial musculature contralateral to the lesion
2. Nuclear and fascicular lesions:
 - a. Ipsilateral complete facial musculature weakness
1. Supranuclear lesions
2. Brainstem (nuclear lesion)
3. Peripheral VIIth nerve lesion
4. Neuromuscular defects
5. Precentral gyrus cortical or subcortical lesions; volitional eye closure is paretic; mimetic (emotionally induced is normal)

6. Acquired inability to blink (Reviloid's sign); is an early sign of corticobulbar disease
7. Compulsive eye opening:
 - a. A bilateral frontal or non-dominant frontal lobe lesion:
 - i. Reflex eye closure is retained
 - ii. The patient is able to comprehend the task
 - iii. Described with Creutzfeldt-Jakob disease
8. Apraxia of eyelid opening:
 - a. Patients often complain of blindness
 - b. Usually from bilateral prefrontal lesions
9. Motor impersistence of eye closure:
 - a. The patient is unable to complete the command to close the eyes
 - b. The eyes close, develop a fine tremor and then open
 - c. This sign is seen with disorders of the basal ganglia, bilateral hemisphere or non-dominant hemispherical disease
10. Decreased blinking:
 - a. Parkinson's disease, subcortical glial sclerosis, progressive supranuclear palsy, multiple system atrophy (basal ganglia predominant), corticobasal ganglia degeneration
 - b. Bálint's syndrome
 - i. Usually vascular disease
 - ii. Head trauma
 1. Anoxic episodes (cardiac arrest)
11. Increased blinking:
 - a. Any induced dyskinesia (dopamine agonists)
 - b. Schizophrenia
 - c. Gilles de la Tourette's syndrome
12. Excessive eyelid closure and blepharospasm:
 - a. Contralateral frontal eye field seizure (often most evident in the orbitalis oculi as rhythmic muscle twitches)
 - b. Blepharospasm:
 - i. Focal dystonia
 - ii. Meige's syndrome:
 1. There may be concomitant spasmodic dystonia or axial dystonia
 - iii. Multiple sclerosis
 - iv. Bilateral infarction of the rostral brainstem, diencephalon and striatum
 - v. Irritative painful eye diseases
 - vi. Tardive dyskinesia
 - vii. Parkinson's disease
 - viii. Wilson's disease
 - ix. Pantothenate kinase deficiency (formerly Hallervorden-Spatz disease)
 - x. Familial apoceruloplasmin deficiency with retinal degeneration
 - xi. Reflex blepharospasm after a stroke if the non-dominant temporoparietal area is involved
 - xii. Bilateral blepharospasm following bilateral parietal lobe degeneration
 - c. Abnormal Facial Movements
 - i. Dyskinesia:
 1. They may be spontaneous in the elderly
 2. A side effect of neuroleptic drugs
 3. Edentulous dyskinesia
 4. Extrapyrmidal disease
 - ii. Dystonia:
 1. Extrapyrmidal disorder
 2. Meige's syndrome:
 - a. Associated blepharospasm
 - b. Sustained abnormal mouthing movements
 - c. Platysma contraction
 - d. Sustained neck flexion
 - e. One or both arms and the trunk may be involved
 3. Hemifacial spasm:
 - a. Intermittent spasm of the orbicularis oculi and the orbicularis oris muscles; the process may spread to all facial muscles; stapedius muscle involvement causes the patient to hear clicking on the involved side
 - b. Aggravated by stress and fatigue
 - c. Rarely the disorder is bilateral
 - d. The syndrome is caused by lesions in the cerebellopontine angle and includes:
 - i. Tumor
 - ii. An aberrant artery (most often AICA that intermittently compresses the nerve)
 - iii. Dolichoectasia of the vertebral artery
 - iv. Lacunar infarction (rare)
 - v. Brainstem displacement
 - vi. MS
 - vii. Lesions of the root entry zone
 - viii. May be associated with multiple cranial neuropathies
 - ix. Follows Bell's palsy
 - x. Trauma
 4. Post-paralysis spasm and synkinetic movements:
 - a. In addition to post-paralytic hemifacial palsy (following a Bell's Palsy), there is usually some residual muscle function
 - i. Crocodile tears (lacrimation with ingesting food)
 - ii. Jaw-winking (opening the mouth causes blinking (Marin-Amat phenomenon))
5. Facial myokymia:
 - a. Multiple sclerosis (rare)
 - b. Pontine glioma (common; often most easily seen in the orbicularis oculi muscle); seen in pontine gliomas of childhood
 - c. GBS
 - d. Myokymia with spastic parietic facial contracture
 - e. A dorsal pontine lesion at the facial nucleus

6. Focal cortical seizures
 - a. Originate from the lower precentral gyrus (the facial component of the cortical homunculus)
 - b. Post-ictal paralysis:
 - i. Sparing the forehead
7. Tics and habit spasms:
 - a. Gilles de la Tourette syndrome
 - b. Psychological causes
8. Myoclonus:
 - a. Associated with palatal myoclonus
 - b. Occurs with lesions within Mollaret's triangle (dentate, inferior olive and the red nucleus or their connections)
- a. Trauma at the time of birth
- b. Congenitally narrow facial canal
- c. Alexander's disease (AD/AR)
- d. Hemifacial spasm:
 - i. Narrow posterior fossa
- e. Newborn neuropathic facial paralysis:
 - i. Intrapartum compression
 - ii. Abnormal intrauterine posture
 - iii. Forceps trauma
 - iv. Nuclear atresia
- f. Moebius syndrome:
 - i. Facial diplegia with Vth nerve palsy
 - ii. Lower lip weakness with VIth nerve palsy
 - iii. The facial paralysis is incomplete in 2/3 of patients with Moebius syndrome:
 1. The frontalis and orbicularis oculi > perioral muscles
 - iv. Associated abnormalities include:
 1. Ptosis
 2. Anterior lingual atrophy
 3. Pectoral muscle defects
 4. Poland's anomaly
 5. Club foot
 6. Cognitive disability arm malformations

Neuropathology

1. Vascular lesions affecting the VIIth nerve:
 - a. Middle cerebral artery:
 - i. Thrombosis or embolic occlusion of the central sulcus artery (a pial branch of the superior division of the MCA)
 - ii. Internal capsule ischemia:
 1. Anterior choroidal artery ("top of the carotid")
 2. Lenticulostriate branches of the MCA
 3. Thalamoperforate branches of the MCA
 4. Recurrent artery of Heubner (A1 of the ACA)
 - b. Lacunar infarction in:
 - i. Corona radiata
 - ii. Pons
 - iii. Centrum semiovale
 - iv. Medulla
 - v. Cerebral peduncle
 1. AVM (pons or anywhere in the intraparenchymal course of the nerve)
 2. Venous telangiectasia of the pons (usually asymptomatic)
 3. Cavernous hemangioma (pons > thalamus/IC > corona radiata)
 4. AICA Infarction:
 - a. Affects the peripheral branches of the nerve outside of the brainstem:
 - i. Internal auditory artery
 - ii. Subarcuate artery
 5. Basilar artery aneurysm:
 - a. Most often fusiform that blocks perforations and short circumferential arteries
 6. AICA aneurysm (vasospasm after rupture)
 - a. Dolichoectasia of the vertebral and basilar artery
 - b. Millard-Gubler syndrome (obstruction of the short circumferential arteries)
 - c. Foville syndrome (obstruction of short circumferential arteries)
2. Congenital Diseases Affecting the VIIth Nerve
 3. Melkersson-Rosenthal syndrome:
 - a. Recurrent facial palsy with facial edema
 - b. Lingua Plicata (scrotal tongue)
 - c. Facial weakness begins prior to age 16
 - d. Edema affects the upper lip most frequently; over time there is permanent lip and facial enlargement
 - e. Cheilitis granulomatosa:
 - i. Small granulomas occur in the diffusely edematous interstitial tissue
 4. Collagen Vascular Diseases/Arteritis that affects the VIIth nerve:
 - a. SLE
 - b. Periarteritis nodosa
 - c. Sarcoid (vasculitic form)
 - d. Giant cell arteries
 - e. Wegener's granulomatosis
 - f. Mixed collagen vascular disease
 5. Immune-Mediated Disorders of the VIIth Nerve:
 - a. MS
 - b. ADEM
 - c. AIDP
 - d. CIDP
 - e. Graft-versus-host disease
 - f. CMF variant of GBS
 - g. Post-immunizations
 - h. Bell's Palsy
 - i. Necrotizing leukoencephalopathy (associated with increased serum IGM)
 - j. PML (leukoencephalopathy in pons)
 6. Systemic disease:
 - a. Diabetes mellitus

- b. Hypertension
- c. Amyloidosis
- d. Whipple's disease
- e. Sarcoid:
 - i. Heerfordt's syndrome:
 - 1. VIIth nerve associated with uveitis
- f. Idiopathic hypertrophic pachymeningitis
- g. Infections Involving the VIIth Nerve
 - i. Herpes Zoster (Ramsay Hunt syndrome)
 - 1. Acute facial paralysis
 - 2. Grouped vesicles in the external auditory canal and over the mastoid bone and behind the ear
 - 3. Less than 1% of patients with Bell's palsy
 - ii. Herpes simplex (HS)
 - iii. VIIth nerve involvement occurs in a few patients with a new infection or reactivation of CMV, adenovirus, EBV, more common in HIV infected patients
 - iv. Otitis media:
 - 1. 0.5 to 1% of chronically infected patients are complicated by facial paralysis
 - 2. Leprosy
 - 3. Syphilis
 - 4. Osteomyelitis of the petrous bone
 - 5. Bacterial meningitis
 - 6. Tuberculous meningitis
 - 7. Fungal meningitis
 - 8. Lyme's disease (Bannwarth's syndrome)
 - 9. Malaria
 - 10. Infectious mononucleosis, mumps, rubella
 - 11. Polio
 - 12. Parvovirus B19
 - 13. Cat-scratch disease (*Bartonella henselae*)
 - 14. *Mycoplasma pneumoniae*
 - 15. HIV
 - 16. Trichinosis
 - 17. Cysticercosis
 - 18. Behçet's disease
 - 19. Rhombencephalitis
- 7. Neoplasms Affecting the VIIth Nerve:
 - a. Pontine glioma
 - b. Pilocystic astrocytoma (Von Recklinghausen's disease)
 - c. (Neurofibromatosis type I)
 - d. Metastases
 - e. Carcinomatosis of the meninges
 - f. Intracranial metastasis from a pinealoma
 - g. Melanoma metastasizes to the nerve
 - h. Leukemia/lymphoma
 - i. Adenocarcinoma of the salivary gland
 - j. Cholesteatoma
 - k. Carcinoma of the ear
 - 1. Glomus jugulare
 - m. Meningioma
 - n. Yolk sac tumor:
 - i. Endodermal sinus tumor
 - o. Rhabdomyosarcoma of the middle ear
 - p. Neurofibroma (Von Recklinghausen's disease, chromosome 17)
 - q. Mixed parotid gland tumor
 - r. Adenocarcinoma of the salivary gland
- 9. Traumatic Facial Nerve Injuries:
 - a. Closed head injury:
 - i. Acute facial nerve paralysis:
 - 1. Longitudinal fracture (parallel to the long axis of the petrous pyramid)
 - 2. Transverse fracture of the petrous pyramid
 - 3. A temporal bone fracture is demonstrated in almost all cases of traumatic fracture
 - b. Delayed onset of facial nerve paralysis:
 - i. Bleeding from the ear and evidence of temporal bone fracture is prognostic for a delayed VIIth nerve paralysis
 - c. Surgical trauma (primarily ear surgery):
 - i. VIIth nerve paralysis may be immediate or delayed
 - ii. Birth trauma
 - iii. Extratemporal lacerations
- 10. Drugs that Affect the VIIth Nerve:
 - a. Lidocaine
 - b. Diatrizoate
 - c. Isoniazid
 - d. Stevens-Johnson syndrome (numerous drugs)
 - e. Thalidomide
- 11. Rarer Causes of VIIth Nerve Palsy:
 - a. Tick bite paralysis
 - b. Diphtheria
 - c. Paget's disease (bone overgrowth)
 - d. Osteopetrosis (constriction of the nerve in its various canals)
 - e. Hyperostosis cranialis interna
 - f. Temporal dysplasias
 - g. Hemorrhage into the facial canal
 - h. Temporal bone arachnoid cyst
 - i. Kawasaki's syndrome
 - j. Dental block
 - k. Hemophilia and other coagulopathies
 - l. Hereditary facial paralysis:
 - i. Juvenile onset in some families
 - ii. Recurrent facial palsy
 - iii. May occur in association with other cranial nerve palsies

Differential Diagnosis of Bilateral VIIth Nerve Palsy

- 1. Syndrome:
 - a. Wernicke-Korsakoff (concomitant IIIrd and VIth nerve involvement)
 - b. Melkersson-Rosenthal (scrotal tongue)
 - c. Moebius syndrome (concomitant VIth nerve)

- d. Poland's anomaly
- e. Stevens-Johnson syndrome (severe mucous membrane involvement)
- f. Familial Finnish amyloidosis (abnormal sagging facies)
- g. Kennedy's disease (fasciculations in the facial musculature)

Cranial Nerve VIII

General Characteristics

1. General Anatomy:
 - a. Auditory nerve:
 - i. Afferents of the cochlea
 - b. Vestibular nerve
 - c. Afferents from the saccular and utricular macula:
 - i. Sense linear acceleration
 - d. Cristae of the semicircular canals:
 - i. Sense angular acceleration
2. An outline of the anatomy and physiology of the auditory pathways:
 - a. The neuroepithelial hair cells of the organ of Corti are the auditory receptors:
 - i. The cochlear apex senses low tones while hair cells at the base are stimulated by high frequency tones
 - b. The first order neurons of the auditory system are located in the spiral ganglion of the cochlear nerve in Rosenthal's canal at the base of the bony spiral lamina. The afferents of these neurons are in contact with the inner hair cells primarily, although a lesser number diverge to contact outer hair cells
 - c. Activation of hair cells depolarize spiral ganglia neurons whose axons make up the cochlear nerve
 - d. The cochlear nerve enters the brainstem at the junction of the medulla and pons where it divides to synapses in:
 - i. The dorsal cochlear nucleus
 - ii. The anteroventral and posteroventral nuclei of the cochlear complex
 - iii. Dorsal components of the complex process afferents from "high frequency" basal hair cells while ventral neurons process afferent information from the "low frequency" apical hair cells
 - iv. The second order neurons of the dorsal and ventral cochlear complex give origin to projections of the contralateral brainstem that form the lateral lemniscus, which in turn synapses in the central nucleus of the inferior colliculus. The three major crossing projections are:
 1. Dorsal acoustic striae (whose origin is the dorsal cochlear nucleus)
 2. The intermediate acoustic stria (derived from the dorsal component of the ventral cochlear nucleus)
 3. The ventral acoustic striae, derived from the ventral cochlear nucleus, a component of the trapezoid body. Decussating fibers from the trapezoid body in conjunction with projections from the superior olivary complex synapse in the contralateral lateral lemniscal nucleus and the inferior colliculus
4. The ventral acoustic striae also project bilaterally to the reticular formation, the superior olivary nuclei, and the trapezoid body
- v. The inferior colliculus:
 1. Is the central relay nucleus of the auditory system and receives both ascending and descending afferent input:
 - a. Lateral lemniscus projections synapse in the central nucleus
 2. Afferent fibers from the inferior colliculus synapse in the medial geniculate body tonotopically; low frequency fibers in an apical lateral location and high frequency fibers in medial nuclei
- vi. Medial geniculate body afferent fibers give rise to the geniculotemporal auditory radiations that synapse in lamina IV of area 41, the primary auditory cortex, and area 42, the associate auditory cortex. High tone afferents terminate medially and low tone afferents synapse laterally
- vii. Core pathway for audition:
 1. Central nucleus of the inferior colliculus
 2. Components of the medial geniculate body
 3. The primary auditory cortex
 4. Tonotopically organized throughout
- viii. The bilaterality of audition is accomplished through commissural connections that include:
 1. Nucleus of the superior olivary complex that receives afferents from both ears
 2. Connections between the cochlear nuclei
 3. Bilateral connections between the dorsal nuclei of the lateral lemniscus through the commissure of Probst
 4. The inferior colliculi are connected through the commissure of the inferior colliculus
 5. Connections between the central nucleus of the inferior colliculus and the contralateral medial geniculate body via the brachium of the inferior colliculus
 6. There are two projection systems from the inferior colliculus:
 - a. The core system:
 - i. The central nucleus of the inferior colliculus
 - ii. A component from the medial geniculate body
 - iii. The primary auditory cortex
 - iv. A direct tonotopically organized direct auditory pathway
 - b. The belt projection:

- i. Pericentral neurons of the inferior colliculus
- ii. Non-laminated medial geniculate body (MGB) neurons
- iii. Area 42 (the secondary auditory cortex)
- iv. This system is less tonotopically organized
- v. Is a polymodal system whose afferents are both auditory and from other sensory domains

The Blood Supply to the Cochlea and Auditory System

1. Primarily the internal auditory artery from the anterior inferior cerebellar artery supplies the cochlea and the auditory brainstem nuclei
2. The internal auditory artery within the internal auditory canal supplies cochlear:
 - a. Ganglion cells
 - b. Nerves
 - c. Dura
 - d. Arachnoid membranes
3. The internal auditory artery divides into the common cochlear artery and the anterior vestibular artery
4. The superior olivary complex and the lateral lemniscus are supplied by circumferential branches of the basilar artery
5. The inferior colliculus is supplied by:
 - a. Branches from the superior cerebellar artery
 - b. Quadrigeminal arteries
6. The medial geniculate body is supplied by thalamogeniculate arteries derived from the P1 division of the PCA (posterior cerebral artery)
7. Branches of the middle cerebral artery supply the primary and associate auditory cortex

An Outline of the Anatomy and Physiology of the Vestibular System

General Characteristics

1. Anatomy:
 - a. The vestibular system monitors angular and linear accelerations of the head and body
 - b. Accelerations are transduced into action potentials in the components of the membranous labyrinth that comprises: 1. utricle; 2. saccule and 3. semicircular canals:
 - i. Linear acceleration is registered by macules, specialized receptors that are located in the utricle and saccule
 - ii. Angular acceleration is registered by the cristae of the semicircular canals. They are composed of hair cells that act as transducers by converting mechanical deformation of sensory hairs to receptor potentials in the hair cells and their afferent neurons

- c. There are three semicircular canals oriented at right angles to each other which detect angular accelerating head movements:
 - i. The horizontal canal has an outward convexity
 - ii. The anterior or superior canal is oriented upward
 - iii. The posterior semicircular canal has a backward convexity
- d. The head in the erect position orients the semicircular canals such that:
 - i. The horizontal canal forms a 30° angle with the horizontal plane
 - ii. The superior and posterior canals are in the vertical plane that form a 45° angle with the frontal and sagittal planes
- e. The utricle and saccule are at right angles; the utricle is parallel to the base of the skull while the saccule is parallel to the sagittal plane:
 - i. Horizontal head movement activates the utricle linearly
 - ii. Tilting the head stimulates the saccule
- f. The cell bodies of cristae and macules are located in the vestibular ganglia of Scarpa in the internal acoustic meatus, which is the origin of the vestibular nerve:
 - i. The anterior, horizontal semicircular canal and the utricular afferents comprise the superior portion of the vestibular nerve
 - ii. The posterior semicircular canal afferents and those from the sacculus are the inferior portion of the nerve
 - iii. The vestibular nerve synapses in the vestibular complex that comprises:
 1. The superior nucleus of Bechterew
 2. The lateral nucleus of Deiters' (afferents from the macules of the utricle, and sacculus) which make up the neurons whose axons make up the spinal vestibular tract
 3. The medial vestibular nucleus of Schwalbe
 4. Inferior nucleus of Roller (afferents from axons of the utricle and sacculus)
- iv. Vestibular nerve efferents:
 1. The medial longitudinal fasciculus (MLF). The superior nucleus is ipsilateral; the other nuclear efferents are contralateral
 2. The medial vestibulospinal tract provides excitation or inhibition to the cervical and upper thoracic spinal segment of the contralateral spinal cord
 3. The lateral vestibulospinal tract:
 - a. This pathway takes origin from the lateral and inferior vestibular nuclei
 - b. Traverses the ipsilateral spinal cord; cervical cord efferents arise from the rostral part of the nucleus, while efferents to the lumbosacral. Segments take origin from its dorsal caudal neurons

- c. This tract enhances extensor trunk and anti-gravity axial muscle tone in keeping with its afferent input from the utricle (the “anti-gravity monitor”)
- d. The cerebellum receives efferents from:
 - i. Inferior and medial nuclei
 - ii. Lateral vestibular nuclei that innervate the ipsilateral floccular nodular lobe as well as the uvula and fastigial nucleus
- e. The reticular formation receives efferents from the vestibular nuclei (primarily its lateral nucleus and the nucleus reticularis pontis caudalis) as does the ventroposterolateral and posterior nuclear group of the thalamus
- f. There are wide areas of the cortex that receive vestibular projections that include:
 - i. The intraparietal sulcus
 - ii. Brodmann’s area 2, 5, and 6
 - iii. Superior temporal gyrus
- 4. The blood supply to the membranous labyrinth:
 - a. The major supply is from the labyrinthine artery whose origin is the internal auditory artery that branches from AICA or less frequently the basilar artery
 - b. The internal auditory artery gives off:
 - i. The anterior vestibular artery that supplies the anterior and lateral semicircular canals and the utricular macula
 - ii. The posterior vestibular artery that supplies the posterior semicircular canal, the saccular macula and a portion of the cochlea
 - iii. The cochlear artery
- b. More frequent with peripheral nerve and external middle ear disease than with central pathologies
- 4. Low roaring tinnitus:
 - a. Cochlear hydrops (Ménière’s disease)
- 5. High-pitched tinnitus:
 - a. Presbycusis
 - b. VIIIth nerve tumor
- 6. Pulsatile tinnitus:
 - a. Glomus jugulare tumor
 - b. Intracranial or cervical aneurysm
 - c. Increased intracranial pressure often associated with idiopathic intracranial hypertension (may be unilateral)
 - d. Middle ear congenital defects
 - e. Arteriovenous malformations
- 7. Rare causes of tinnitus:
 - a. Gaze-evoked tinnitus following removal of tumors of the CPA angle; may occur with saccadic, smooth pursuit or vestibular induced movements
 - b. TMJ disease
 - c. Labyrinthitis
 - d. Brainstem lesions
 - e. High cardiac output
 - f. Palatal myoclonus – patients hear clicking in association with the myoclonus

Localization of Lesions Causing Sensorineural Deafness by Clinical Manifestation

Clinical Manifestations

- 1. Decreased perception of tones or speech:
 - a. The lesion is central to the oval window
- 2. Cochlear deficit (sensory):
 - a. Decreased perception of sound
- 3. Abnormalities of the cochlear nerve, nuclei or central pathways:
 - a. Decreased perception of sound
- 4. Sensorineural hearing loss:
 - a. Definition:
 - i. A deficit in perceiving either tones or speech that is due to a lesion proximal to the oval window
 - ii. Manifestations of sensorineural hearing loss:
 - 1. Greater difficulty appreciating high-pitched sounds
 - 2. Loss of speech discrimination > pure tone deafness
 - 3. Tinnitus (varies in pitch and intensity):
 - a. May be paroxysmal or continuous
- b. Peripheral nerve and cochlea:
 - a. Cochlear lesion:
 - i. Deafness
 - ii. Tinnitus
 - iii. High-frequency hearing loss
 - b. Peripheral nerve lesions:
 - i. Sensorineural hearing loss (unilateral)
 - ii. Causes:
 - 1. Basal skull fracture
 - 2. Syphilis/bacterial infection
 - 3. Deep fungal or any cause of suppurative meningitis
 - 4. Siderosis
 - 5. Toxins (gentamicin)
 - 6. AICA aneurysm
 - 7. CPA tumors
 - c. Brainstem lesions:
 - i. Lesions above the cochlear nucleus do not cause clinical hearing loss
 - ii. Bilateral hearing loss:
 - 1. Trapezoid body (stroke or hemorrhage)
 - 2. Pons (stroke or hemorrhage)
 - 3. Midbrain tegmentum:
 - a. Hemorrhage

- b. Pineal and other tumors (central deafness from pressure on the isthmus acousticus)
- 4. Lower midbrain or rostral pons:
 - a. Auditory hallucinations:
 - i. Release type
 - ii. Clear sensorium
 - iii. Hearing loss
 - iv. Auditory hallucinosis has been reported with lower pontine tegmental hemorrhages
- iii. Irritative lesions of the temporal cortex
 - 1. Simple auditory hallucinations (tinnitus) > complex hallucinations (voice or music)
 - 2. Involvement of Brodmann's areas BA42 and BA22 cause more hallucinations than Brodmann's area 41
 - 3. Temporal lobe seizures have both acoustic and vertiginous auras
- iv. Cerebral lesions of Brodmann's areas BA41, BA42 and BA22
 - 1. There is no complete deafness even with bilateral lesions of the cortex
 - 2. Unilateral cortical lesions:
 - a. The hearing loss is subtle
 - b. Patients have difficulty locating sounds
 - c. If the lesions are primarily posterior temporal or bilateral temporal lesions (head injury or blast injuries):
 - i. Patients may suffer pure word deafness:
 - 1. Inability to comprehend spoken language, with normal auditory acuity retained
 - 2. Reading, writing, naming and comprehension of non-language sounds is intact
 - 3. Bilateral lesions of the auditory cortex cause:
 - a. Cortical deafness
 - b. Generalized auditory agnosia
 - c. Selective auditory agnosia
 - d. Pure word deafness
 - e. Amusia
 - f. Depressed temporal analysis of sound
- ii. Optic atrophy
- iii. Deafness
- iv. Urinary tract anomalies
- v. Abnormalities of endocrine glands
- vi. Norrie disease (atrophia oculi congenita)
- vii. X-linked recessive inheritance
- viii. Bilateral deafness at birth
- ix. Phthisis bulbi
- x. Dementia or psychosis in 25% of patients
- xi. Pseudotumor of the retina
- xii. Lens and corneal opacities
- d. Differential diagnosis of Norrie disease
 - i. Retinoblastoma
 - ii. Retrolental fibrous dysplasia
 - iii. Toxoplasmosis
 - iv. Falciform detachment of the retina
 - v. Juvenile retinoschisis
 - vi. Sex-linked micro-ophthalmia
 - vii. Sex-linked cataract and congenital retinal detachment
- e. Romano-Ward syndrome
 - i. AD [autosomal dominant] (mutations in the HERG gene)
 - ii. Long QT interval
 - iii. Sudden death from tachyarrhythmia
- f. LEOPARD syndrome
 - i. Lentigines of the skin
 - ii. Ocular hypertelorism
 - iii. Cognitive dysfunction
 - iv. Growth retardation
 - v. Deaf mutism
- g. Albinism with Deafness
- h. Vogt-Koyanagi-Harada
 - i. White forelock
 - ii. Dementia
 - iii. Cerebellar degeneration
 - iv. Uveitis
 - v. Recurrent meningitis
 - vi. Sensorineural deafness
- i. Pendred syndrome:
 - i. AR [autosomal recessive]
 - ii. Congenital bilateral sensorineural hearing loss
 - iii. Progressive visual loss from retinitis pigmentosa
 - iv. Type 1 that maps to chromosomes 14q, 11q, 10q, 21q
 - 1. Congenital deafness
 - 2. Absent vestibular function
 - v. Type II Usher syndrome (USH2) that maps to chromosome 1q
 - 1. Moderate to severe congenital hearing loss
 - 2. Normal vestibular function
 - vi. Type III Usher syndrome (USH3) that maps to chromosome 3q
 - 1. Progressive hearing loss

Neuropathology

- 1. Syndromic deafness (selected)
 - a. Ménière's disease
 - b. Susac's syndrome
 - i. Retinal vascular loops
 - ii. Stroke
 - iii. Sensorineural hearing loss
 - iv. Vertigo
 - c. Wolfram syndrome (DIDMOAD): familial or sporadic
 - i. Diabetes insipidus

2. Normal vestibular function
- vii. Myo7A gene (encodes myosin VIIA) in Usher syndrome type 1B
- viii. USH2A (Laminin is encoded)
- j. Alström syndrome:
 - i. AR [autosomal recessive]; French Canadians; North Africans
 - ii. Retinal pigment degeneration
 - iii. Neurogenic deafness
 - iv. Infantile obesity
 - v. Hyperlipidemia
 - vi. Non-insulin-dependent diabetes mellitus
 - vii. Chromosome 2p12-13 mutation
- k. Rogers syndrome
 - i. Thiamine-responsive megaloblastic anemia
 - ii. AR [autosomal recessive] that maps to chromosome 1q23.2-1q23.3
 - iii. Diabetes mellitus
 - iv. Sensorineural deafness
 - v. SLC19A2 gene encodes the thiamine transporter 1 (THTR-1)
- l. Otodental syndrome
 - i. AD [autosomal dominant]
 - ii. Bulbous canine teeth; globe-shaped posterior teeth; agenesis of the maxillary premolars
 - iii. High frequency sensorineural hearing loss
 - iv. Abnormalities of deciduous and permanent dentition
- m. Branchio-oto-renal syndrome (BOR)
 - i. AD [autosomal dominant]; BOR maps to chromosome 8q13
 - ii. Pre-auricular pits
 - iii. Branchial fistulas
 - iv. Renal anomalies
 - v. Sensorineural hearing loss
 - vi. In some families, there are branchial anomalies, pre-auricular pits and hearing loss with no renal anomalies; other families have branchial and renal anomalies with no hearing impairment
- n. CHARGE syndrome
 - i. Coloboma (70%)
 - ii. Heart malformations (85%)
 - iii. Choanal atresia (57%)
 - iv. Genital anomalies (34%)
 - v. Deafness (62%)
 - vi. Ear anomalies (91%)
 - vii. Semicircular canal hypoplasia
 - viii. Cranial nerve palsies
 - ix. Facial dysmorphism
 - x. Neonatal brainstem deficits
 - xi. Developmental deficits that involve the neural tube and neural crest cells
- o. Large Vestibular Aqueduct syndrome – progressive sensorineural hearing loss
- p. Cogan's syndrome
 - i. Ocular inflammation
 - ii. Vestibular-auditory dysfunction
 - iii. Vasculitis of cerebral, abdominal, and mesenteric arteries
- q. Vohwinkel syndrome
 - i. Mutilating keratoderma
 - ii. Papular and honeycomb keratoderma
 - iii. Constriction of the digits with autoamputation
 - iv. Starfish acral keratosis
 - v. Sensorineural deafness
 - vi. Mutation in the connexin 26 gene (CX26 gene)
 1. Encodes portions of intercellular gap junctions
 2. Non-conservative mutation of D66H in CX26
- r. SAPHO syndrome
 - i. Synovitis
 - ii. Acne
 - iii. Palmoplantar pustulosis
 - iv. Hyperostosis
 - v. Osteitis
 - vi. Diffuse sclerosing osteomyelitis of the mandible; inflammatory spread from the TMJ to the cochlea that causes sudden deafness
- s. Perrault syndrome
 - i. Ovarian dysgenesis
 - ii. Deafness
- t. Treacher Collins (Mandibular Dysostosis) syndrome
 - i. Clinical manifestations:
 1. Antimongoloid slant of the eye
 2. Coloboma of the lid
 3. Micrognathia
 4. Microtia and other ear deformities
 5. Hypoplastic zygomatic arches and macrostomia
 6. Cleft palate
 7. Conductive hearing loss
 - ii. Genetic heterogeneity of the syndrome exists:
 1. Treacher Collins syndrome 1; AD (autosomal dominant); mutation in the TCOF1 gene that maps to chromosome 5q32
 2. Treacher Collins syndrome 2; heterozygous mutation in the POLR1D gene that maps to chromosome q12.2
 3. Treacher Collins syndrome 3; caused by compound heterozygous mutations in the POLR1C gene that maps to chromosome 6
 - iii. The disorder is putatively thought to involve a defect in a nucleolar trafficking protein that is required for craniofacial development; in TCOF1 gene mutations there are truncated proteins mis-localized within the cell
- u. Wildervanck syndrome:
 - i. A variant of the Klippel-Feil syndrome
 - ii. Retraction of the globe of the eye
 - iii. Deaf mutism

- v. Waardenburg syndrome:
 - i. AD [autosomal dominant]; mutations of the PAX3 gene that maps to chromosome 2q36.1 in type 1
 - ii. Lateral displacement of the medial canthus
 - iii. Approximation of the eyebrows
 - iv. White forelock
 - v. Heterochromia iridis
 - vi. Absence of the organ of Corti
 - vii. Atrophy of the spinal ganglion
 - viii. Congenital sensorineural hearing loss
- w. Alport syndrome:
 - i. Alport syndrome is genetically heterogeneous:
 - 1. All mutations cause defects in type IV collagen, which is a major structural component of the basement membrane
 - 2. Approximately 85% of patients are X-linked and 15% are autosomal recessive
 - ii. Progressive renal failure (glomerulopathy)
 - iii. Variable sensorineural hearing loss
 - iv. Variable ocular anomalies
- x. Cockayne syndrome (type A):
 - i. The syndrome is caused by homozygous or compound heterozygous mutation in the AR [(autosomal recessive)] ERCC8 gene that maps to chromosome 5q12.1:
 - 1. The encoded protein is the group 8 excision repair cross-complementing protein
 - 2. There is defective DNA repair in the disorder
 - ii. Abnormal slow growth and development that is seen within early childhood ("cachectic dwarfism")
 - iii. Cutaneous photosensitivity
 - iv. Thin, dry hair
 - v. Progeroid dysmorphism
 - vi. Progressive pigmentary retinopathy
 - vii. Sensorineural hearing loss
 - viii. Disproportionate long limbs and large hands
 - ix. Flexion joint contractures
 - x. Delayed development and cognitive impairment
 - xi. Cerebellar ataxia
 - xii. Peripheral neuropathy
 - xiii. Loss of subcutaneous fat
- y. Laurence-Moon-Biedl syndrome:
 - i. AR [autosomal recessive]; genetic heterogeneity occurs in the syndrome
 - ii. Genes responsible for the syndrome have been mapped to chromosome 11q13 (type 1), 16q21 (type 2), 3p12 (type 3) and 15q22 (type 4). The most common type is type 1 and the rarest is type 3
 - iii. Retinitis pigmentosa
 - iv. Sensorineural hearing loss
 - v. Cognitive dysfunction
 - vi. Obesity
- vii. Polydactyly
- viii. Hypogonadism
- ix. Optic atrophy
- x. Cataracts and glaucoma
- z. Refsum's disease
 - i. AR [autosomal recessive]; caused by mutation in the gene that encodes phytanoyl-CoA hydroxylase (PHYH or PAHX) that maps to chromosome 10p13
 - ii. Classic tetrad of abnormalities include:
 - 1. Retinitis pigmentosa
 - 2. Intermittent peripheral neuropathy
 - 3. Cerebellar ataxia
 - 4. Elevated CSF protein
 - iii. All patients have phytanic acid (an unusual branched chain fatty acid) in the blood and tissues
 - iv. Variable features include:
 - 1. Cardiac disease
 - 2. Sensorineural hearing loss
 - 3. Ichthyosis
 - 4. Multiple epiphyseal dysplasia
- aa. Retinitis and hearing loss
 - i. OPCA [Olivopontocerebellar atrophy]
 - ii. Juvenile and adult onset lipidoses
- ab. Optic Atrophy, Hearing Loss and Peripheral Neuropathy
 - i. Some patients with Friedreich's ataxia
- ac. Hearing Loss and Optic Atrophy
 - i. Sylvester syndrome:
 - 1. AD [autosomal dominant]
 - 2. Optic atrophy
 - 3. Ataxia
 - 4. Progressive hearing loss
 - ii. Nyssen-van Bogaert syndrome
 - 1. Opticocochleodentate degeneration
 - iii. Rosenberg-Chutorian syndrome
 - 1. Optic atrophy
 - 2. Polyneuropathy
 - 3. Sensorineural hearing loss
- ad. Brown-Vialetto-Van Laere syndrome
 - i. Caused by homozygous or compound heterozygous mutation in the SLC52A3 gene that maps to chromosome 20p13
 - ii. Sensorineural hearing loss
 - iii. Involvement of the motor components of the seventh and ninth to twelfth cranial nerves. Rarely, the third, fifth and sixth cranial nerves are involved
 - iv. Spinal motor nerves and upper motor neurons may be affected
 - v. The onset is most often in the second decade
 - vi. There is severe loss of axons of the auditory and vestibular nerves
- ae. Rare Associations of Hearing Loss

- i. Spinal muscular atrophy
- ii. Fascioscapular humeral dystrophy
- iii. Roussy-Lévy syndrome
- iv. Myotonic dystrophy
- 2. Non-Syndromic Hereditary Hearing Loss
 - a. Mitochondrial genetic disease:
 - i. MELAS
 - ii. MERRF
 - iii. PEO
 - iv. Kearns-Sayre syndrome
 - b. Identified Genes/Chromosomal Loci/Genetic Associations
 - i. CX25 (mutated in 50% of all recessive deafness)
 - ii. Myosin7A mutation – Usher type 1B – identified with syndromic and non-syndromic hearing loss
 - iii. X-linked deafness type 3 – POU3FH gene mutations
 - iv. DFNA6 that maps to chromosome 4p16.3 – progressive low frequency hearing loss
 - v. Mitochondrial mutation 12 s RNA deficit
 - vi. Enlarged vestibular aqueduct – the same 7q31 locus as Pendred syndrome
 - vii. X-linked cochlear degeneration
 - viii. Autosomal dominant cerebellar atrophy type I
 - ix. Complicated familial spastic paraparesis
 - x. Autosomal dominant recurrent VIIIth nerve deafness
 - xi. Familial amyloidosis type IV
 - xii. Late-onset peroxisomal deficiency
 - xiii. X-linked deafness
 - xiv. CADASIL
 - xv. Osteogenesis imperfecta
 - xvi. Hereditary sensory autonomic neuropathy
 - xvii. X-linked motor-sensory neuropathy type II
- b. Unilateral high-pitched tinnitus
- c. Progressive sensorineural hearing loss
- d. Early loss of speech discrimination
- e. Less than 10% have sudden deafness
- f. Vertigo, dizziness, ipsilateral unsteadiness (vestibular nerve involvement)
- g. V, VI, VIIIth nerve involvement (facial movement weakness, loss of taste anterior 2/3 of the tongue): Hitzelberger's sign (numbness of the external auditory canal)
- h. Decreased corneal reflex
- i. Hydrocephalus
- 15. Anterior extension of the tumor:
 - a. Vth (facial pain; decreased corneal reflex)
 - b. Vth nerve weakness of the tumor
- 16. Posterior inferior extension:
 - a. IXth nerve involvement with dysphagia
 - b. Absent pharyngeal reflex
 - c. Xth nerve involvement with hoarseness
 - d. XIth nerve involvement with trapezius and sternocleidomastoid muscle weakness
- 17. Infections Involving the VIIIth nerve
 - a. Blood borne infection:
 - i. Reaches the inner ear by invasion of the endolymphatic system
 - ii. Meningoencephalitis:
 - 1. Invasion along the nerves and vessels of the internal auditory meatus
 - iii. Streptococcus, pneumococcus, meningococcus, and haemophilus influenza:
 - 1. Direct invasion of the labyrinth with subtotal destruction of sensory and neural elements
 - 2. Total vestibular destruction may cause oscillopsia if any vestibular function remains; central compensation can occur with no vestibular symptoms but with profound hearing loss
 - iv. Syphilitic labyrinthitis:
 - 1. The most common cause of hearing loss in a syphilitic patient
 - v. Borrelia burgdorferi (Lyme's disease):
 - 1. There is both cochlear and vestibular involvement
 - vi. Petrositis (chronic middle ear infection)
 - 1. Gradenigo's syndrome:
 - a. Requires pneumatized petrous bone through which infection can spread to the petrous apex
 - b. Usually chronic bacterial otitis media; may be tuberculous
 - c. The VIth nerve is involved as it crosses under the petroclinoid ligament; pain behind the ipsilateral eye is from involvement of the Vth nerve ganglion in Meckel's cave

Tumors Affecting the VIIIth Nerve

- 1. Carcinomatosis of the meninges
- 2. Leukemia
- 3. Lymphoma
- 4. Acoustic Schwannoma (NF1 chromosome17)
- 5. Meningioma
- 6. Epidermoid (primary and secondary)
- 7. Metastasis
- 8. Pinealoma (CSF spread); dysgerminoma and pineocytoma
- 9. Ependymoma
- 10. Malignant melanoma (metastatic)
- 11. Exophytic glioma
- 12. Neurofibromatosis type II
 - a. Bilateral acoustic neuroma
- 13. Intravascular malignant lymphoma
- 14. Acoustic Neurinoma
 - a. The origin is on the vestibular portion of the VIIIth nerve in the IAC (internal auditory canal)

- d. Vertigo and hearing loss are due to erosion of the bony labyrinth or involvement of the VIIIth nerve in its bony canal
- vii. *Pseudomonas aeruginosa*:
 1. Malignant external otitis
 2. Debilitated patients (immunosuppressed)
 3. Severe diabetes
 4. Renal failure
 5. The organisms invade the junction of the cartilaginous and osseous portion of the external auditory canal to invade adjacent bones
- b. Viral infections that affect the VIIIth nerve:
 - i. Viruses may damage the cochlea to a greater degree than the VIIIth nerve itself
 - ii. Meningoencephalitis (viral) directly invades along the nerves and blood vessels (HZ and mumps)
 - iii. Infection of Scarpa's ganglion has been demonstrated with Herpes simplex, rubella and reovirus infection
 - iv. Vestibular neuronitis from a viral etiology:
 1. Affects patients who are:
 - a. 30–60 years of age
 - b. Have a sudden onset of vertigo that involves one ear and usually lasts for 1–3 weeks
 - c. The nystagmus is opposite to the involved ear (fast component)
 - d. There is no hearing loss or other neurologic signs
 - e. Recovery usually occurs over months
 - f. The superior and ampullary branches of the vestibular nerve are involved
 - g. The cochlea is normal
 - v. Tuberculosis (meningitis)
 - vi. Cryptococcosis (meningitis)
 - vii. Blastomycosis (meningitis)
 - viii. Histoplasmosis (meningitis)
 - ix. HIV
 - x. CMV
 - xi. Purulent bacterial meningitis
 - xii. EBV
 - xiii. Cysticercosis (racemose cyst of the CPA angle)
 - xiv. Coccidiomycosis (meningitis)
18. Drugs/toxins/physical agents:
 - a. Cisplatinum
 - b. Aminoglycosides (gentamicin the most common; especially with renal insufficiency)
 - c. Superficial siderosis (recurrent bleeding from cavernous hemangioma, other vascular malformations and subarachnoid hemorrhage)
 - d. Furosemide diuretics (loop-diuretics)
 - e. Zidovudine
 - f. Dideoxyadenosine
 - g. Interferon gamma 1
 - h. Depakote
 - i. X-RT
 - j. Increased ICP
 - k. Midbrain trauma
 - l. Basilar skull fracture
 - m. Blast injuries
 - n. Alcohol
 - o. Lead
 - p. Mercury
19. Disorders of the temporal bone
 - a. Otosclerosis:
 - i. A disease of the bony labyrinth
 - ii. Immobilization of the stapes
 - iii. Compression by otosclerotic foci of cochlear neural elements
 - b. Paget's disease:
 - i. Hearing loss is usually bilateral
 - ii. Sensorineural deficit may also have a synergistic conductive deficit
 - iii. Vestibular symptoms are usually progressive but may be episodic
 - c. Fibrous dysplasia of bone:
 - i. Compression of the VIIIth nerve in its bony canals
 - d. Osteopetrosis:
 - i. VIIIth and VIIIth nerve compression with deficits may be early symptoms
 - ii. Conductive defect:
 1. Narrowing of the internal auditory meatus
 2. Encroachment of the bones of the middle ear on the ossicles
 - iii. Sensorineural hearing loss is from compression of the cochlear nerve in the IAC
 - e. Recessive osteosclerosis (Van Buchem syndrome or hyperostosis corticalis generalisata):
 - i. Hyperostosis of the skull, ribs, clavicles, long bones and pelvis
 - ii. VIIIth and VIIIth nerve palsy occurs in approximately 50% of patients
 - iii. Encroachment of bone into the neural foramina
 - f. Hyperostosis cranialis interna:
 - i. Hyperostosis and osteosclerosis of the calvarium and base of the skull can occur in isolation
 - ii. AD inheritance
 - iii. Recurrent VIIth nerve palsy, decreased vision as well as decreased hearing and vestibular function
 - iv. Cranial nerve foraminal encroachment
 - g. Synchrondrosis of the skull
 - h. Congenitally small IAC (internal and auditory canal)
20. Trauma of the VIIIth Nerve:
 - a. Blunt trauma:
 - i. Transverse or longitudinal fracture (in relation to the long axis of the petrous bone)
 - ii. Longitudinal fractures:
 1. More common than transverse
 2. Usually no VIIIth nerve damage

- iii. Transverse fractures
 - 1. Anteroposterior trauma
 - 2. The roof of the internal auditory meatus is fractured
 - 3. There is usually complete deafness with vertigo; 40–50% of patients have a concomitant VIIIth nerve paralysis
 - iv. Blunt head trauma with a temporal bone fracture:
 - 1. Concussion of the inner ear
 - 2. Concomitant secondary neural degeneration
 - v. There may be VIIIth nerve injury from commercial and sports diving
21. Developmental Defects in the VIIIth nerve:
- a. Atresia
 - i. Complete absence of the otic capsule and VIIIth nerve from thalidomide exposure
 - b. Incomplete development of the bony and membranous labyrinth that includes dysgenesis of the spiral ganglion
 - c. Membranous cochleosaccular dysplasia of the VIIIth nerve in the porous acousticus
- The Vestibular Component of the VIIIth Nerve**
- 1. General Characteristics:
 - a. Vertigo is manifested by a combination of perceptual, ocular, motor and postural signs and symptoms
 - 2. Clinical Manifestations:
 - a. Peripheral (vestibular labyrinthine) disorders
 - i. Semicircular canal disorders cause rotational sensation; disorders of utricle and saccule (the otolith) are affected; there is a sensation of tilt or levitation
 - ii. Acute vertigo from the labyrinth:
 - 1. The diseased site may be irritated and more active for hours to days that (with the eyes closed) causes a rotational sensation to the side opposite the affected labyrinth
 - 2. In the paretic phase (the labyrinth is hypoactive)
 - a. Patients fall and past-point to the affected side (while standing with their eyes closed)
 - b. The slow component of nystagmus is to the affected side (eyes slowly deviated to the affected side with the post-cortical corrective jerk nystagmus to the opposite side)
 - iii. Patients lie on their side with the affected side upmost
 - iv. Acoustic stimuli may induce:
 - 1. Paroxysms of vertigo
 - 2. Oscillopsia (abnormal movement of objects in the environment)
 - 3. Postural unsteadiness
 - 4. The ocular tilt reaction
 - 5. Nystagmus
 - 6. The above constellation is Tullio's phenomenon
 - v. The major manifestations of peripheral vestibular disorders are:
 - 1. Short duration
 - 2. Severe paroxysmal vertigo
 - 3. May be accompanied by tinnitus and hearing loss
 - 4. The fast phase of nystagmus is to the side opposite to the lesion, is horizontal, rotary and is dampened by ocular fixation
 - 5. Subjective environmental sensations, falls, past-pointing are to the side of the lesion
 - 6. Reflex fixation saccades to the opposite side are induced when the head is rotated to the side of the lesion
 - 7. Bilateral vestibular paresis:
 - a. Head movement dependent oscillopsia (movement of the visual environment only with head movement)
 - 3. Neuropathology:
 - a. Benign positional vertigo:
 - i. Degeneration of the macula of the otolith
 - ii. Obstruction of endolymph flow
 - iii. Lesions of the posterior semicircular canal (PSCC)
 - iv. Otoconia from degenerating reticular macula attach to the cupula of the PSCC
 - v. Differential diagnosis of cupulolithiasis:
 - 1. Trauma
 - 2. Infection (herpes simplex)
 - 3. Labyrinthine fistula
 - 4. Ischemia
 - 5. Demyelinating disease
 - 6. Posterior fossa tumor
 - 7. Arnold-Chiari malformation
 - b. The nystagmus of benign positional vertigo (BPPV) and peripherally induced nystagmus:
 - i. Latency of 2–15 seconds
 - ii. Fatigue (lasts less than 10 seconds)
 - iii. Has a torsional component
 - iv. No associated cochlear or central signs or symptoms
 - v. Vertigo (less than 60 seconds)
 - vi. In the upright position (after sitting the patient up from the supine position that induced the nystagmus) there is rebound nystagmus to the opposite side
 - vii. Lying in a lateral position may cause protracted nystagmus
 - viii. May have a protracted course (years)
 - ix. The nystagmus habituates (lessens with repositioning)
 - c. The manifestations of central nystagmus and vertigo:
 - i. Short latency
 - ii. Does not fatigue
 - iii. There is no habituation

- iv. Vertigo may be absent or mild and may last ~60 seconds
- v. The nystagmus is direction-changing rather than fixed
- vi. Induced by several head positions
- vii. There are associated CNS signs

Matutinal Vertigo

1. Refers to vertigo precipitated by rising on awakening or turning over in bed prior to arising:
 - a. May be central or peripheral
 - b. Seen in disorders that cause positional vertigo
2. Vestibular neuronitis:
 - a. Acute severe vertigo associated with prominent nausea and vomiting
 - b. Absent calorics on the affected side
 - c. Self-limited; usually lasts for 7–10 days
 - d. No cochlear symptoms or other neurologic signs
 - e. Unrelated to head position
 - f. May reoccur
3. Acute labyrinthitis:
 - a. Severe vertigo, nausea and vomiting
 - b. Associated tinnitus
 - c. Hearing loss
 - d. May follow bacterial or viral labyrinthitis; aminoglycoside antibiotics, or loop diuretics
4. Aberrant branch of AICA that compresses the VIIIth nerve
 - a. Constant positional vertigo
 - b. Severe nausea
 - c. Tinnitus

Ménière's Disease

1. Episodic severe vertigo
2. Fluctuating sensorineural hearing loss
3. Fullness or pressure sensation in the ear
4. It is bilateral in 30–40% of patients
5. Endolymphatic hydrops:
 - a. An increased volume of endolymph
6. Roaring tinnitus
7. Attacks last minutes to hours
8. Between attacks some patients have dysequilibrium
9. Hearing loss occurs in low tones (<3 kHz)

Variants of Ménière's Disease

1. Cochlear Ménière's:
 - a. Vertigo is absent
2. Vestibular Ménière's disease
 - a. Severe vertigo
 - b. Hearing loss and tinnitus are later features
3. Tumarkin's otolithic catastrophe:
 - a. Severe episodic vertigo
 - b. Loss of muscle tone; the patient falls to the ground
 - c. There is no loss of consciousness

Medical Disorders That Cause Vertigo

1. Anemias:
 - a. Polycythemia vera
 - b. Waldenström's macroglobulinemia (hyperviscosity)
 - c. IgM monoclonal gammopathies
2. Hypoglycemia:
 - a. Dizziness and presyncope
 - b. Cold perspiration
 - c. Convulsion (usually the sugar peripherally is less than 30–40 mg/dl)
3. Hypothyroidism:
 - a. Sensorineural hearing loss
 - b. Cerebellar ataxia
 - c. Vertigo
4. Hyperventilation:
 - a. Perioral paresthesia
 - b. Tingling fingers (paresthesia)
 - c. Fasciculations
5. Cardiac Insufficiency:
 - a. Cardiac arrhythmia:
 - i. Tachyarrhythmia with decreased stroke volume
 1. Presyncopal sensation
 2. Visual loss (closing in from the side)
 3. Fading out of hearing
 4. "Light headed" or dizzy
 - b. Congestive heart failure
 - c. Aortic stenosis
 - d. Carotid sinus hypersensitivity
6. Infections
 - a. Congenital syphilis (bilateral disease) associated with interstitial keratitis and strawberry molars (Cogan's syndrome)
 - b. Viral and bacterial labyrinthitis
 - c. Ramsay Hunt syndrome:
 - i. HZ of the geniculate ganglion
 - ii. Vesicular eruption of external auditory canal
 - iii. Peripheral facial paralysis
 - iv. Vertigo and hearing loss
 - d. Chronic ear infections
 - e. Multiple sensory deficit syndrome:
 - i. Elderly patients
 - ii. Visual impairments (cataracts and macular degeneration)
 - iii. Proprioceptive sensory loss (neuropathy)
 - iv. Cervical spondylosis
 - v. Depression

Vascular Causes of Vertigo

1. Vertebrobasilar insufficiency
 - a. Vertigo and dizziness are moderately severe
 - b. Deafness or hearing loss is rare
 - c. Associated frequently with brainstem, cerebellar, cranial nerve or long tract signs

- d. Ischemia of the central auditory pathways or the labyrinth (internal auditory or subordinate arteries)
2. Lateral medullary syndrome (Wallenberg; PICA; most often from vertebral artery atherosclerosis)
 - a. Vertigo, dizziness, nausea and vomiting
 - b. IXth and Xth nerve involvement
 - c. Rotary nystagmus to the side of the lesion (vestibular nuclei)
 - d. Ipsilateral ataxia (involvement of the restiform body)
 - e. Ipsilateral Vth nerve involvement with decreased sensation of the face; loss of sensation below the clavicle contralaterally (temperature and pain); involvement of the ascending spinothalamic tract that decussates at its level of origin; the leg is involved to a greater degree than the arm
 - f. If the lateral branch of PICA is involved in isolation:
 - i. Patients may only have vertigo and dizziness (a rare example of a central lesion without other associated neurological signs)
3. Labyrinthine stroke:
 - a. Occlusion of the internal auditory artery (its origin is AICA); rarely occlusion is directly from the basilar artery)
 - i. Involvement of the superior vestibular branch from the internal auditory artery (IAA) causes vertigo, nausea and vomiting
 - ii. Infarction of the cochlear branch of the IAA causes sudden deafness (usually a sign of AICA infarction)
4. Bickerstaff migraine:
 - a. Vertebrobasilar migraine
 - b. Tingling and paresthesias
 - c. Dizziness, dysarthria and ataxia
 - d. Patients may have a short loss of consciousness
5. Subclavian steal syndrome:
 - a. There is severe stenosis of the subclavian artery prior to the origin of the vertebral artery
 - b. Dizziness, dysarthria and diplopia:
 - i. Occurs during continued uses, often overhead, of the right arm
 - ii. Most often this is a radiographic (angiographic) finding that is asymptomatic
6. Cerebellar infarction or hemorrhage
7. Benign positional vertigo may occur secondary to labyrinthine ischemia
8. Dolichoectasia of the vertebral, basilar and AICA arteries that compress the VIIIth nerve
9. AICA or PICA aneurysm with distal emboli or vasospasm

Vertigo from Head or Cervical Trauma

1. Inner ear concussion
2. Fracture of the temporal bone with labyrinthine and/or VIIIth nerve damage; MRI has demonstrated blood in the labyrinth and cochlea
3. Uncovertebral joint arthritis of the cervical spine as well as cervical plexus injuries:
 - a. There is unequal afferent input to the vestibular nuclei

Cranial Nerve IX

General Characteristics

1. The glossopharyngeal nerve is comprised of motor, sensory and parasympathetic fibers
2. It emerges from the brainstem in close approximation to the Xth and XIth nerves to exit the skull through the jugular foramen
3. In the upper neck the IXth nerves between the ICA and the jugular vein
4. It innervates the stylopharyngeus muscle (which elevates the pharynx) and along with the vagus nerve the constrictor muscles of the pharynx
5. It also innervates the cricopharyngeus muscle which is the external pharyngeal sphincter
6. Parasympathetic fibers take origin from the inferior salivatory nucleus and branch from the main nerve at the petrous ganglion to travel with the tympanic and superficial petrosal nerve to the otic ganglion. Post-ganglionic fibers travel with the auriculotemporal branch of the Vth nerve to innervate the parotid gland
7. Afferent sensory fibers innervate the posterior 1/3 of the tongue, the tonsils, nasopharynx, inferior surface of the soft palate, uvula, eustachian tube, tympanic cavity, a small area anterior to the tragus and a small portion of the anterior wall of the external auditory meatus
8. Taste from the posterior 1/3 of the tongue is subserved from neurons in the petrous ganglion which synapse in the nucleus of the tractus solitarius
9. It gives off the carotid sinus nerve:
 - a. That contains afferents from the chemoreceptors of the carotid bodies
 - b. Baroreceptors of the carotid sinus wall
 - c. Projects to the nucleus tractus solitarius

Clinical Manifestations

1. It is involved with the vagus in mediating:
 - a. Taste from the posterior 1/3 of the tongue
 - b. Mediates the gag reflex
 - c. Salivary secretion from the parotid gland
 - d. Bilateral surgical or traumatic section causes transient hypertension
 - e. Intramedullary involvement (Bonner syndrome)
 - i. VIIIth, IXth and Xth nerve involvement
 1. Vertigo, dysphagia and dysarthria
 2. Contralateral hemiplegia
 3. IXth nerve involvement
 4. Bonner syndrome may also be caused by tumors, syringobulbia and autoimmune disorders
 - f. Paroxysmal lacrimation (Bogorad syndrome)
 - i. Abnormal lacrimation with normal production of saliva
 - ii. Following middle ear surgery the lesser superficial petrosal nerve to the parotid gland is damaged

- iii. There is aberrant innervation from the parasympathetic fibers from the otic ganglion. Aberrant innervation of the lacrimal gland; may also be seen in Bell's palsy with lesions that are proximal to the geniculate ganglion (that supplies preganglionic fibers to the lacrimal gland, submandibular and sublingual glands)
- iv. Sphenopalatine ganglion post-ganglionic parasympathetic fibers supply the lacrimal gland

Neuropathology

1. Vascular disorders
 - a. Wallenberg's syndrome
 - b. Bonner's syndrome
 - c. Cavernous hemangioma, AVM, telangiectasia and hypertensive hemorrhage
 - d. An absent vertebral artery or DICA itself may compress the nerve
2. Tumors of the IXth nerve
 - a. Glomus jugulare
 - b. Schwannoma
 - c. Meningioma
 - d. Chordoma
 - e. Metastatic disease
 - f. Jugular foramen syndrome of Vernet:
 - i. IXth, Xth, XIth nerves are affected
3. Glossopharyngeal neuralgia:
 - a. Idiopathic or secondary to a structural lesion
 - b. Onset is between 40–60 years of age; there is an equal male and female incidence
 - c. Stabbing, severe unilateral neuropathic pain
 - d. The pain radiates to the base of the tongue, faucial areas (tonsils) in or behind the external auditory meatus and beneath the angle of the jaw
 - e. Trigeminal and glossopharyngeal neuralgia may occur concomitantly
 - f. A hacking cough may accompany the paroxysms of pain
 - g. The triggers are: swallowing, talking, pressure on the tragus or auricle, sneezing or moving the head
 - h. Associated with episodes are: salivation, flushing, sweating, tinnitus, lacrimation, tachycardia, hypertension and rarely seizures or cardiac asystole from activation of the cardiac depressor nerve
 - i. Bradycardia and syncope:
 - i. Afferents to the brainstem vasomotor centers that excite cranial nerve X
 - j. Paroxysms occur usually 2–3×/year; usually last a few minutes but may occur intermittently over several days
 - k. Differential diagnosis of glossopharyngeal neuralgia (structural lesions)
 - i. Occlusion of the ICA
 - ii. Elongation of the stylomastoid process

- iii. Tumors of the posterior foramen
 - iv. Local infection
 - v. Tortuosity of PICA
 - vi. Neck trauma
4. Carotid sinus hypersensitivity
 - a. Syncope with head and neck movement
 - b. Rarely from pressure on the neck (tight collar)
 - c. Stretching the neck
 - d. Response to carotid artery massage:
 - i. Decrease of heart rate of 50%
 - ii. Asystole if greater than 3 seconds
 - iii. A fall of blood pressure of 50 mm Hg
 - e. Cardioinhibitory effects of carotid sinus hypersensitivity:
 - i. Isolated decrease of heart rate
 - f. Mixed form:
 - i. The heart rate is maintained in the face of a falling blood pressure
 - g. Vasodepressor form:
 - i. There is isolated hypotension

Differential Diagnosis of IXth Nerve Syncope

1. Digoxin
2. Beta-adrenergic blocking drugs
3. Biliary disease:
 - a. A high bilirubin depresses the SA and AV node of the cardiac conduction system
4. Elderly patients with atherosclerotic disease of the cardiac conduction system
5. Takayasu disease
6. Chromaffin tumors of the carotid body
7. Post-carotid endarterectomy
8. Elicitation of the cardiodepressor reflex by pressure
 - a. May cause ventricular fibrillation
 - b. The right side is more dangerous to compress than the left
9. Peripheral IXth nerve involvement:
 - a. Diphtheria
 - b. AIDP
 - c. CIDP
 - d. Meningeal involvement:
 - i. Infection
 - ii. Tumor
 - iii. Pachymeningitis
 - e. Tabes dorsalis
 - i. Carotid and baroreceptor dysfunction
 - f. Hencken's syndrome
 - i. Loss of taste of the posterior 1/3 of the tongue and pharynx
 - g. Lesions within the retropharyngeal or retroparotid space
 - h. Nasopharyngeal cancer
 - i. Abscess
 - j. Adenopathy

- k. Aneurysms
 - l. Trauma
- m. Surgical procedures
 - i. Head and neck cancer surgery
- n. Carotid endarterectomy
- o. Pure glossopharyngeal syndrome:
 - i. Minimal dysphagia
 - ii. Depressed gag reflex
 - iii. Ipsilateral palatal weakness
 - iv. Loss of taste of the posterior 1/3 of the tongue
 - v. IXth sensory nerve loss
- p. Associated syndromes
 - i. Collet-Sicard syndrome:
 - 1. IXth, Xth, XIth and XIIth nerves are involved
 - ii. Villaret syndrome:
 - 1. IXth, Xth, XIth and XIIth
 - 2. Sympathetic chain
 - 3. Occasionally the VIth nerve is involved
- q. Basilar skull fracture
- r. Bogorad syndrome
 - i. Crocodile tears from aberrant regeneration of the lesser superficial petrosal nerve
- e. In the neck:
 - i. It travels with the internal carotid artery and jugular vein in the carotid sheath. It gives off:
 - 1. Cardiac rami to the cardiac plexus
 - 2. Recurrent laryngeal nerve:
 - a. On the right side the nerve ascends in the tracheoesophageal sulcus
 - b. On the left side, it travels beneath the aortic arch to the tracheoesophageal sulcus
 - c. The recurrent laryngeal nerve divides into anterior and posterior rami which supply all of the muscles of the larynx except the cricothyroid
 - d. The dorsal motor nucleus of the vagus and the nucleus ambiguus supply the motor fibers carried in the nerve:
 - i. The dorsal motor nucleus is located in the floor of the IVth ventricle lateral to the hypoglossal nucleus. It provides preganglionic parasympathetic fibers to:
 - 1. The pharynx
 - 2. Esophagus
 - 3. Trachea
 - 4. Stomach
 - 5. Heart
 - 6. Small intestine
 - 7. Ascending and transverse colon
 - 8. Liver
 - 9. Pancreas

Cranial Nerve X

General Characteristics

Anatomy

1. The vagus nerve contains motor, sensory and parasympathetic nerve fibers
2. The vagus nerve shares a dural sheath with cranial nerve XI in the jugular foramen (pars venosum)
3. Inferior to the jugular foramen or within it are its two ganglia
 - a. Jugular ganglia (general somatic afferent)
 - b. Nodose ganglia (special and general visceral afferent fibers)
- c. Between the two ganglia the nerve gives off:
 - i. The auricular ramus (the nerve of Arnold) that innervates that concha of the external ear
 - ii. The meningeal ramus that innervates the dura of the posterior foramen
 - iii. The pharyngeal ramus
 - 1. Forms the pharyngeal plexus with cranial nerve IX to innervate the muscle of the pharynx and most of the palate (except for the stylopharyngeus that is innervated by IX and the tensor veli palatini innervated by V)
- d. The superior laryngeal nerve arises from the vagus near the nodose ganglion:
 - i. Its external motor branch innervates the cricothyroid muscle
 - ii. Its internal ramus provides sensory fibers to the larynx
4. The nucleus ambiguus innervates:
 - a. All striated musculature of the soft palate, pharynx and larynx except the stylopharyngeus muscle which is innervated by cranial nerve IX and the tensor veli palatini innervated by cranial nerve V
 - b. The nodose ganglia mediates taste from the epiglottis, hard and soft palate, pharynx and projects to the nucleus tractus solitarius
 - c. Cells of origin in the nodose ganglion also mediate general visceral sensation from the oropharynx, larynx, lining of the abdominal viscera and projects to the nucleus tractus solitarius
 - d. Exteroceptive sensation from the concha is mediated by fibers that project to the jugular ganglion and then to the descending tract of V
 - e. Xth nerve lesions cause the vocal cords to assume the cadaveric position that is in between abduction and adduction

Clinical Manifestations

1. Supranuclear lesions:
 - a. The cortical representation is at the foot of the precentral gyrus
 - b. Lesions of homunculus, corona radiata and centrum semiovale cause solitary unilateral palatal weakness with no associated limb weakness

- c. Bilateral upper motor lesions may result in pseudobulbar palsy that is characterized by:
 - i. Emotional dyscontrol
 - ii. Increased gag reflex (rarely it is decreased)
 - iii. Dysphagia
 - iv. Pathologic laughing and crying
 - v. A spastic tongue
 - vi. Explosive spastic dysarthria
 - vii. The gag reflex when elicited may be associated with retching and vomiting
 - viii. Extremity spasticity
- 2. Medullary lesions of X:
 - a. Wallenberg's syndrome
 - b. Syringobulbia
 - c. Motor neuron disease
 - d. Inflammatory disease (demyelinating)
 - e. Paraneoplastic disorders
 - f. Primary and metastatic tumors
- 3. Injury to the rostral component of the nucleus ambiguus:
 - a. Palatal pharyngeal paralysis of Avellis
 - b. The larynx is spared
- 4. Vagal autonomic functional deficits:
 - a. Esophageal, gastric and intestinal motility:
 - i. Esophageal motility:
 - 1. There is denervation hypersensitivity to cholinomimetic drugs (after vagotomy) in the lower 1/3 of the esophagus
 - 2. Achalasia:
 - a. Cholinergic medicines cause uncoordinated and painful contraction of the esophagus
 - ii. Gastric motility:
 - 1. Gastroparesis when the nerve is involved primarily with diabetes and amyloidosis
 - 2. Hyperactivity:
 - a. Following gastrojejunostomy and pyloroplasty:
 - i. Increased gastric emptying may cause early dumping syndrome that manifests with:
 - 1. Post-prandial weakness
 - 2. Lightheadedness
 - 3. Flushing
 - 4. Sweating
 - 5. Palpitation
 - 6. Tachycardia
 - ii. Later dumping syndrome:
 - 1. Insulin release following sugar ingestion
 - 2. Reactive hypoglycemia
 - 3. Associated diarrhea
 - iii. Intestinal motility
 - 1. Measured by evaluation of myenteric complexes (MMCs) intestinal motility physiology
 - 2. Absent MMC is caused by a neuropathy (Xth nerve) or Intestinal muscle impairment

- iv. Pancreatic polypeptide release:
 - 1. Is vagal nerve dependent
 - 2. There are increased levels with hypoglycemia
 - 3. Polypeptide level is a measure of abdominal vagal activity
 - 4. Autonomic failure with vagal denervation is associated with:
 - a. Decreased levels of pancreatic peptide levels with hypoglycemia
 - 5. Vagovagal syncope increases pancreatic peptide level

The Clinical Manifestations of Efferent Vagal Nerve Dysfunction

- 1. Cardiac:
 - a. The neural control of heart rate is primarily under vagal control
 - b. If the vagal nerve is blocked, the heart rate is 100–110 beats per minute
 - c. Diminished cardiac vagal tone occurs with:
 - i. Multiple system atrophy:
 - 1. Degeneration of the vagal nerve nuclei
 - 2. Primary autonomic failure:
 - a. Peripheral vagal nerve degeneration
 - 3. In diabetic autonomic failure:
 - a. The heart rate is initially high and then falls with progression of the illness
 - ii. Chronic autonomic failure:
 - 1. There is a decreased heart rate response to hyperventilation
 - 2. There is a similar response with polyneuropathies and autonomic failure secondary to alcohol
 - iii. There is vagal dysfunction earlier than sympathetic loss with:
 - 1. Alcoholism
 - 2. Non-alcoholic liver disease
 - 3. Cardiac transplantation
- 2. Impaired vagal innervation of the GI tract:
 - a. Primary autonomic failure:
 - i. Decreased gastric emptying
 - ii. Impaired pancreatic polypeptide response to hypoglycemia
 - b. Diabetic neuropathy:
 - i. Peripheral vagal degeneration
 - ii. Gastric dilation with reduced peristalsis and delayed emptying
 - iii. Nocturnal watery diarrhea
 - c. There is gastrointestinal atrophy with botulism
 - d. Pure cholinergic dysautonomia:
 - i. Putative immune-mediated
 - e. Destruction of vagally innervated intrinsic gut plexuses:
 - i. Achalasia
- 3. The esophageal sphincter degenerates and fails to relax

- a. Chagas disease:
 - i. Causes a cellular immune response
 - ii. Antiparasymphathetic neuronal IgG antibodies are detected
4. Vagal nerve hyperactivity:
 - a. Vagovagal syncope:
 - i. The sight or thought of a specific stimulus triggers the episode
 - ii. Bradycardia
 - iii. Loss of consciousness (usually for seconds)
 - b. Oculocardiac reflex:
 - i. Pressure or stimulation of the globe cause loss of consciousness
 - c. Vagal reflexes are often augmented by drugs and anesthetics
 - d. Glossopharyngeal neuralgia
 - i. Some sensory radiations are into the sensory innervation territory of cranial nerve X
 - e. Syncope triggered by swallowing (Charcot's syncope)
 - f. Carotid sinus hypersensitivity
 - g. Syncope during pleural aspiration
 - h. Increased vagal nerve activity with high cervical spinal cord lesions may be caused by associated:
 - i. Hypoxia
 - ii. Pulmonary emboli
 - iii. Acidemia
 - iv. Decreased cardiac sympathetic tone
 - v. Paralysis or depression of respiration:
 1. Decreased activation of the pulmonary stretch reflex which inhibits the vagus
 - vi. Tracheal intubation in quadriplegics enhances vagal activity
 - vii. Hyperactive diving reflex; cold water in the face causes bradycardia
5. Vagal afferent dysfunction:
 - a. Cough reflex:
 - i. Supplies sensation to the mucous membranes of the larynx and the tracheobronchial tree
 - ii. The afferent limb of the cough reflex
 - iii. Bilateral lesions cause aspiration
 - iv. Stimulation of the trachea and larynx in tetanus
 - v. Cause severe hypertension:
 1. Sympathetic overactivity
 2. Hypotension and bradycardia in tetraplegia
 - b. Superior laryngeal neuralgia:
 - i. Paroxysmal lancinating pain in the larynx
 - ii. Radiation of the pain is from the side of the thyroid
 - iii. Cartilage to the angle of the jaw; occasionally to the ear
 - iv. Trigger:
 1. Pressure over the skin that overlies the thyrohyoid membrane
 - c. Pulmonary vagal afferents:
 - i. Pulmonary stretch receptors increase their activity with inspiration
 - ii. Receptors in the chest wall for stretch are more active than pulmonary afferents
 - iii. Vagal lung irritant receptors:
 1. Respond to irritants, causes over- or underexpansion of the lung, emboli or congestion (reflexes may be neuropeptide mediated)
 - d. Cardiac receptors:
 - i. Activation of cardiac vagal receptors in the ventricle are:
 1. Mechanoreceptors (substance P (SP) is the putative cotransmitter)
 2. Induces bradycardia, hypotension and syncope
 - ii. Stimulated by forceful contraction:
 1. Aortic stenosis
 2. Tilt table stress
 3. Coronary arteriography

Syndromes Involving the Xth Nerve

1. Jugular foramen (Vernet):
 - a. IX, X, XI are involved
2. Schmidt:
 - a. X, XI (the venous component); the pars venosum in the jugular foramen
3. Hughlings-Jackson:
 - a. X, XI, XII are involved
4. Collet-Sicard:
 - a. IX, X, XI, XII are involved in the neck
5. Trunk vagal nerve lesions:
 - a. Occur from neck or thorax involvement of the nerve
 - b. Ipsilateral vocal cord paralysis and unilateral laryngeal anesthesia
 - c. Differential Diagnosis:
 - i. Tumor of the lung
 - ii. Internal carotid artery aneurysm
 - iii. Trauma (MVA, sports, falls)
 - iv. Enlarged lymph nodes
6. Superior laryngeal nerve:
 - a. The nerve is primarily a sensory branch:
 - i. Cricothyroid muscle weakness
 - ii. Minimal hoarseness and hypophonia
 - b. The usual causes are surgery, trauma or tumor
7. Recurrent laryngeal nerve:
 - a. Left is damaged > than the right
 - b. A longer course of the nerve
 - c. Unilateral paralysis is associated with:
 - i. Transient hoarseness
 - ii. Flaccid dysphoria:
 1. Harshness and breathiness of speech
 2. Decreased voice volume
 3. Inhalational stridor
 - iii. Plate pharyngeal function is normal
 - iv. Diplophonia
 1. Two pitch levels are produced by unequal frequency of vibration between the two vocal cords

- v. Semon's law:
 - 1. Abductor muscles of the larynx are affected first with a peripheral nerve injury
- vi. Differential diagnosis of recurrent laryngeal disorders:
 - 1. In approximately 25% the cause cannot be identified
 - 2. Aneurysms of the aortic arch or the subclavian artery
 - 3. Enlarged tracheobronchial lymph nodes
 - 4. Mediastinal tumor
 - 5. Thyroidectomy
 - 6. Cancer that extends behind the carotid sheath at C6:
 - a. There is usually a combination of deficits that include:
 - i. Recurrent laryngeal, vagal, phrenic nerves
 - ii. Preganglionic sympathetic fibers
 - iii. Constitutes the Rowland-Payne syndrome
- 8. Bilateral recurrent laryngeal nerve disorders are caused by:
 - a. Thyroidectomy
 - b. Carcinoma of the thyroid
 - c. Carcinoma of the esophagus
 - d. AIDP (the descending form)
 - e. Bilateral abductor muscle paralysis causes:
 - i. The vocal cords to be at or near the midline
 - ii. Approximation of the vocal cords
 - iii. A weak voice that is clear
 - iv. Inspiratory stridor
 - v. Dyspnea on exertion
- 9. Bilateral lesions that affect the superior laryngeal nerve:
 - a. Lesions above the nodose ganglion
 - b. Associated palatal and pharyngeal paralysis
 - c. The vocal cords are in the cadaveric position
 - d. Phonation is severely compromised
 - e. Vocal pitch cannot be changed
- 10. Rarer disorders and syndromes that affect the Xth nerve:
 - a. Wolfram syndrome:
 - i. Adductor spasm
 - ii. Sjögren's syndrome
 - iii. Tapia's syndrome
 - 1. Ipsilateral tongue and vocal cord weakness
 - iv. Shy-Drager disease:
 - 1. Cricoarytenoid muscle weakness (recurrent laryngeal nerve)
 - 2. Upper airway dysfunction
 - 3. Central respiratory dysfunction
 - 4. Sudden death during sleep
 - b. Isra's syndrome of the larynx
 - c. Idiopathic adductor weakness or spasm (spastic dysphonia)

- d. Arnold-Chiari (type 1) syndrome
- e. Laryngeal nerve neuralgia
- f. Swallow syncope (Charcot's syncope)

Neuropathology

- 1. Vascular disease:
 - a. Wallenberg's syndrome (nucleus ambiguus)
 - b. Hypertensive hemorrhage (rare < 1% of hypertensive)
 - c. Hemorrhages in the medulla
 - d. Cavernous hemangioma, AVM, and telangiectasia of the medulla
 - e. Aortic arch aneurysm
 - f. Recurrent laryngeal nerve paralysis
 - g. Dissection of the internal carotid artery
 - h. Left atrial distension (mitral stenosis) or congestive heart failure
- 2. Autoimmune failure disorders:
 - a. AIDP
 - b. Idiopathic
 - c. Neuralgia amyotrophica (may be viral)
 - d. Sarcoidosis
 - e. Myasthenia gravis
 - f. Cholinergic dysautonomia
- 3. Neuropathy:
 - a. Neuritic Beriberi
 - b. Sjögren's syndrome
 - c. AIDP
 - d. Drug-induced
 - e. SLE
 - f. HMSN type II (vocal cord involvement)
 - g. CMTHC
 - h. Vincristine
 - i. Alcohol
 - j. Idiopathic pachymeningitis (Ig4 by compression)
- 4. Trauma:
 - a. Insertion of nasogastric or endotracheal tubes
 - i. Injury to the posterior branch of the recurrent laryngeal nerve
 - ii. The posterior cricoarytenoid and interarytenoid muscles are affected
 - iii. The nerve is damaged behind the thyroid cartilage
 - b. Bilateral laryngeal nerve injury by thyroidectomy
 - c. Injury to the recurrent laryngeal nerve:
 - i. Distension of the esophagus that causes achalasia, may be bilateral and reversible
 - ii. Delayed post-operative palsy (neuropractic injury)
 - d. Severe neck trauma
 - e. Pharyngeal plexus injury:
 - i. The terminal branches of IX and X are involved
 - ii. Flexion extension neck injury
 - iii. Surgery (tonsillectomy)
- 5. Tumors of the Xth nerve:
 - a. Schwannoma
 - b. Chemodectoma
 - c. Chordoma

- d. Meningioma (jugular foramen)
- e. Carcinomatosis of the meninges
- f. Metastatic cancer primarily from the lung, breast and thyroid
- g. Recurrent laryngeal nerve:
 - i. Malignant mediastinal tumors
 - ii. Esophageal cancer
 - iii. Lymphoma
 - iv. Thyroid cancers
- 6. Idiopathic Xth nerve palsy:
 - a. Males are affected $2\times$ > females
 - b. Usually occurs in the 3rd decade
 - c. Comprise approximately 20% of Xth nerve lesions
 - d. The left side is more frequently affected than the right
- 7. Aberrant regeneration of cranial nerve IX and X:
 - a. Gustatory sweating:
 - i. Hyperhidrosis during eating
- 8. Damage to the lesser superficial petrosal nerve:
 - a. Aberrant post-ganglionic sympathetic nerve fibers are found in the auriculotemporal distribution (Frey's syndrome):
 - i. May be caused by neck operations, thoracotomy or T2 sympathectomy
 - ii. Gustatory piloerection may be associated with the hyperhidrosis from aberrant innervation of the sympathetic ganglia
- h. Corticobulbar fibers to the trapezius muscle are primarily crossed; there is an ipsilateral termination to the SCM (sternocleidomastoid muscle); it has been postulated that there is a decussation to the opposite pons and then a decussation back to terminate on the side of origin (the ipsilateral hemisphere). The second decussation is postulated to occur in the pons
- i. The sternal head of the SCM muscle may receive bilateral cortical innervation (IPSI > contralateral) and double decussates first in the pons and then back in the cervical cord; the clavicular head of the SCM muscle tilts the head ipsilaterally
- j. Corticobulbar innervation to the SCM is located dorsally in the brainstem tegmentum while fibers to the trapezius muscle are located in the ventral brainstem
- k. The trapezius muscle:
 - i. Retracts the head
 - ii. Raises the abducted arm above the horizontal
- l. Bilateral SCM weakness causes weakness of neck flexion and the head falls backwards
- m. Unilateral trapezius weakness from lesions of the spinal accessory nerve:
 - i. Affects upper trapezius fibers; lower fibers are supplied by the anterior roots of the cervical plexus:
 - 1. A droopy shoulder on the affected site
 - ii. The scapular is displaced down and laterally
 - iii. Paresis of shoulder elevation and retraction; the patient is unable to raise the arm above the horizontal, after it has been abducted (accomplished by the deltoid and the supraspinatus)
 - iv. Bilateral trapezius weakness causes decreased neck extension

The XIth Cranial Nerve

General Characteristics

1. Anatomy:
 - a. The XIth cranial nerve arises from the medulla, the internal ramus and from the cervical spinal cord, the external ramus
 - b. The cranial component arises from the caudal part of the nucleus ambiguus and exits the medulla laterally below the vagal roots
 - c. The external ramus or spinal component of the nerve arises from the first to sixth cervical segments of the dorsal lateral ventral horn. Cord segments C1 and C2 innervate the ipsilateral sternocleidomastoid muscle while the C3–C6 segments innervate the ipsilateral trapezius muscle
 - d. The cranial part of the nerve (origin is in the N ambiguous) supplies the pharynx and larynx
 - e. The cranial and spinal components of the nerve unite and exit the skull through the jugular foramen
 - f. The internal ramus (cranial portion) branches off to join the vagus and innervate the pharynx and larynx
 - g. The external ramus (spinal component) lies between the internal carotid artery and the jugular vein and in-

Clinical Manifestations

1. Weakness of the SCM or trapezius:
 - a. The usual lesions are of the spinal accessory nerve distal to its bifurcation
 - b. SCM and trapezius weakness of the same site:
 - i. A contralateral brainstem lesion
 - ii. An ipsilateral high cervical cord lesion that interrupts the second decussation from the pons
 - iii. A proximal accessory nerve lesion
 - c. SCM weakness with spared trapezius muscle function:
 - i. A lesion of the dorsal brainstem tegmentum (SCM is represented dorsally in the tegmentum)
 - ii. Lesions of the upper anterior cervical roots affect the SCM while C3 and C4 innervate the trapezius muscle
 - d. Nuclear lesions of XIth:

- i. Atrophy, weakness and fasciculation of the affected SCM and trapezius muscles

Neuropathology

1. Nuclear lesions are caused by:
 - a. Astrocytoma
 - b. Metastatic lesions
 - c. AVM or cavernous hemangioma
 - d. Syringobulbia
2. Lesions within the skull and the foramen magnum:
 - a. Syndromic associations:
 - i. Vernet's syndrome at the jugular foramen:
 1. Tumor
 2. Fracture
 3. Infection
 - b. Schmidt's syndrome (Xth and XIth)
 - c. Collet-Sicard (IXth, Xth, XIth, XIIth):
 - i. Retroparotid or retropharyngeal space:
 1. Infection
 2. Tumor
 - d. Garcin's syndrome:
 - i. All cranial nerves may be affected on one side:
 1. Tumor (lymphoma, leukemia)
 2. Following chemotherapy
 3. Diabetes mellitus
3. Lesions that affect the XIth nerve within the neck and shoulders:
 - a. Posterior triangle surgery (usually lymph node biopsy)
 - b. Internal jugular vein catheterization
 - c. Blunt trauma to the neck or shoulder
 - d. Radiation therapy (myokymia; hypertrophy)
 - e. Dislocation of the shoulder
 - f. Brachial plexus traction injury with an associated brachial plexus injury
 - g. Partial hanging:
 - i. Suicide attempt
 - h. Aberrant vessel:
 - i. Causes cervical dystonia from pressure on the nerve
 - i. Cervical cord tumor
4. Tumors:
 - a. Meningioma
 - b. Schwannoma
 - c. Chordoma (at the jugular foramen)
 - d. Glomus jugulare
 - e. Base of the skull metastases
 - f. Cervical syrinx with astrocytoma
 - g. Hemangioblastoma with a cervical syrinx
 - h. Nasopharyngeal cancer
5. Differential diagnosis of neck extensor weakness:
 - a. MG
 - b. Motor neuron disease:
 - i. Dropped head syndrome
 - ii. Polymyositis/dermatomyositis (usually the flexors are much weaker than the extensors)

Cranial Nerve XII

General Characteristics

1. Anatomy:
 - a. The hypoglossal nerve is the motor nerve of the tongue
 - b. Its origin is from a longitudinal column of neurons that extend in the paramedial medulla, beneath the hypoglossal trigone of the floor of the IVth ventricle, from the caudal medulla to the medullary pontine formation
 - c. There are two discrete axon bundles intracranially that join after the nerve exits the skull through the hypoglossal canal
 - d. The nerve passes over the internal and external carotid artery and lies beneath the digastric, stylohyoid and mylohyoid muscles
 - e. Muscular or lingual branches supply the intrinsic tongue muscles and the extrinsic hypoglossus, styloglossus, genioglossus and geniohyoid muscles
 - f. A descending hypoglossal ramus forms the ansa hypoglossi in the neck:
 - i. Fibers from C1–C3 cervical roots are associated
 - ii. The ansa hypoglossi innervates the infrahyoid, sternohyoid, omohyoid, sternothyroid, thyrohyoid and geniohyoid muscles
 - g. Corticobulbar fibers that innervate the genioglossus are crossed: the other tongue muscles have bilateral supranuclear innervation
 - h. The lateral movements of the non-protruded tongue are executed by intrinsic muscles. The patient cannot turn the tip of the tongue to the affected side

Clinical Manifestations

1. Abnormal tongue movements:
 - a. Oral buccal lingual dyskinesia
 - b. Athetosis
 - c. Palatal myoclonus (with associated tongue movement)
 - d. Trombone tongue (moves rhythmically in and out; usually from syphilis)
 - e. Galloping tongue:
 - i. Putative pontine lesion
 - ii. Episodic
 - iii. Rhythmic
 - iv. Involuntary
 - v. May spread to the head and neck
 - vi. Starts posteriorly in the midline
 - vii. Three per second waves
 - viii. Focal tongue contractions
 - ix. Continuous lingual myoclonus after head injury
 - f. Glossodynia:
 - i. Burning pain of the tongue and oral mucosa
 - ii. Occurs in middle aged and elderly patients

- g. Macroglossia:
 - i. Cerebral gigantism
 - ii. Syndromic
 - iii. Primary amyloidosis
 - iv. Acromegaly
 - v. Hypothyroidism
 - vi. Mucopolysaccharidosis

Neuropathology

1. Vascular disease:
 - a. Medial medullary syndrome (Dejerine's):
 - i. Infarction of the vertebral or anterior spinal artery
 - ii. Ipsilateral XIIth paresis (atrophy and fasciculations)
 - iii. Contralateral hemiplegia
 - iv. Contralateral loss of lemniscal sensation (proprioception and vibration sensibility)
 - v. May occur bilaterally (quadriplegia with facial sparing):
 1. Bilateral lower motor neuron tongue paralysis
 2. Loss of lemniscal sensation of all extremities
 3. The tongue may occasionally be spared in the anterior spinal artery syndrome
 - b. Rare XIIth nerve involvement from vertebral artery ectasia due to prolonged severe hypertension
 - c. AVM, cavernous hemangioma or telangiectasia
 - d. Carotid artery dissection with pseudoaneurysm that compresses the nerve in the neck
 - e. Dolichoectasia of the vertebral artery in the medulla
2. Trauma:
 - a. Blunt head traumas with fractures through the hypoglossal canal in the foramen magnum
 - b. Penetrating neck wounds:
 - i. Pseudoaneurysms of the cervical carotid artery
 - ii. Fistula of the carotid artery
 - c. Dental operative procedures
 - d. Subluxation of the odontoid process:
 - i. Rheumatoid arthritis
 - ii. Severe flexion injury of the neck
 - iii. Tearing of the alar and cruciate ligaments
 - e. Surgical neck trauma
3. Tumors Involving the XIIth Nerve:
 - a. Retroparotid tumors
 - b. Retropharyngeal tumors
 - c. Adenocarcinoma of the salivary gland
 - d. Squamous cell carcinoma of the tongue
 - e. Metastatic tumors (bronchial, thyroid and esophageal)
 - f. Hodgkin's and non-Hodgkin's lymphoma
 - g. Leukemia
 - h. Meningioma of the foramen magnum
 - i. Tumor of the occipital condyle:
 - i. Metastases to the posterior occipital condyle
 - ii. Ipsilateral XIIth nerve involvement

- iii. Mediastinal tumors
 - j. Metastasis to the ansa hypoglossi and cervical plexus:
 - i. Numb tongue-neck syndrome:
 1. Cervical plexus (C2–C4) involvement
 2. Vth neck mandibular branch involvement
4. Anterior horn cell peripheral nerve involvement:
 - a. Kennedy's disease
 - b. Bulbar ALS
 - c. Motor neuron disease
 - d. Myasthenia gravis
 - e. Lambert-Eaton syndrome
 - f. Diphtheritic neuropathy
 - g. AIDP
 - h. CIPD
 - i. EBV (infectious mononucleosis)
 - j. Polio
 - k. X-RT
 1. Machado-Joseph disease (Facial and lingual fasciculations)
 - m. Tongue fibrillations:
 - i. Motor neuron disease
 - ii. Hyperthyroidism
 - iii. Hyperparathyroidism
5. Intraparenchymal Lesions affecting the XIIth Nerve:
 - a. Syring (syringobulbia)
 - b. Tumor
 - c. Demyelinating disease
 - d. Autoimmune diseases
 - e. Paraneoplastic syndromes
 - f. Infections (rhombencephalitis)

Differential Diagnosis of Multiple Cranial Neuropathies

1. Neuromuscular Junction disease:
 - a. MG/Lambert-Eaton syndrome
 - b. Tetanus
 - c. Botulism
 - d. Snake envenomation
2. Autoimmune cranial neuropathies:
 - a. AIDP
 - b. CIDP
 - c. CM Fisher Variant of GBS (GD1b; GQ1b epitopes)
 - d. Descending AIDP (cervical-pharyngeal variant)
3. Tumor:
 - a. Carcinomatosis of the meninges
 - b. Leukemia
 - c. Lymphoma (Hodgkin's and non-Hodgkin's)
 - d. Garcin's syndrome:
 - i. All cranial nerves are involved on one side
 - ii. Nasopharyngeal cancer
 - e. Nasopharyngeal cancer (spread along the clivus)
 - f. Adenoid cystic carcinoma of the salivary gland ("sugar coats the nerves")
 - g. Cylindroma of the parotid gland

- h. Chromophobe adenoma:
 - i. Bilateral CN palsy with visual field loss
- i. Glomus jugulare or tympanicum tumors
- j. Melanoma (metastatic to the cranial nerves)
- k. Pinealoma (CSF pathways with metastases to the nerves)
- l. Cerebellopontine angle mass or tumor (compression of adjacent nerves)
- m. Retroparotid or retropharyngeal tumors (IXth, Xth, XIth, and XIIth are affected)
- n. Mucoepidermoid cancer
- 4. Vascular disease:
 - a. Intraparenchymal syndromes
 - b. Occlusion of the peripheral blood supply:
 - i. Inferolateral branch of the external carotid artery (IIIrd, IVth, VIth)
 - ii. Ascending pharyngeal artery (IXth, Xth, XIth), arises from the arch of the aorta
 - iii. Internal maxillary artery (Vth and VIIth)
 - iv. Carotid dissection in the neck (IXth, Xth, XIIth)
 - v. Chemotherapy:
 - 1. Internal carotid artery infusion with cisplatinum (IIIrd–VIth)
 - 2. External carotid artery infusion with cisplatinum (Vth–VIIth)
 - 3. Garcin's syndrome:
 - a. Nasopharyngeal cancer in conjunction with chemotherapy (all cranial nerves are affected on one side)
 - 4. Vincristine/Vinblastine (sympathetic and parasympathetic supply of the cranial nerves are affected)
 - vi. Infectious disease:
 - 1. Mycobacterium pneumonia
 - 2. Bartonella henselae (cat-scratch fever)
 - 3. Tuberculosis meningitis
 - 4. Cysticercosis
 - 5. Deep fungal meningitides:
 - a. Histoplasmosis
 - b. Cryptococcosis
 - c. Coccidiomycosis
 - 6. Chagas disease (trypanosoma cruzi)
 - 7. Syphilis
 - 8. Lyme's disease (Borrelia burgdorferi)
 - 9. Pseudomonas aeruginosa (malignant external otitis)
 - vii. Bone disease:
 - 1. Paget's disease
 - 2. Osteogenesis imperfecta
 - 3. Hyperostosis and osteosclerosis
 - 4. South African sclerostenosis
 - 5. Congenitally small posterior fossa and internal auditory canal
 - 6. Fibrous dysplasia
 - viii. Systemic disease:

- 1. Familial primary amyloidosis
- 2. Tolosa-Hunt syndrome (cavernous sinus involvement of IIIrd, IVth, VIth and first division of Vth)
- 3. Diabetes mellitus

Congenital Abnormalities of the Brainstem

- 1. Craniocervical junction abnormalities:
 - a. General characteristics:
 - i. The craniocervical congenital abnormalities include those of the occipital bone, the foramen magnum and the first two cervical vertebrae
 - ii. Clinical manifestations are:
 - 1. Neck Pain
 - 2. Syringomyelia
 - 3. Cerebellar deficits
 - 4. Lower cranial nerve palsy
 - 5. Spinal cord deficits
 - 6. Vertebrobasilar ischemia
 - iii. Neuropathology:
 - 1. Fusion of the atlas (C1) and the occipital bone:
 - a. The occipital cervical synostosis can be complete or incomplete; the complete synostosis is more frequent
 - 2. Multiple variations of partial assimilation involve any aspect of the atlanto-occipital articulation
 - 3. The anomaly is due to defective segmentation and separation of the most caudal sclerotome during the fourth week of gestation
 - 4. Most often the fusion occurs between the anterior atlas and the anterior margin of the foramen magnum
 - 5. Associated conditions include:
 - a. Spina bifida of the atlas
 - b. Occipital vertebra
 - c. Basilar invagination
 - d. Klippel-Feil syndrome
 - e. Arnold-Chiari syndrome

Clinical Manifestations

- 1. Spinal cord compression may occur if the center to posterior diameter of the foramen magnum behind the odontoid process is <19 mm, the normal is 28–38 (sagittal) and 25–40 mm in the transverse plane
- 2. Symptoms usually develop in the second decade of life
- 3. Spinal cord compression:
 - a. Neck pain and an abnormal head posture
 - b. Lower cranial nerve palsies with dysphagia and dysarthria
 - c. Long tract motor and sensory signs
 - d. Effects of vertebral artery compression

Basilar Invagination*General Characteristics*

1. Recent craniometric studies suggest that Chiari malformation and basilar invagination belong to a spectrum of malformations
2. The common characteristics of these malformations are:
 - a. Underdevelopment of the occipital bone
 - b. Cerebrospinal fluid and neural compression at the craniocervical junction
 - c. Basilar invagination type:
 - i. The tip of the odontoid process is within the foramen magnum
 - ii. Associated with craniovertebral instability
 - iii. In basilar invagination type II the dens is oriented towards the base of the skull and not toward the foramen magnum
 - iv. Basilar invagination may be primary from a congenital or developmental anomaly or secondary from bony softening and remodeling
 - d. Chamberlain's line:
 - i. Drawn from the back of the hard palate to the posterior lip of the foramen magnum
 - ii. The Chamberlain line violation (the most common method to identify BI, type I) varies between 1 and 6.6 mm
 - e. Basilar invagination has also been defined as upward bulging of the occipital condyles

Clinical Manifestations

1. A short neck
2. Compression of the ventral brainstem, lower cranial nerves and upper spinal cord with appropriate symptomatology
3. Axial cranial dislocation or instability may be the primary cause of all types of basilar invagination. Its clinical manifestations include:
 - a. Short neck with a low hairline
 - b. Web-shaped neck muscles
 - c. Torticollis
 - d. Decreased range of motion of the neck
 - e. Associated with bone fusion abnormalities
 - f. Instability of the atlantoaxial function is suggested by neck pain, spasm and restriction of neck movement. The instability is manifested by alteration of the alignment of the facets

Acute Basilar Invagination

1. Type A where the odontoid migrates superiorly and posteriorly that compresses the brain stem
 - a. Occurs in younger patients
 - b. Clinical symptoms are acute and severe
 - c. Other neural malformations are not prominent
 - d. There is progressive slippage of the facet of the atlas over the axis (similar to spondylosis thesis of the lumbosacral cord)

- e. Chronic atlantoaxial subluxation
 - i. Chronic spinal cord compression

Klippel-Feil Malformation*General Characteristics*

1. There is fusion of the upper cervical vertebrae of the atlas to the occipital bone
2. It is putatively caused by faulty segmentation of cervical vertebrae
3. It is often associated with Platybasia
4. General associations:
 - a. Sprengel's deformity
 - b. Renal agenesis
 - c. Aortic and cardiac anomalies
 - d. Sensorineural hearing loss
 - e. Cervical cord dysraphism
 - f. Diastematomyelia
 - g. Chiari malformations

Clinical Manifestations

1. The associated neurologic malformations may be responsible for the neurologic feature of the disorder
2. There is hypermobility of the adjacent unfused segments of the cervical spinal cord with degenerative changes
3. Patients may have a smaller cross-sectional spinal cord area
4. C2–C3 are the most common congenital fusion levels followed by C3–C4
5. A significant proportion of patients are asymptomatic

Platybasia*General Considerations*

1. Is a flattening of the skull base in which the angle formed by the intersection of the clivus and the plane of the anterior fossa is greater than 135°

Clinical Manifestations

1. May be asymptomatic
2. Platybasia increases the depth of the velopharynx
3. Associated with the 22q11.2 deletion syndrome
4. May cause enlargement of the nasopharyngeal space with decreased velopharyngeal closure

Abnormalities of the Odontoid Process*General Characteristics*

1. Congenital atlantoaxial dislocation (the atlas has slipped forward in relation to the axis)
2. In Morquio syndrome:
 - a. There is absence or severe hypoplasia of the odontoid process
 - b. In conjunction with laxity or redundancy of the cruciate, alar and apex ligament cause atlantoaxial subluxation
 - c. Spinal cord compression ensues with spastic quadriplegia

Chiari Malformations

General Characteristics

1. There are four types of Chiari malformation:
 - a. Type I:
 - i. Is the most common form of the malformation
 - ii. An extension of the cerebellar tonsils into the foramen magnum
 - b. Type II:
 - i. There is extension of both the cerebellar tonsils and a component of the brainstem into the foramen magnum
 - ii. The cerebellar veins may be partially absent
 - iii. Type II is often accompanied by a myelomeningocele and syrinx
 - iv. The medulla and pons are elongated and there may be a narrow aqueduct
 - c. Type III:
 - i. The cerebellum and brainstem protrude through the foramen magnum into the spinal cord
 - ii. An occipital encephalocele may be associated
 - d. Type IV:
 - i. Cerebellar hypoplasia in association with the other deficits
2. Associated neurologic features:
 - a. Meningomyelocele of the cervical cord
 - b. Syringomyelia of the cervical cord
 - c. Polymicrogyria
 - d. A tethered cord

Clinical Manifestations

1. Type I (without meningocele):
 - a. Symptoms may not develop until adolescence or adulthood
 - b. Headache that is exacerbated by any valsalva maneuver; C2 pain
 - c. Cerebellar ataxia
 - d. Spastic quadripareisis
 - e. Downbeating nystagmus
 - f. Signs and symptoms of an associated syringomyelia:
 - i. Segmental wasting
 - ii. Loss of pain and temperature sensibility of the hands
 - iii. Charcot joint of the shoulder
 - iv. Short neck
2. Type II (childhood):
 - a. Hydrocephalus
 - b. Lower cervical nerve involvement
 - c. Fasciculations of the tongue
 - d. Weakness of the sternocleidomastoid muscle with a consequent head lag and weakness of head
 - e. Bilateral VIth nerve palsy
 - f. Deafness

These patients may also have both basilar invagination and atlantoaxial instability and often develop scoliosis

Syringobulbia

1. Associated with Chiari I malformations as well as:
 - a. Thoracic scoliosis
 - b. Klippel-Feil anomaly
 - c. Platybasia
 - d. Basilar invagination
2. Clinical manifestations:
 - a. Depends on associated anomalies
 - b. Chiari associated developmental syrinx is associated with:
 - i. Symptoms often begin in early adult life
 - ii. The onset is often insidious and the cause may be irregularly progressive
 - iii. There can be an acute onset triggered by valsalva maneuvers
 - iv. Segmented weakness and atrophy of the hands and arms
 - v. Asymmetric loss of reflexes in the upper extremities
 - vi. Loss of pain and temperature sensibility in a "shawl" distribution of the neck, shoulders and arms. The sense of touch is preserved; with progression there is weakness and ataxia of the legs
 - vii. Associated kyphoscoliosis
 - viii. Rarely the dissociated sensory loss may be the only manifestation
 - ix. Rarely in patients with the Chiari I type malformation, the reflexes are retained and may be exaggerated in the upper and lower extremities
 - x. A Horner's syndrome may occur if the syrinx extends to involve the intermediolateral column at C8-T1
 - xi. Severe central pain develops in approximately 50% of patients

Brainstem Tumors in Adults

Diffuse Intrinsic Brainstem Glioma in Adults

1. General characteristics:
 - a. Account for 12% of adult gliomas
 - b. Molecular analysis (gain or loss of function):
 - i. Increased chromosome 1q gain, 9q gain and 11q loss compared to supratentorial high grade gliomas
 - ii. Histone gene mutations are frequent
2. Clinical manifestations:
 - a. Median survival is approximately 32 months
 - b. Several patterns of signs and symptoms:
 - i. Diffuse intrinsic low grade tumors
 1. Young adults
 2. Long clinical history
 3. Diffusely enlarged brainstem on MRI without contrast enhancement
 - c. Anaplastic transformation (appearance of contrast enhancement) and progressive growth

Malignant Glioma

1. Occur in elderly patients
2. Short clinical history
3. Contrast enhancement and necrosis is common on MRI
4. Median survival of 11.2 months

Focal Tectal Gliomas

1. Occur in less than 10% of brainstem gliomas in adults
2. Occur in young patients
3. Isolated hydrocephalus
4. Indolent course
5. Median survival of 10 years

Oligodendroglioma

1. General characteristics:
 - a. An extremely rare brainstem location in an adult patient
 - b. Deletion of chromosome 1p and/or 19q; tumors with these genetic markers have a more classic morphology
 - c. A significant percentage of low grade tumors progress to higher grade tumors
2. Clinical manifestations:
 - a. Only a few oligodendrogliomas have been described in the brainstem in adult patients
 - b. Possibly more aggressive than their supratentorial counterpart and present at an earlier age

Ependymoma

1. General characteristics:
 - a. This neoplasm is of neuroectodermal origin and arises from the neuroepithelial lining of the ventricles, central canal of the spinal cord, choroid plexus, white matter adjacent to a ventricular surface and the filum terminale
 - b. A frequent site of origin is the floor of the IVth ventricle
 - c. Posterior fossa ependymomas:
 - i. Exhibit a CpG island methylated phenotype
2. Clinical manifestations:
 - a. Symptoms of increased intracranial pressure
 - b. If there is cerebellar tonsillar herniation, a head tilt may be appreciated
 - c. The tumor may extend into the cerebellar pontine angle via the foramen of Luschka to produce facial weakness, hearing loss and dysphagia
 - d. If the tumor origin is in the area postrema or obex there may be severe nausea without other signs of increased intracranial pressure

Tumors of the Choroid Plexus**General Characteristics**

1. Comprise .4-.8% of all primary neoplasms of the brain
2. Approximately 70% of these tumors occur in childhood (children are less than 2 years of age)

3. 40% occur in the fourth ventricle; both IVth ventricle and CPA locations increase with age
4. Derive from ventricular ependymal cells
5. Genetic syndromes that predispose to the formation of choroid plexus papillomas include:
 - a. Li-Fraumeni (alterations of p 53)
 - b. Neurofibromatosis type II
 - c. Aicardi syndrome
 - d. Down syndrome
 - e. Von Hippel-Lindau disease
 - f. Germline mutations in p53 and hSNF5/IN1 (familial patients)

Clinical Manifestations

1. Hydrocephalus:
 - a. Obstruction of CSF flow or its overproduction from the papilloma
 - b. Increased intracranial pressure symptomatology:
 - c. Nausea and vomiting with IVth ventricular tumors
 - d. A new marker is 5-lipoxygenase
 - e. Papilloma may be differentiated from carcinoma by utilizing arterial spin labeling (the papilloma has much greater blood flow)

Medulloblastoma in Adults**General Characteristics**

1. These are very rare tumors in adults
2. The genetic profile in adults and children < 3 years of age includes:
 - a. Activation of the sonic hedgehog pathway
 - b. Mutations of the PTCH and SUFU genes
 - c. Loss of 9q and positivity for GLI1 and SFRP1
 - d. Commonly associated with desmoplastic histology

Clinical Manifestations

1. Present with a lateral cerebellar syndrome
2. Late relapses
3. Posterior fossa symptomatology

Neuronal and Glioneuronal Neoplasms**General Characteristics**

1. A diverse group of growths that include hamartoma-like tumors as well as cellular and locally aggressive neoplasms
2. It has been suggested that glioneuronal hamartomas and neoplasms have common precursors that diverge and differentiate separately
3. Glioneuronal tumors have these basic features:
 - a. They occur in children and young adults
 - b. They are less aggressive than the usual infiltrating astrocytoma
 - c. They have two phenotypically distinct cell populations

Gangliocytoma and Ganglioglioma

General Characteristics

1. The tumors are indolent and well circumscribed
2. They occur equally in both sexes
3. They are most common in the temporal lobe but occur throughout the neuraxis that includes:
 - a. Cerebellum
 - b. Optic chiasm
 - c. Hypothalamus
 - d. Brainstem
 - e. Spinal cord
 - f. Within the sella turcica

Clinical Manifestations

1. The most common presenting symptom is seizures
2. Focal neurologic signs and symptoms depending on location

Pineal Parenchymal Tumors

General Characteristics

1. Pineal parenchymal tumors are less common than those of germ cell origin and account for less than 1% of primitive CNS tumors
2. The WHO (World Health Organization) classifies the tumors into:
 - a. Pineocytoma (PC):
 - i. Well differentiated
 - b. Pineoblastoma:
 - i. Poorly differentiated
 - c. Mixed pineocytoma and pineoblastoma with intermediate differentiation
3. Pineocytoma:
 - a. Are slow growing pineal parenchymal neoplasms that are well differentiated

Clinical Manifestations

1. Headache, nausea and vomiting due to obstruction of the aqueduct and hydrocephalus
2. Vertical gaze paresis associated with pupillary defects and other cranial nerve paresis and hearing loss
3. Convergence spasm
4. Nystagmus retractorius
5. Late cerebellar ataxia from compression of the superior cerebellar peduncle

Meningioma

General Characteristics

1. The tumor arises from the arachnoid cap cell
2. The incidence is between 2–15 per 100,000 people and accounts for approximately 20–26% of primary intracranial neoplasms
3. Approximately 2% of benign meningiomas transform into malignant forms

4. Progression from benign to atypical forms is associated with mutations that cause losses in chromosomes 1p, 6q, 14q and 10q and gain from mutations on 1q, 9q, 12q, 5q, 17q, and 10q
5. The loss of the NF2 in chromosome 22 occurs in 40–70% of all meningiomas
6. Possibly the complete loss of merlin is the major mechanism for tumorigenesis

Clinical Manifestation

1. Depends on the location of the tumor and the compression of surrounding structures. Typical symptoms include:
 - a. Olfactory groove (Foster-Kennedy)
 - b. Optic nerve sheath (Schwalbe)
 - c. At the foramen magnum (most often severe spasticity)
 - d. The cerebellopontine angle
 - e. Sub- and dorsal frontal lobe (behavioral change)
 - f. Parasagittal (seizures, precipitate micturition)
 - g. Compression of cranial nerves
 - h. Parasellar
 - i. Planum sphenoidale
 - j. Intraventricular
 - k. En plaque (on the cortex)

Craniopharyngioma

General Characteristics

1. Benign epithelial neoplasms in the sellar area
2. Arise from the embryonic squamous cells of the hypophyseal duct
3. They have a bimodal age distribution; age 5–10 years and a second peak between 50 and 60 years
4. The adamantinomatous subtype affects children and the papillary form is seen in adults
5. Both types arise from Rathke's cleft
6. A subset of tumors has increased expression of insulin-like growth factor while approximately 30% express estrogen and progesterone receptors. Elevated beta human chorionic gonadotrophins levels are seen in the CFS

Clinical Manifestations

1. Symptoms of increased intracranial pressure
2. Hydrocephalus
3. Compression of the optic chiasm
4. Headache
5. Visual symptoms occur in 80% of adult patients
6. See-saw nystagmus occurs in 5–20% of patients
7. Endocrine Dysfunction:
 - a. Children present with short stature and delayed linear growth
 - b. Adolescents may have delayed or arrested puberty
 - c. Men have a loss of libido and women have secondary amenorrhea
 - d. Endocrine deficits include: 1. GH loss (75%); 2. luteinizing hormone or follicle stimulating hormone (40%); ACTH decrease (24%) and TSH (25%)

- e. Hyperprolactinemia occurs in 20% due to:
 - 1. Hypothalamic involvement
 - 2. Pituitary stalk compression
- f. Diabetes insipidus occurs in between 9% to 12% of patients:
 - i. Behavioral abnormalities:
 - 1. Mental status changes occur in approximately 25% of adults most often from tumor growth into the frontal lobes
 - 2. Tumor extension into the temporal lobe causes complex partial seizures or if it extends into the hippocampus memory deficits

Pituitary Adenoma

General Characteristics

- 1. Benign adenomas of the pituitary gland account for approximately 10% of operated intracranial tumors
- 2. Microadenomas are less than 10 mm in diameter

Clinical Manifestations

- 1. Visual field deficits, the most common of which is heteronymous superior quadrantic hemianopsia
- 2. The most common subtypes of adenomas are prolactinomas and non-functional tumors:
 - a. Prolactinomas may present with hypogonadism and galactorrhea
- 3. Chromophobe adenomas compress hormone-secreting cells and failure appears first in LH then thyroid and last adrenocortical levels
- 4. Pituitary apoplexy causes:
 - a. Sudden infrabrow headache
 - b. Visual field deficit
 - c. Cranial nerve III or VI dysfunction
 - d. MRI has demonstrated that the clinical sequelae are not as devastating as once thought

Vascular Disease

See: Headache of Idiopathic Intracranial Hypertension (IIH)

Demyelinating Disease

Multiple Sclerosis

General Characteristics

- 1. The current view is that multiple sclerosis is an inflammatory demyelinating disease of the central nervous system. The areas of the CNS particularly prone to demyelination are the optic nerve, spinal cord, periventricular white matter and subpial gray matter
- 2. There are three major clinical patterns of MS:
 - a. Relapsing remitting
 - b. Secondary progressive

c. Primary progressive

- 3. Approximately 85% of patients are initially relapsing remitting with episodes of neurologic deficit that alternates with periods of recovery. In 20–25 years of this pattern 60–70% of RRMS patients progress to a secondary progressive pattern that is manifest by progressive neurologic dysfunction. Approximately 10% of patients are primary progressive and demonstrate a relentless decline in neurologic function

Clinical Manifestations

- 1. Deficits are separate in space and time
- 2. The brainstem deficit of great significance is a unilateral or bilateral internuclear ophthalmoplegia
- 3. Almost all patients develop over time:
 - a. Some cognitive deficit
 - b. Corticospinal movement deficits
 - c. Optic atrophy
 - d. Cerebellar ataxia
 - e. Hyperactive reflexes
 - f. Sensory loss
 - g. Loss of abdominal reflexes

Neuropathology

- 1. Acute MS:
 - a. Break down of the blood-brain barrier
 - b. Multifocal inflammation
 - c. Demyelination
 - d. Reactive gliosis
 - e. Loss of oligodendrocytes
 - f. Axonal degeneration
- 2. Axonal loss in relapsing MS:
 - a. A dramatic increase of non-phosphorylated neurofilament epitopes
 - b. Transected axons occur with axonal ovoids that occur early in the disease course when inflammatory demyelination is active and continuous
 - c. Demyelinated axons are vulnerable to proteolytic enzymes, matrix metalloproteinases, cytokines, and free radicals that are released from glial and activated immune cells that also release glutamate
 - d. The transformation of RRMS to SPMS may be due to the inability of the brain to compensate for axonal loss
 - e. The pathology of chronic progressive lesions:
 - i. These lesions contain a hypocellular gliotic core and show no acute inflammation
- 3. Cortical demyelination in MS:
 - a. Cortical and deep gray matter demyelination are significant in MS
 - b. The two major types of cortical lesions in MS are leukocortical and subpial:
 - i. Axonal and dendritic transection are prominent in the cortical portion of active leukocortical lesions
 - ii. Subpial cortical lesions are the major component of cortical lesion load; they demonstrate myelin loss in layers 1–4 and may span several gyri

- iii. B-cell follicles in deep sulci may be essential in inducing subpial demyelination
- iv. Subpial lesions are abundant in both primary progressive and SPMS and rare in acute MS or RRMS
- v. B-cell follicles may lead to an increase in meningeal infiltrates that activate microglia which may accelerate disease progression

Laboratory Evaluation

1. Prominence of CSF IgG and Oligoclonal bands

Neuroimaging

1. The utilization of 7 Tesla MRI has demonstrated that demyelination in plaques surround veins
2. White matter demyelinating lesions may be seen throughout the CNS but are particularly prominent in the:
 - a. Optic nerve
 - b. Corpus callosum (Dawson's fingers)
 - c. Periventricularly
 - d. Spinal cord

Acute Disseminated Encephalomyelitis

General Characteristics

1. In general, ADEM is an immune-mediated inflammatory disorder of the CNS of children. It can be seen in adolescence and early adulthood:
 - a. The illness most often follows infection and rarely occurs after vaccination
 - b. It is most often transitory and self-limiting

Clinical Manifestations

1. Encephalopathy and focal neurological deficits 1–3 weeks after a viral illness
2. Neurologic deficits progress rapidly
3. Possibly 25% of patients develop MS within 5 years after the initial presentation
4. Confusion and headache are often prominent

Neuropathology

1. Immune-mediated inflammatory demyelinating disease of the brain and spinal cord

Laboratory Evaluation

1. MRI Evaluation:
 - a. T2/FLAIR sequence demonstrates diffuse, ill-defined, systemic irregular and patchy areas of homogeneous signal hypersensitivity
 - b. Involves both gray and white matter
 - c. All lesions appear to be of the same age
 - d. Approximately 50% involve infratentorial structures and 30% the spinal cord
2. The CSF may demonstrate increased IgG and Oligoclonal bands

Devic's Disease (Neuromyelitis Optica)

General Characteristics

1. Neuromyelitis optica is an immune-mediated chronic inflammatory disease of the CNS
2. Its prevalence is 1–4.4/100,000 people in the western world
3. Diagnostic criteria include:
 - a. One episode of optic neuritis and one episode of myelitis with two of the three supporting features:
 - i. Contiguous spinal cord MRI lesion that extends at least 3 or more vertebral segments
 - ii. Brain MRI that meets the diagnostic criteria for MS at onset
 - iii. NMO-IgG seropositive antibodies

Clinical Manifestations

1. The optic neuritis is more severe than in MS, the lesions are longer and recovery of vision is poor
2. AQP4-Ab may be seen in isolated LETM, recurrent or isolated optic neuritis and in brainstem encephalitis (in the diencephalon or the medulla)
3. Brainstem manifestation includes:
 - a. Intractable hiccups or vomiting
 - b. Narcolepsy
 - c. Neuroendocrine dysfunction
 - d. Posterior reversible encephalopathy (PRES)
4. In a significant number of patients simultaneous bilateral myelitis and bilateral optic neuritis manifests seriatim
5. Brainstem symptoms, neuropathic pain and painful tonic spasms are more frequent than in MS

Neuropathology

1. Inflammatory demyelination
2. AQP4-Ab directed against glial endfeet

Laboratory Evaluation

1. Serum AQP4 antibodies
 - a. Brainstem encephalitis presentations are less frequently positive as are patients who present with isolated NMO
2. A subset of patients may be AQP4-AB negative
3. Oligoclonal bands are positive in approximately 30% of patients
4. Concentration of IL-6 or its receptor may be elevated
5. Visual evoked potentials may be positive; prolonged P100 latencies occur in approximately 40% of patients and reduced amplitudes or absent potentials occur in 25%
6. MRI:
 - a. Predominantly, central spinal cord lesions extend over three or more vertebral segments. Most often, enhancing may last for months after the onset of symptoms
 - b. Enhancement may be patchy and inhomogeneous
 - c. T2/FLAIR hyperintensities are seen in 60% of patients in the cortex; often they are not oval shaped as is more typical of MS, they are often clinically silent

- d. Ultra high field MRI (7 Tesla):
 - i. NMO lesions in the brain are not characterized by central veins
 - ii. There are no cortical lesions
- e. Optical Coherence Tomography (OCT):
 - i. A single acute attack may demonstrate damage to the retinal nerve fiber layer (RNFL)

Clinically Isolated Syndrome

General Characteristics

1. Approximately 85% of patients with MS present with a single demyelinating event, a clinically isolated syndrome (CIS)

Clinical Manifestation

1. Lesions involve:
 - a. The optic nerves
 - b. Brain stem
 - c. Spinal cord

Neuropathology

1. Inflammatory demyelination
2. Axonal damage occurs in CIS

Laboratory Evaluation

1. Oligoclonal bands:
 - a. A medium impact prognostic factor for conversion to MS
- b. Chitinase 3-like 1 (in the CSF):
 - i. Has been validated on a biomarker for conversion to MS
- c. Elevated CD4/CD14 ratio:
 - i. Possibly rapid transition from CIS to multiple sclerosis
- d. MRI:
 - i. Clinically silent brain lesions are detected on MRI in 50 to 89% of patients with CIS at first clinical presentation
 - ii. 10 or more brain lesions increase the risk of conversion to MS

Acute Hemorrhagic Leukoencephalitis

General Characteristics

1. Acute hemorrhagic leukoencephalitis (Hurst's disease) is a fulminant demyelinating disease
2. Possibly a hyperacute variant of ADEM

Clinical Manifestations

1. Most patients die within one week from onset of symptoms
2. Seizures
3. Severe headache
4. Focal neurological deficits (in some patients predominantly left-sided)
5. Rapid progression to coma

Neuropathology

1. Hemorrhagic perivascular demyelination has been considered the histopathologic hallmark of acute hemorrhagic leukoencephalitis (AHL); pathology varies with the acuteness of the disease
2. Later AHL:
 - a. Perivascular demyelination; perivascular microglial foci and macrophages with myelin breakdown products
 - b. Hypertrophic reactive astrocytes may be seen in patients with a longer duration of illness; a case report demonstrates astrocytic involvement (swelling of end-feet and degeneration of processes)

Laboratory Evaluation

1. MRI:
 - a. Decreased apparent diffusion coefficient (ADC) consistent with cytotoxic edema may be present prior to blood-brain barrier disruption
 - b. Meningeal inflammation
 - c. Hemorrhages have been reported in frontal, temporal and parietal lobes (some mimicking herpes simplex infection)

Stiff Person Syndrome

General Characteristics

1. A condition of persistent and intense spasms of axial, proximal lower extremity and lumbar paraspinal muscles
2. A central origin of the process is supported by its disappearance during sleep, general anesthesia and proximal nerve block

Clinical Manifestations

1. Insidious onset usually in middle age
2. The spasms are at first intermittent and then become continuous
3. They are most acute axially and in the proximal leg muscles
4. Spasms are painful; increased by external stimuli
5. In severe disease the muscles of the face, respiration and swallowing are involved; there is no trismus which is a differential point against tetanus; eye muscles are rarely affected
6. The involved muscles may hypertrophy
7. Associated hyperlordosis
8. "Stiff limb" syndrome:
 - a. Only one limb is affected (leg)
 - b. The majority of patients have antibodies to glutamic acid decarboxylase (GAD)
 - c. In general, the disorder involves one leg and may spread to the opposite leg. The spasms and rigidity remain in the lower extremities
 - d. Jerking stiff person syndrome

Neuropathology

1. Primary autoimmune immunology

2. B-cell mediated clonal production of antibodies against presynaptic inhibitory epitopes in the enzyme glutamic acid decarboxylase

Laboratory Evaluation

1. EMG:
 - a. Continuous motor unit activity in the affected limbs
 - b. Elevated levels of anti-GAD antibodies, primarily the GAD-65 isoform are present in both the serum and CSF of 60–80% of SPS patients

Paraneoplastic Variant

General Characteristics

1. The paraneoplastic variant has a different clinical and antibody profile from other variants and the classic form of SPS

Clinical Manifestations

1. Predominantly or exclusively female patients
2. Mean age of 60 years
3. Account for approximately 5% of SPS patients
4. Patients are older than classic SPS patients
5. There is no associated diabetes
6. Cervical muscle involvement
7. May improve with cancer therapy
8. Sudden death from unexplained metabolic acidosis or autonomic mechanisms

Neuropathology

1. Underlying breast cancer
2. Interruption of inhibitory spinal circuits

Laboratory Evaluation

1. Antibodies to amphiphysin in the serum and CSF
2. EMG:
 - a. Continuous muscle unit activity

Progressive Encephalomyelitis with Rigidity and Myoclonus (PERM)

General Characteristics

1. A series of patients with PERM have been identified with glycine receptor (GlyR antibodies in the absence of GAD antibodies)
2. GlyR antibodies have also been identified in saccadic oscillations that include ocular flutter or opsoclonus and opsoclonus myoclonus hyperekplexia

Clinical Manifestations

1. Generalized increased stiffness
2. Brainstem signs
3. Trismus
4. Myoclonus
5. Spasms
6. Hyperekplexia

Neuropathology

1. Antibody (primarily to the glycine receptors) in brainstem nuclei and spinal cord inhibitory interneurons

Laboratory Evaluation

1. Antiglycine receptor (anti-GlyR) antibodies are detected primarily in PERM
2. A significant percentage have GA1 (anti-asialo-GM1) antibodies as well
3. Associated diseases include:
 - a. Thyroiditis
 - b. Diabetes mellitus
 - c. Thymoma and Addison's disease
 - d. Continuous muscle fiber activity

Differential Diagnosis of Stiff Person Syndrome

1. Tetanus
2. Isaacs' syndrome
3. Subacute Myoclonic spinal neuronitis

Central Pontine Myelinolysis (CPM)

General Characteristics

1. Osmotic myelinolysis is an acute demyelinating process most often confined to the central pons after too rapid correction of hyponatremia; extrapontine myelinolysis occurs

Clinical Manifestations

1. The disorder affects males and females equally, may be seen at any age
2. Approximately 50% of patients have been reported in the late stages of chronic alcoholism often associated with Wernicke's syndrome
3. In children it has frequently been reported in burn patients
4. Small lesions may be asymptomatic (2–3 mm)
5. Other patients may be in coma from metabolic or other causes
6. The classic patient with a large ventral pontine lesion demonstrates:
 - a. A flaccid paralysis of all extremities
 - b. Bulbar involvement with inability to chew, swallow or speak
 - c. Pupillary reflexes, extraocular movement, and facial sensation may be spared
 - d. Some patients may demonstrate nystagmus and failure of conjugate horizontal gaze
 - e. If patients survive, there is spasticity of the extremities and hyperactive reflexes
 - f. Some patients may recover but are left mute and paralyzed but with intact sensation and comprehension
 - g. Rarely patients may have confusion and stupor without signs of corticobulbar or pseudobulbar palsy

Neuropathology

1. There is a rim of intact myelin between the lesion and the surface of the pons

2. The lesion may extend posteriorly to the medial lemniscus and tegmental structures; rarely it may involve the midbrain but does not extend to the medulla
3. Extrapontine myelinolysis may involve the:
 - a. Internal capsule
 - b. Deep cerebral white matter
 - c. Corpus callosum
4. Destruction of myelin sheaths is the fundamental lesion
5. Rarely there are symmetric lesions in the thalamus, subthalamic nucleus, striatum, amygdala, lateral geniculate body and white matter of the cerebellar folia
6. Destruction of myelinated sheaths is initiated in the central pons
7. There is reactive gliosis but no sign of inflammation
8. Associated conditions include:
 - a. Marchiafava-Bignami disease
 - b. Chronic alcoholism
 - c. Severe immunosuppressed state
9. Prior to correction, the usual initial serum sodium is between 110–130 meq/L; in general, slowly corrected hyponatremia <12 meq/dl and severe hyponatremia does not cause the syndrome
10. In severely burned patients, hyponatremia was not prominent and it has been suggested that the disorder is one of rapidly rising osmolarity
 1. Upright posture and controls muscles of the trunk
 2. Important for sitting, standing and walking
2. The globosus and emboliformis nuclei:
 - a. Involved with segmental reflexes that control stability
 - b. Important for initiation of movement derived from somatosensory input (proprioception)
 - c. Stabilizes proximal joints that facilitate pyramidal movement (fractionated fine movements of the fingers)
 - d. Lesions cause:
 - i. Delayed check
 - ii. Truncal titubation
 - iii. Oscillation of the extremities (when held outstretched)
 - e. Facilitate the control of oscillations during the last 1/3 of movement
3. The dentate nucleus:
 - a. Important for the facility of fine movement by promoting their initiation, coordinating extensor and flexor musculature at multiple joints, and controlling the spatial coordination of hand and finger movements
 - b. Lesions of the nucleus and its connections cause postural kinetic tremor (rubral tremor). This tremor is distinguished by its increase of amplitude of oscillation that occurs at right angles to the line of movement

Cerebellum Diseases

Overview

1. The cerebellum is parcellated both anatomically and functionally into specific zones:
 - a. The archicerebellum consists of the flocculonodular lobe; it has major connections with the vestibular system and is important for control of eye movements
 - b. The paleocerebellum is composed of the vermis of the anterior lobe (lobules I–V) as well as the pyramid, uvula and paraflocculus. Most of its afferents are from the spinal cord. Its major functional role involves muscle tone and control of axial and limb movements
 - c. The neocerebellum comprises the middle vermis and the cerebellar hemispheres
 - d. The cerebellar cortex is divided into longitudinal zones that project to specific deep nuclei
 - i. The vermal zone projects to the fastigial nucleus
 - ii. The intermediate zone projects to the nucleus globosus and emboliformis
 - iii. The lateral zone projects to the dentate nucleus
 - e. The somatotopic representation within each nucleus is:
 - i. Caudal body parts are anterior; rostral parts posterior; the trunk is lateral and the limbs are medial
 - f. Functional anatomy of the nuclei:
 - i. Fastigial nucleus:
 1. Inferior cerebellar peduncle: this cerebellar peduncle is known as the restiform body and is most often clinically involved by vertebral artery and PICA strokes, as well as compression by tumors and inflammatory demyelination in autoimmune processes
 - a. It is comprised of:
 - i. The dorsal spinal cerebellar tract which carries proprioceptive and exteroceptive information from the lower extremity and trunk. Cervical spondylosis and spinal cord compressive disease, as well as the reviewed acquired and congenital diseases of the cervical cord affect this pathway. No patient with significant cervical stenosis from any cause can tandem walk well. It takes origin from Clarke's column of the spinal cord
 - ii. The cuneocerebellar tract that arises from the external arcuate nucleus and relays proprioceptive information from the arm and neck
 - iii. The vestibular cerebellar tract projects bilaterally to the flocculonodular lobe. A cause of cervically induced nystagmus
 - iv. The reticulocerebellar tracts from the lateral and paramedian nuclei of the brainstem are important for tone and cerebellar influences on segmental reflexes
 - v. The arcuate cerebellar tract that arises from the medullary arcuate nuclei

The Afferent and Efferent Cerebellar Pathways of Clinical Relevance

1. Inferior cerebellar peduncle: this cerebellar peduncle is known as the restiform body and is most often clinically involved by vertebral artery and PICA strokes, as well as compression by tumors and inflammatory demyelination in autoimmune processes
 - a. It is comprised of:
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- vi. The trigeminocerebellar tract which originates in the spinal and main sensory nuclei of cranial nerve V. This nucleus is important for migraine, head pain and facial reflexes (trigeminal reflexes i.e. light causing cough)
- vii. Olivocerebellar tract which carries afferents for somatic modalities from the contralateral inferior olivary nucleus
- viii. Efferent tracts in the inferior cerebellar peduncle
 - 1. Fastigobulbar tract and cerebellar reticular efferents

The Middle Cerebellar Peduncle (The Brachium Pontis)

Connects the cerebellum to the pons. Corticospinal fibers synapse in the pontine gray nuclei, project to the intermediate zone of the cerebellum and then to the cerebellar area of the ventrolateral nucleus of the thalamus. These afferents project to area 3b (of S1) of the somatosensory cortex and then to area 4 of the primary motor cortex.

Lesions of this distributed pathway cause Bruns' ataxia, that demonstrates specific signs at each level of involvement.

Pontine gray lesions cause hemiparesis and ataxia of the contralateral side. Descending corticospinal fibers are responsible for the weakness and are the origin of the middle cerebellar peduncle (MCP) which projects to the intermediate zone of the cerebellum and then to the VL of the thalamus and motor cortex. Lesions are a cause of ataxia of gait.

The lateral zone cerebellar lesions cause greater ataxia of the arm than the leg as does involvement of the MCP itself. Thalamic VL lesions that involve the cerebellar radiations are notable for "ataxia of stance". Disruption of cerebellar connections from 3b of S1 to area 4 cause Bruns' frontal lobe ataxia.

The Superior Cerebellar Peduncle (SCP)

The superior cerebellar peduncle is the primary connection of the cerebellum to the midbrain. The clinically most important efferent pathways are the dentatorubral and the dentatothalamic tracts which are the anatomic basis of the postural kinetic and cerebellar outflow tremors seen with both midbrain and thalamic lesions.

Specific Anatomically Based Cerebellar Syndromes

Rostral Vermis Syndrome

1. General characteristics:
 - a. Most often seen in alcoholic patients
 - b. The anterior and superior vermis are involved (the lingula, centrales and culmen)
2. Clinical manifestations:
 - a. "Martinet" gait; broad-based with predominance of truncal extensor tone
 - b. Minimal arm ataxia
 - c. Minimal or no dysarthria and extraocular muscle impairment
 - d. No heel to shin ataxia in recumbency

Caudal Vermis Syndrome

1. General characteristics:
 - a. The primary damage is to the floccular nodular lobe
 - b. Medulloblastoma is causative in children
 - c. Posterior fossa cysts and hemorrhages, Chiari malformations are the most common etiologies in adults
2. Clinical manifestations:
 - a. Titubation
 - b. Inability to sit with a straight back
 - c. Minimal limb ataxia
 - d. Extraocular movements:
 - i. Downbeating nystagmus accentuated in lateral gaze
 - ii. Rotary nystagmus
 - iii. Hypermetric saccades (overshoot of the fixation point)

Posterior Vermal Split Syndrome

1. General characteristics:
 - a. Caused by surgical disruption of parallel fibers that cross the midline cerebellar cortex
2. Clinical manifestations:
 - a. Severe difficulty in performing tandem gait
 - b. Normal regular gait, standing and unilateral hopping

Cerebellar Hemispheric Syndrome

1. General characteristics:
 - a. Usually caused by metastases, abscesses and infarction
 - b. The muscles controlled by the precentral cortex are primarily affected
2. Clinical manifestations:
 - a. Poor fine finger movement and incoordination of the ipsilateral extremity
 - b. Dysarthria

Pancerebellar Syndrome

1. General characteristics:
 - a. Signs and symptoms of all cerebellar syndromes
 - b. Caused by autoimmune and infectious processes, hypoglycemia, paraneoplastic syndromes (anti-Yo and anti-Hu), hyperthermia, solvents, toxins, hypothyroidism and inherited disorders
2. Clinical manifestations:
 - a. Bilateral signs of cerebellar dysfunction that are both appendicular and truncal
 - b. Extraocular movements are affected

Vascular Diseases of the Cerebellum

Differential Diagnosis of Major Cerebellar Arterial Disease

1. PICA:

- a. The distinguishing features of a PICA infarction are nausea, vomiting, hoarseness, rotary nystagmus to the side of the lesion and inability to walk out of proportion to other aspects of the stroke
- b. A pure medial branch occlusion may primarily involve the nucleus ambiguus
- c. A pure lateral branch occlusion may cause isolated vertigo and dysmetria without dysarthria or vestibular signs
- d. The sensory loss is to pain and temperature of the ipsilateral face and the contralateral body below the clavicle
2. AICA Infarction:
 - a. The hallmark of an AICA occlusion is sudden hearing loss, a peripheral ipsilateral paresis (VIIIth nerve), a branch of the artery supplies the nerve peripherally and ataxia of the ipsilateral arm greater than the leg
3. The Superior Cerebellar Artery
 - a. The superior cerebellar artery is frequently infarcted by an embolus to the top of the basilar artery
 - b. The occlusion is manifest by ataxia of the ipsilateral extremities, an ipsilateral IIIrd, IVth nuclear lesion and contralateral sensory loss. In top of the basilar occlusion, there is often various degrees of midbrain, thalamic, parietal and occasionally occipital symptomology from embolic infarction of the posterior cerebral artery
 - c. If the interpeduncular artery that arises from the top of the basilar artery is involved, there is involvement of the decussation of the superior cerebellar peduncle at the level of the inferior colliculus (Wernickinck's commissure) which causes ataxia of all extremities
 - d. Rarely, patients have a contralateral IVth nerve and hearing loss (crossed fibers of the lateral lemniscus)

Oculomotor Deficits of Superior Cerebellar Artery Occlusion

1. Contrapulsion of saccadic eye movements. These complex eye movements have three major components:
 - a. Horizontal saccades away from the lesion (to the contralateral side) on upgaze, which causes an oblique rotary nystagmus
 - b. Hypermetria of contralateral saccadic movement
 - c. Hypometria of ipsilateral saccades
2. These eye movements are opposite to those seen with PICA infarction
 - a. Lateral pulsion to the side of the lesion (torsional nystagmus on attempted upgaze)
 - b. Hypometric saccades to the contralateral side
3. Lateral branch occlusion of the superior cerebellar artery signs and symptoms:
 - a. Ipsilateral extremity dysmetria
 - b. Axial lateral pulsion (ipsilaterally)
 - c. Contrapulsion of saccades
 - d. Dysarthria
 - e. Clumsy hard dysarthria syndrome
4. Medial branch superior cerebellar artery syndrome:
 - a. Dysarthria and gait abnormalities are the most prominent feature
 - b. Rarely, ipsilateral appendicular dysmetria, extensor posturing of the trunk and all extremities

Autosomal Recessive Ataxias

Overview

The autosomal recessive cerebellar ataxias are a group of inherited neurodegenerative diseases characterized by cerebellar ataxia in association with spasticity, peripheral neuropathy, seizures, optic atrophy and other neurologic deficits. More than 20 causative genes have been defined. Most have a childhood onset although there are adult onset patients. Consanguinity is higher than in the general population but is not required. The parents are asymptomatic. In small families only one child may be affected. Approximately one thousand mutations that map to 60 different loci have been identified in cerebellar ataxias. Almost 50% of patients are genetically not defined and there are differences in prevalence and the phenotypic spectrum of ataxias among geographical areas.

Friedreich's Ataxia (Classic Phenotype)

1. General characteristics:
 - a. Friedreich's ataxia is the most common recessively inherited ataxia
 - b. Most patients have a GAA repeat expansion of the first intron of the frataxin gene:
 - i. Frataxin is a nuclear encoded mitochondrial protein
 - c. The FRDA gene maps to chromosome 9q13
 - d. Long normal alleles have 25–40 repeats in Caucasian patients
 - e. 95% of patients have homozygous GAA expansions in both alleles
2. Clinical manifestations:
 - a. The onset is less than 25 years of age (mean 11–12 years)
 - b. The presentation is usually gait ataxia
 - c. Rare presentations:
 - i. Cardiac dysfunction
 - ii. Scoliosis
 - d. Loss of position and vibration sensibility of the lower extremities occurs early
 - e. Dysarthria
 - f. Pes cavus
 - g. Bilateral Babinski sign
 - h. Square wave jerks are noted with eye movement recordings
 - i. Inability to walk supervenes between 10–15 years of illness
 - j. Loss of muscle strength is late
 - k. Flexor spasms
 - l. Dysphasia
 - m. Optic atrophy

- n. VIIIth nerve involvement (late)
- 3. Neuropathology:
 - a. Reduced levels of frataxin due to the GAA-triplet repeat in the first intron of the FXN gene:
 - i. Leads to decreased frataxin levels (mitochondrial protein) that controls:
 - 1. Fe^{2+} entry into the cell and/or sulfide production
 - 2. Is essential for the assembly and production of the Fe-S cluster during the initial stage of biogenesis
 - b. Degeneration of the dorsal root ganglia and spinal roots
 - c. Dorsal column degeneration
 - d. Spinocerebellar and corticospinal tract degeneration
 - e. Degeneration of the dentate nucleus
 - f. Associated medical conditions:
 - i. Cardiomyopathy
 - ii. Diabetes
 - iii. Pes cavus and scoliosis
 - g. Lack of frataxin causes iron accumulation and impaired electron transport in the respiratory chain of mitochondria that leads to free radical formation and oxidative stress
 - h. Disease causing alleles of the FXN gene have between 70–1500 GAA repeats; 50% of the variation in phenotype is due to GAA expansion size

Atypical Phenotype of Friedreich's Ataxia

- 1. General characteristics:
 - a. Onset is later than age 25; very late onset is after 40 years of age
 - b. Another variant is a classic onset with preservation of ankle jerks
 - i. Occurs in 5–13% of patients
 - ii. A small number of patients have a late onset with preserved ankle reflexes
 - c. Larger repeat size:
 - i. May be correlated with hypertrophic cardiomyopathy and diabetes mellitus
 - ii. Somatic mosaicism may account for variability of presentation

Early Onset Friedreich's Ataxia

- 1. General characteristics
 - a. Associated with two missense mutations that are located in the amino terminal half of the frataxin gene
 - b. Loss of function mutations (D12 G130V)
- 2. Clinical manifestations:
 - a. Atypical and milder clinical presentation
 - b. Early onset of a spastic gait
 - c. Slow disease progression
 - d. No dysarthria
 - e. Retained or brisk reflexes
 - f. Minimal cerebellar ataxia
 - g. Optic disk pallor:
 - i. More severe in compound heterozygotes than in expansion homozygotes

Interfamilial Phenotypic Variability in Friedreich's Ataxia Associated with the G130V Mutation in the FXN Gene

General Characteristics

- 1. GAA expansion on one allele and a point mutation on the other allele

Clinical Manifestations

- 1. Slow disease progression
 - a. Minimal or no ataxia
 - b. Increased deep tendon reflexes
 - c. Mild gait spasticity

Neuropathology

- 1. Loss of myelinated fibers in the peripheral nerves
- 2. Decrease of large dorsal root ganglia cells
- 3. Demyelination of the dorsal columns
- 4. Distal degeneration of the corticospinal pathways
- 5. Loss of neurons occurs in Purkinje cells, cranial nerve neurons and the dentate nucleus
- 6. The cerebellum and brainstem are less affected

Laboratory Evaluation

- 1. Genetic screening
 - a. MRI of the head and spinal cord
 - i. Atrophy of the upper cervical cord is greater than cerebellar atrophy
 - b. Electrodiagnosis:
 - i. Early decrease of SNAPs
 - ii. Central conduction defects occur later in the illness

Ataxia Telangiectasia

General Characteristics

- 1. Caused by mutations in the ATM gene that maps to chromosome 11q22-23; the mutations are gene splicing and missense
- 2. It is the second most common recessive ataxia; it has an incidence of 1 in 400,000 live births in the US. It is most frequent in ethnic groups with high consanguinity

Clinical Manifestations

- 1. Early onset with a progressive course
- 2. Ataxia may be appreciated by age 2
- 3. Usually patients are wheelchair bound by 12 years of age
- 4. The oculocutaneous telangiectasia occurs several years after disease onset
- 5. Oculomotor apraxia
- 6. Dysarthria
- 7. The patients are immunodeficient and suffer frequent sinopulmonary infections
- 8. Lymphoid cancer occurs in 1/3 of patients
- 9. Short stature and cognitive deficits are common
- 10. Choreaethetosis may be prominent
- 11. The telangiectasia usually develops by age 3–5, but a few patients may not develop them

12. Choreoathetosis and/or dystonia develop in 90% of patients
13. Patients develop a large fiber neuropathy by age 8 and lose deep tendon reflexes
14. Telangiectasia of the sclera may be seen at 1 year; it develops over upper extremity flexor creases
15. Patients in their late 20s and 30s develop progressive spinal muscular atrophy

Neuropathology

1. Mutations of the ATM gene is the cause of the disorder
2. The ATM protein functions as a DNA damage responsive kinase and coordinates DNA damage response pathways
3. Involved in DNA double strand break repair (DSBR)
4. AT cells are abnormally sensitive to ionizing radiation
5. The ATM protein is also associated with cell cycle checkpoint regulation
6. Lymphomas in AT patients in general are B-cell in type; the B-cell chronic lymphocytic leukemias are B-CLL
7. Defects in the immune system with thymic hypoplasia are seen in greater than 60% of patients
8. There is cerebellar atrophy, retinal and brain telangiectasia

Laboratory Evaluation

1. Serum IgG₂ and IgA levels are decreased; IgM can be decreased or normal; IgE levels may be decreased
2. Some patients have low T-cell levels with a poor response to nitrogen
3. In vitro ionizing radiation sensitivity of AT cells
4. MRI:
 - a. Decreased volume of the cerebellum by age 10; there is progressive cerebral atrophy
 - b. In adults with AT:
 - i. 60% of patients had intracerebral telangiectasia with multiple punctuate hemosiderin deposits. They appear to be similar to radiation induced telangiectasia
 - ii. White matter hyperintensities may be seen

Ataxia Telangiectasia Variants

General Characteristics

1. A heterogeneous group of patients that is characterized by later onset of clinical symptoms, slower progression of the disease and longer life span

Clinical Manifestations

1. Telangiectasia and immunological deficiencies may be absent while neurologic signs are present
2. Some patients have no cognitive dysfunction

Neuropathology

1. The genotype of the AT variants most often is compound heterozygous
 - a. A severe mutation coupled with a mild mutation
 - b. Some ATM protein is expressed with kinase activity

Laboratory Evaluation

1. MRI:
 - a. Some cerebellar atrophy
 - b. EMG evidence of peripheral neuropathy in some patients
 - c. 15% of patients have some ATM protein

Nijmegen Breakage Syndrome Variant of AT

General Characteristics

1. Similar cellular phenotype to AT

Clinical Manifestations

1. Microcephaly
2. Cognitive impairment
3. No ataxia or telangiectasia

Neuropathology

1. NBN gene that maps to chromosome 8q21 is mutated
2. Cells are radiosensitive and there are translocations of chromosome 7 and 14
3. Immunodeficiency
4. Predisposition to cancer

Laboratory Evaluation

1. Decreased immunoglobulins
2. Radiosensitive cells

Oculomotor Apraxia Type 1

General Characteristics

1. Ataxia with oculomotor apraxia type 1 is autosomal recessive and is caused by bi-allelic mutations in the APTX gene that maps to chromosome 9p21.1

Clinical Manifestations

1. Onset of ataxia is between 2–6 years of age
2. Oculomotor apraxia
 - a. Increased horizontal saccade latencies
 - b. Hypometria
3. Sensorimotor neuropathy
4. Choreic or dystonic movements
5. Distal atrophy (some patients)

Neuropathology

1. Immunoglobulins, alpha-fetoprotein, T- and B-lymphocyte markers and chromosome 7 and 14 are normal
2. APTX interacts with poly (ADP ribose) polymerase (PARP1) that is important in the detection of DNA single strand breaks
3. Increased DNA damage (experimental models)
4. Deficiency in base excision repair

Laboratory Evaluation

1. Some patients have low serum albumin with high serum cholesterol

2. A few patients have demonstrated alpha-fetoprotein (AFP)
3. EMG:
 - a. Sensory neuropathy in some patients; primary motor peripheral motor neuropathy in others; axonal neuropathy in 100% of patients

Oculomotor Apraxia Type 2

General Characteristics

1. The oculomotor apraxia type 2 is autosomal recessive; involves the SETX gene and maps to chromosome 9q34.13

Clinical Manifestations

1. Onset is between 11–22 years of age
2. Oculomotor apraxia is not universal in these patients
3. Different signs in various families include:
 - a. Progressive ataxia; gait difficulties
 - b. Dentatorubral tremor
 - c. Distal amyotrophy (consistent with a neural form of CMT)
 - d. Strabismus
 - e. Choreic movements
 - f. Head and postural tremor
 - g. Dysarthria and dysphagia
 - h. Cognitive impairment
 - i. Nystagmus and slow saccades
 - j. Absent deep tendon reflexes (legs)
 - k. Sensorimotor neuropathy

Neuropathology

1. The SETX gene that encodes a large DNA/RNA helicase protein
 - a. Defense against DNA damage
 - b. Processing RNAs
 - c. SETX gene mutations have been described in autosomal dominant juvenile amyotrophic lateral sclerosis and dominant tremor ataxia syndromes
2. Cerebellar atrophy

Laboratory Evaluation

1. Increased serum alpha-fetoprotein
2. EMG:
 - a. Axonal sensorimotor neuropathy
 - b. MRI:
 - i. Cerebellar atrophy
 - ii. Decreased brain volume

Ataxia-Telangiectasia-Like Disorder 1 (ATLD1)

General Characteristics

1. ATLD1 is caused by homozygous or compound heterozygous mutations in the MRE11A gene that maps to chromosome 11q21

Clinical Manifestations

1. Progressive cerebellar ataxia and oculomotor apraxia

2. Telangiectasia and immune deficits do not occur

Neuropathology

1. Mutations in MRE11A from two families demonstrated:
 - a. Chromosomal instability
 - b. Sensitivity to ionizing radiation
 - c. Defective induction of stress activated signal transduction pathways
 - d. Radio resistant DNA synthesis
 - e. MRE11-RAD50-NBS1 regulates the response to DNA double strand breaks
2. It has been suggested that 6% of AT patients have MRE11-A mutations

Laboratory Evaluation

1. Ionizing radiation sensitivity
2. Some patients demonstrate spontaneous chromosome aberrations in peripheral blood lymphocytes
3. MRI:
 - a. Most but not all patients demonstrate cerebellar atrophy
 - b. No increase of alpha-fetoprotein, and normal immunoglobulin concentrations in the serum

Ataxia-Oculomotor Apraxia Type 3 (AOA3)

General Characteristics

1. AOA3 is caused by a homozygous mutation in the P1K3R5 gene that maps to chromosome 17 p13.1

Clinical Manifestations (Described in One Family)

1. Onset of a progressive unsteady gait by age 14
2. Subsequent arm dysmetria and dysarthria; wheelchair bound by age 23
3. Extraocular movements:
 - a. Slowed saccadic eye movements
 - b. Eye lag with head thrust
 - c. Normal smooth pursuit
4. Distal atrophy and weakness affecting the lower extremities to a greater degree than the upper

Neuropathology

1. The receptor-regulated class 1-phosphoinositide 3-kinases
 - a. Phosphorylate the membrane lipid phosphatidylinositol 4,5-bisphosphate (PtdIns [4,5] P2 to PtdIns [3,4,5] P3)
 - b. This reaction recruits and activates cytosolic effectors that are pleiotropic for proliferation, survival or chemotaxis
 - c. P1K3R5 is a regulatory subunit of D13 kinase

Laboratory Evaluation

1. EMG:
 - a. Absent SNAPs in the lower extremities
 - b. Increased serum alpha-fetoprotein
 - c. MRI:
 - i. Atrophy of cerebellar folia and the vermis

Autosomal Recessive Ataxia with Oculomotor Apraxia from Mutations in PNKP (AOA4)

General Characteristics

1. Ataxia-oculomotor apraxia 4 is an autosomal recessive disorder due to homozygous mutations in the PNKP gene that maps to chromosome 19q13.33

Clinical Manifestations

1. Age at onset ranges from 1–9 years (4.3 ± 2.3 years). Dys-tonia may be the presenting sign but fluctuates during the course of the disease
2. Cerebellar ataxia
3. Oculomotor apraxia
4. Distal muscle wasting weakness that in some patients is associated with tetraplegia and short atrophic hands and feet
5. Loss of the ability to walk occurs between 7–21 years after the onset of the disease
6. Cognitive impairment occurs in a proportion of patients
7. Large fiber peripheral neuropathy

Neuropathology

1. PNKP is a modular protein
 - a. The FHA domain mediates interaction with scaffold proteins (XRCC1 and XRCC4)
 - b. A DNA phosphatase domain
 - c. A DNA kinase domain
 - i. The homozygous variant (pTh or 42 GLy) located in the kinase domain causes progressive cerebellar atrophy with microcephaly, early onset and intractable seizures with developmental delay (MCS7)
 - ii. Missense substitutions in the FHA and phosphatase domains are only associated with developmental syndromes
 - d. The different mutations cause:
 - i. Defects in phosphatase or kinase activity
 - ii. Conformational protein alterations that disrupt protein-protein interactions or substrate recognition
 - e. PNKP is a component of multiple pathways involved in DNA-damage repair of both single- and double-strand breaks
2. DNA strand breaks that cause non-ligable DNA ends are from:
 - a. Ionizing radiation
 - b. Oxidative stress
 - c. Some chemotherapeutic agents
 - d. A base excision repair (BER) intermediates
 - e. Two common dirty ends, 3^1-P and 5^1-OH are processed by PNKP

Laboratory Evaluation

1. Albumin may be low or normal and cholesterol levels are normal or elevated

2. Alpha-fetoprotein is elevated in some patients
3. MRI:
 - a. Cerebellar atrophy
4. EMG:
 - a. Sensorimotor peripheral neuropathy

Autosomal Recessive Spinocerebellar Ataxia with Axonal Neuropathy (SCAN1)

General Characteristics

1. SCAN1 is caused by a homozygous mutation in the tyrosyl DNA phosphodiesterase-1 gene (TDP1) that maps to chromosome 14q 32.11
2. CAN topoisomerase, glycosylases, methyltransferases and recombinases function by forming a transient covalent intermediate with DNA; if these DNA-processing enzymes become covalently trapped on the DNA they cause DNA damage
3. SCAN1 results from a failure to repair DNA-protein covalent complexes

Clinical Manifestations

1. Ataxia
2. Normal cognitive function
3. Severe axonal sensorimotor and motor neuropathy
4. Distal muscular atrophy
5. Pes cavus
6. Steppage gait

Neuropathology

1. TDP1 is sequestered into multiprotein single-strand break repair (SSBR) complexes by interaction with DNA ligase III-alpha which is deficient in this disorder:
 - a. It cleaves the phosphodiesterase bond between a covalently stalled topoisomerase and the 3^1 strand of DNA which has occurred from DNA damage

Laboratory Evaluation

1. Mild hypercholesterolemia and borderline hypoalbuminemia
2. EMG:
 - a. Axonal sensorimotor peripheral neuropathy
3. MRI:
 - a. Mild generalized brain atrophy

Hypogonadotropic Hypogonadism with Ataxia (Gordon Holmes Syndrome)

General Characteristics

1. Mutations in the RNF216 gene that maps to chromosome 7p22.1 alone or in combination with mutations in OTVD4 that maps to chromosome 4q31.21 cause this disorder
2. Both genes encode enzymes in the ubiquitin pathway

Clinical Manifestations

1. Abnormal sexual development

2. Neurologic symptoms develop in the 3rd decade
3. Dysarthria
4. Nystagmus is most often absent
5. Progressive gait and limb ataxia
6. Cognitive dysfunction to dementia
7. Distal muscle weakness
8. Choreoathetosis:
 - a. Dorsal column defects
 - b. Retinopathy
 - c. Increased reflexes

Neuropathology

1. Normosmic hypogonadotropic hypogonadism (nHH)
2. PNPLA 6:
 - a. Encodes neuropathy target esterase (NTE) which is a lysophospholipase:
 - i. Maintains intracellular phospholipid homeostasis that converts lysophosphatidylcholine to glycerophosphocholine
3. Experimental studies support that NTE-dependent alteration of phospholipid homeostasis in GHS causes neurodegeneration and impaired LH release from pituitary gonadotropes that cause nHH
4. Autopsy (1 patient)
 - a. Cerebellar and inferior olive atrophy
 - b. Ubiquitin immune reactive nuclear inclusions were present in 1–5% of the pyramidal neurons

Laboratory Evaluation

1. Low levels of LH
2. Diminished response to GnRH
3. MRI:
 - a. Cerebellar and cortical atrophy
 - b. Patchy areas of subcortical white matter hyperintensities on T₂-weighted sequences
4. RNF26aE4 ubiquitin ligase and OTUD4, a deubiquitinase may synergize to cause the disorder

STUB1 Mutation as a Cause of Gordon Holmes Syndrome

General Characteristics

1. Exome sequencing has demonstrated that mutations in the STUB1 gene may cause the Gordon Holmes syndrome
2. STUB1 (ST1P1 homologous and U-box containing protein1) maps to chromosome 16p13.3; its alternative name is CHiP (C terminus of HSC70-interacting protein)
3. CHiP functions as:
 - a. Co-chaperone and an E3 ubiquitin ligase
 - b. Couples protein folding and proteasome mediated degradation through its interaction with heat shock proteins (HSP 70)
 - c. It ubiquitinates the misfolded heat shock protein client proteins which targets them for proteasomal degradation

Clinical Manifestations

1. Dimorphic features:
 - a. Aged appearance
 - b. Long slender fingers, increased space between the 4th and 5th digits
 - c. Adducted thumbs
 - d. Slight facial dysmorphisms
2. Neurologic features:
 - a. Delayed development
 - b. Gait ataxia
 - c. Head tremor and postural tremor
 - d. Rarely, myokymia
 - e. Cerebellar ataxia
 - f. High frequency hearing loss

Neuropathology

1. The STUB1 gene encodes CHiP which is an E3 ubiquitin protein ligase
2. Putatively, the failure of CHiP to promote N-methyl-D-aspartate subunit degradation is the underlying mechanism of the disorder

Laboratory Evaluation

1. MRI:
 - a. Cerebellar hypoplasia
 - b. Thin posterior corpus callosum
 - c. Mild pontine atrophy
2. Diabetes (some patients)
3. Secondary infertility
4. Delayed menarche

AR Cerebellar Ataxias with Defects in Ubiquitin Genes

1. STUB1
2. PNPLA6
3. OTUD4

Boucher-Neuhäuser Syndrome

General Characteristics

1. Boucher-Neuhäuser and Gordon Holmes syndromes are allelic diseases caused by recessive PNPLA6 mutations

Clinical Manifestations

1. PNPLA6-associated spectrum of neurodegenerative disorders include major features:
 - a. Ataxia
 - b. Motor neuron disease:
 - i. Both upper motor neuron with or without lower motor involvement
2. Hypogonadism
3. Chorioretinal dystrophy
4. Spinocerebellar ataxia
5. Hypogonadotropic hypogonadism
6. Onset is usually during the first decade of life
7. Mild cognitive impairment in some patients

Neuropathology

1. Atrophic pons and cerebellum (some patients)
2. Diffuse atrophy of the cerebellar hemispheres
3. Atrophic changes of the retinal pigment epithelium and chorio capillaries
4. PNPLA6 proteins:
 - a. Patatin-like phospholipase domain containing proteins
 - b. Mutations affect the phospholipid domain (EST) and effects the de-esterification of phosphatidylcholine into fatty acids and glycerophosphocholine which is a precursor for the biosynthesis of acetylcholine (decreases its availability)
 - c. PNPLA6 also has lipophospholipase activity, and when mutated alters neuronal lipid metabolism

Laboratory Evaluation

1. Loss of LH with hypogonadotrophic hypogonadism
2. Ophthalmologic evaluation for chorioretinal dystrophy (majority of patients)
3. MRI:
 - a. Primarily cerebellar hemisphere atrophy
 - b. Pontocerebellar atrophy (some patients)

PMM2-CDG (Jaeken Syndrome)*General Characteristics*

1. Congenital disorders of glycosylation (CDGs) are:
 - a. Autosomal recessive and heterogeneous
 - b. Cause defective synthesis and processing of asparagine (N)-linked glycans (oligosaccharides) on glycoproteins which are important for metabolism, cell recognition, adhesion, migration and host defense
 - c. Jaeken syndrome is caused by:
 - i. Homozygous or compound heterozygous mutations in PMM2 that maps to chromosome 16p13
 - ii. Encodes phosphomannomutase 2

Clinical Manifestations

1. Usually presents in neonatal life with:
 - a. Encephalopathy
 - b. Axial hypotonia
 - c. Abnormal eye movements
 - d. Severe psychomotor retardation
 - e. Retinitis pigmentosa
 - f. Peripheral neuropathy
 - g. Esotropia
2. Abnormal distribution of subcutaneous fat
3. Nipple retraction
4. Hypogonadism
5. Adult PMM2 – CDG:
 - a. Adults may be mildly affected with:
 - i. Mild ataxic phenotypes
 - ii. Hand tremor
 - iii. Cognitive impairment
 - iv. Dysarthria and dysphonia

Neuropathology

1. Defect in processing of N-linked oligosaccharides or their defective synthesis
2. Cerebellar trophy

Laboratory Evaluation

1. MRI:
 - a. Cerebellar hemisphere and vermal atrophy

Autosomal Recessive Cerebellar Ataxia from Mutation of ADCK3*General Characteristics*

1. ADCK3 gene maps to chromosome 1q42.13
2. Encodes the homologue of Coq8
3. CoQ10:
 - a. Lipid soluble
 - b. Located in the inner mitochondrial membrane
 - c. Shuttles electrons derived from NADH ubiquinone oxidoreductase and succinic ubiquinone oxidoreductase to complex III (ubiquinol cytochrome C oxidoreductase)
 - d. Is an antioxidant by its action on pyrimidine metabolism
4. The ADCK3 gene:
 - a. Contains the AarF domain which is in the biosynthetic pathway for CoQ10
 - b. Encodes a mitochondrial protein which is a component of the electron transferring membrane protein complex

Clinical Manifestations

1. Disease onset is usually in infancy or early childhood
2. May present with pure cerebellar ataxia
3. Complex phenotype that includes:
 - a. Cerebellar ataxia
 - b. Cognitive dysfunction
 - c. Depression
 - d. Peripheral neuropathy
 - e. Strabismus
 - f. Exercise intolerance
 - g. Myoclonus (2 patients)

Neuropathology

1. CoQ10 deficiency causes defect in bioenergetics
2. Deficit of CoQ10 is best detected in fibroblasts although most often is demonstrated in muscle

Laboratory Evaluation

1. Increased serum lactate
2. Molecular genetic analysis
3. MRI:
 - a. Mild cerebellar atrophy

Adult-Onset Autosomal Recessive Ataxia from Mutations in the Lipofuscinosis Type 5 Gene*General Characteristics*

1. The CLN5 gene maps to chromosome 13q22.3
2. Most patients are of Finnish origin

Clinical Manifestation

1. 2 adult patients:
 - a. Presentation in the mid-fifties
 - b. Gait ataxia
 - c. Dysarthria
 - d. Cognitive decline (progressive)

Neuropathology

1. Bioinformatics and in vitro studies suggest that the mutation would affect ER-lysosome protein trafficking

Laboratory Evaluation

1. MRI:
 - a. Severe cerebellar atrophy most prevalent in the vermis
 - b. Marked cortical atrophy

ANO10 Gene Mutations and AR Cerebellar Ataxia*General Characteristics*

1. ANO10 gene mutations which map to chromosome 3P22.1 cause ARSCA10
2. Some patients have low levels of coenzyme Q10 and have some improvement with supplementation

Clinical Manifestations

1. Onset is teenage years or as a young adult
2. Gait instability
3. Dysarthria
4. Limb ataxia
5. Nystagmus:
 - a. Gaze-evoked downbeat
6. Hypermetric saccades
7. Hyperactive deep tendon reflexes

Neuropathology

1. Muscle biopsy:
 - a. Isolated complex III deficiency
 - b. Low CoQ10 levels

Laboratory Evaluation

1. MRI:
 - a. Marked cerebellar atrophy

SYT14 Mutation in Adult-Onset Autosomal Recessive Spinocerebellar Atrophy*General Characteristics*

1. SYT14 gene mutations cause an autosomal recessive cerebellar ataxia that maps to chromosome 1q32.2:
 - a. The gene encodes synaptotagmin 14 which is a membrane-trafficking protein

Clinical Manifestations

1. Japanese patients that demonstrated:
 - a. Childhood onset of cognitive difficulties
 - b. Gait instability
 - c. Dysphagia
 - d. Poor smooth pursuit eye movements
 - e. Limb and truncal ataxia

Neuropathology

1. Synaptotagmins are transmembrane proteins associated with exocytosis of secretory vesicles. It is located in Purkinje cells. Disruption of exocytosis mechanisms have been suggested as a pathogenic mechanism in this degeneration
2. In functional expression studies in COS1 cells, the mutant protein formed a reticular pattern in the cytoplasm rather than the normal perinuclear and submembranous intracellular localization. The abnormal protein was retained in the endoplasmic reticulum which is consistent with improper folding

Laboratory Evaluation

1. Mild atrophy of the cerebellar vermis and hemispheres; no apparent atrophy of the brainstem or the cerebral cortex

Rundataxin Recessive Cerebellar Ataxia*General Characteristics*

1. Rundataxin AR cerebellar ataxia is caused by mutations in the K1AA0226 gene that maps to chromosome 3q28-qter:
 - a. The gene encodes the protein rundataxin that may be associated with vesicular trafficking and signaling through its RUN domain and diacylglycerol binding-like domain

Clinical Manifestations

1. Three siblings from a consanguineous Saudi Arabian family have been studied
2. Childhood onset of gait abnormalities
3. Seizures
4. Cognitive dysfunction

Neuropathology

1. The K1AA0226 gene encodes the protein rubicon which is involved in vesicular trafficking and late endosome maturation. The neuropathology may be caused by defects of Rubicon which is a negative regulator of autophagy and endocytic trafficking

Laboratory Evaluation

1. MRI:
 - a. Cerebellar atrophy

SYNE1 Mutations in Autosomal Recessive Cerebellar Ataxia*General Characteristics*

1. The SYNE1 gene (Synaptic Nuclear Envelope Protein gene that maps to chromosome 6q25.1-q25.2)
 - a. Encodes a spectrin structural protein which links the plasma membrane to the actin cytoskeleton
 - b. The mutated protein is in the synaptic nuclear envelope protein 1

Clinical Manifestations

1. Gait ataxia
2. Dysarthria
3. Limb ataxia
4. Mild oculomotor deficits
5. Variable brainstem involvement

Neuropathology

1. The protein encoded is Nesprin-1:
 - a. Forms a linking network between organelles and the actin cytoskeleton which maintains subcellular spatial organization
 - b. The protein functions as a scaffold and linker both at the nuclear envelope and subcellular domains

Laboratory Evaluation

1. MRI:
 - a. Diffuse cerebellar atrophy

Autosomal Recessive Ataxia of Charlevoix-Saguenay*General Characteristics*

1. Charlevoix-Saguenay spastic ataxia is caused by homozygous or compound heterozygous mutations in the SACS gene that maps to chromosome 13q11. ARSACS is not limited to Quebec. There are over 100 mutations that have been defined worldwide

Clinical Manifestations

1. Early childhood onset of cerebellar ataxia
2. Pyramidal tract signs
3. Peripheral neuropathy
4. Increased visibility of retinal nerve fibers (myelinated)
5. Phenotypic spectrum:
 - a. No spasticity, extensor plantar sign or cerebellar ataxia but demonstrates a severe sensorimotor axonal demyelinating neuropathy
 - b. Patients may have cerebellar ataxia without neuropathy or pyramidal signs
 - c. Patients may not have retinal nerve fiber abnormalities
 - d. Patients may demonstrate pes cavus, hammer toes and scoliosis
 - e. Rarely, the disorder may be of late onset

Neuropathology

1. Arachnoid cyst and herniation of cerebellar tonsils in some patients suggest a developmental component to the disorder
2. The function of the SAC protein has not been defined
3. Alteration of the mitochondrial network has been noted in some patients

Laboratory Evaluation

1. MRI:
 - a. Atrophy of the superior cerebellar vermis

- b. An enlarged pons with T2 sequence hypointense stripes (corticospinal tract fibers)
- c. Thinning of the corpus callosum
- d. A rim of T2-hyperintensity surrounding the thalamus
- e. Diffusion tensor imaging:
 - i. Overrepresented transverse pontine fibers
 - ii. Microstructural alterations of the supratentorial white matter of the forceps, cingulum and the superior longitudinal fasciculus
- f. Bilateral cerebral parietal atrophy (subgroup of patients)
2. EMG:
 - a. Axonal demyelinating sensorimotor neuropathy

Autosomal Recessive Ataxia from Mutations in POLG*General Characteristics*

1. Mutations in the POLG gene cause mitochondrial recessive ataxia syndrome
2. The POLG gene maps to chromosome 15q26.1
3. Homozygous or compound heterozygous mutation in the nuclear-encoded DNA polymerase-gamma gene cause SANDO (sensory ataxic neuropathy, dysarthria and ophthalmoparesis)
4. Recessive mutations in POLG may also cause a progressive external ophthalmoplegia
5. The phenotype of SANDO varies widely among families and within affected families
6. POLG mutations cause a broad spectrum of mitochondrial disorders

Clinical Manifestations

1. SANDO:
 - a. Adult onset of sensory ataxic neuropathy
 - b. Dysarthria
 - c. Ophthalmoparesis
2. The phenotype may include:
 - a. Myopathy
 - b. Seizures
 - c. Sensorineural hearing loss

Neuropathology

1. Muscle biopsy:
 - a. Myopathic changes with ragged red fibers
 - b. Molecular analysis of muscle and nerve detects multiple mitochondrial DNA deletions
2. Sural nerve biopsy:
 - a. Loss of myelinated fibers and axonal degeneration

Laboratory Evaluation

1. MRI:
 - a. Bilateral thalamic lesions
 - b. High-intensity signals in the cerebellar white matter
2. EMG:
 - a. Sensory axonal neuropathy

Spinocerebellar Ataxia with Epilepsy*General Characteristics*

1. Four unrelated families with spinocerebellar ataxia and seizures have demonstrated POLG mutations

Clinical Manifestations

1. Childhood onset (5–17 years of age)
2. By twenty years of age patients have developed:
 - a. Cerebellar and sensory ataxia
 - b. Dysarthria
 - c. Progressive external ophthalmoplegia
 - i. Myoclonus
 - ii. Migraine
 - d. Status epilepticus developed in 3 patients; others suffered recurrent seizures

Neuropathology

1. Muscle biopsy:
 - a. COX-negative fibers
 - b. mtDNA deletions

Laboratory Evaluation

1. MRI:
 - a. Deep cerebellar white matter lesions
 - b. Thalamic lesions

Ataxia with Vitamin E Deficiency (AVED)*General Characteristics*

1. Ataxia with vitamin E deficiency is an autosomal recessive disorder from mutations in the alpha-tocopherol protein gene (TTPA gene) that maps to chromosome 8q13
2. Vitamin E deficiency is usually caused by defective uptake rather than reduced intake
3. Patients with vitamin E deficiency due to malabsorption most often present with neuropathy
4. Mutations in the TTPA gene cause a defect in the integration of vitamin E in VLDL and the transfer of vitamin E from the liver to the CNS

Clinical Manifestations

1. Onset is late childhood and adolescence but varies in different ethnic groups
2. Mutations that cause a truncated protein are associated with severe neurologic deficits while missense mutations are correlated with a milder phenotype
3. Slowly progressive cerebellar ataxia
4. Diminution of vibratory and proprioceptive sensibility
5. Retinitis pigmentosa
6. Dysarthria
7. Loss of deep tendon reflexes
8. Differential points versus Friedreich's ataxia:
 - a. In AVED:
 - i. Head titubation
 - ii. Retinopathy
 - iii. Dystonia

- b. In Friedreich's ataxia:
 - i. Cardiomyopathy
 - ii. Glucose intolerance
 - iii. Scoliosis
 - iv. Pes cavus

Neuropathology

1. Vitamin E is an essential dietary antioxidant
2. In experimental models, it has been demonstrated that vitamin E deficiency causes an increase in cerebellar oxidative stress (Increased protein nitrosylation); cellular atrophy and decreased branching of Purkinje cells

Laboratory Evaluation

1. Low serum levels of vitamin E

Rare AR Cerebellar Ataxias**Behr's Syndrome***General Characteristics*

1. The disorder has been reported with OPA1, OPA3 or C12ORF65 gene mutations

Clinical Manifestations

1. Onset in infancy
2. Progressive optic atrophy
3. Cerebellar ataxia
4. Pyramidal signs
5. Athetosis in some patients

Neuropathology

1. Occurs in patients with the C19ORF12 gene mutation (previously reported with a subtype of NBIA (neurological brain iron accumulation))
2. MRI evidence of basal ganglia iron deposition

Laboratory Evaluation

1. MRI:
 - a. Bilateral hypointense basal ganglia signals compatible with brain iron accumulation
2. In patients with OPA3 there may be excretion of 3-methylglutaconic acid in the urine

Marinesco-Sjögren Syndrome*General Characteristics*

1. Marinesco-Sjögren syndrome is caused by homozygous or compound heterozygous mutations in the SIL1 gene that maps to chromosome 5q31.2
2. There are overlapping features with CCFDN (congenital cataracts, facial dysmorphism and neuropathy) that is caused by mutation in the CTDP1 gene that maps to chromosome 18q23
3. The SIL1 gene:
 - a. Encodes an endoplasmic reticular cochaperone
 - b. SIL1 mutations are associated with the combination of cerebellar ataxia and chronic myopathy

Clinical Manifestations

1. Early onset ataxia
2. Cataracts
3. Short stature
4. Myopathy
5. Delayed sexual development
6. Cognitive impairment (Some patients are normal)
7. Some patients have skeletal abnormalities
8. Chronic nail infections
9. Strabismus
10. Skeletal deformities

Neuropathology

1. Muscle biopsy:
 - a. Neurogenic atrophy
2. Electron microscopy:
 - a. Increased lysosomes in fibroblasts
 - b. Autophagic vacuoles with myeloid bodies
3. An inbred family demonstrated:
 - a. Myopathic changes on muscle biopsy
4. Electron microscopy in other patients:
 - a. Enlarged lysosomes that contained whorled lamellar bodies
5. Cerebellar atrophy with both Purkinje and granular cell loss

Laboratory Evaluation

1. Hypogammaglobulinemia (some patients)
2. EMG:
 - a. Most often myopathic
3. Mildly elevated CK (some patients)

Wolfram Syndrome (DIDMOAD)*General Considerations*

1. Wolfram syndrome-1 is caused by mutations in the WFS1 gene that map to chromosome 4p16.1

Clinical Manifestations

1. Diabetes mellitus
2. Optic atrophy
3. Diabetes insipidus
4. Deafness (higher frequencies)
5. Additional manifestations include:
 - a. Ataxia
 - b. Renal dysfunction
 - c. Cognitive disability
 - d. Psychiatric illness
6. Autosomal dominant mutations in WFS1 have:
 - a. Low frequency non-syndromic deafness
 - b. Wolfram syndrome-like phenotype
 - c. Hearing loss with diabetes mellitus or optic atrophy

Neuropathology

1. The WFS1 protein is an endoplasmic reticulum (ER) protein that functions in ER calcium homeostasis and unfolded protein responses

2. The dysfunction of the protein may cause ER stress that leads to apoptosis
3. WFS1 protein functions in insulin secretory granule acidification
4. Mitochondrial deletions in some patients

Laboratory Evaluation

1. Insulin dependent diabetes mellitus
2. Hemoglobin concentration and water loss (osmolality changes) consistent with diabetes insipidus
3. Ophthalmologic evaluation for optic atrophy and audiometric evaluation for sensorineural hearing loss

Cerebrotendinous Xanthomatosis (CTX)*General Characteristics*

1. CTX is an autosomal recessive lipid storage disease
2. Caused by mutations in the CYP27A1 gene that maps to chromosome 2q33-qter
3. The prevalence is 25/100,000 of the general population

Clinical Manifestations (Neurologic)

1. The average age of onset is 35 years of age
2. Ataxia
3. Dystonia
4. Dementia
5. Seizures
6. Psychiatric disorder
7. Peripheral neuropathy
8. Myopathy

Non-Neurologic Manifestations

1. Tendon xanthomas
2. Childhood onset cataracts
3. Infantile onset diarrhea
4. Premature atherosclerosis
5. Osteoporosis
6. Respiratory insufficiency

Neuropathology

1. Patients with CTX have decreased bile acid synthesis due to impaired oxidation of the cholesterol side-chain:
 - a. Lack mitochondrial sterol 27-hydroxylase which is located on the inner mitochondrial membranes which is important in both classic and alternative bile acid synthetic pathways
2. Brain atrophy with generalized yellowish deposits in the choroid plexus and white matter
3. Multiple dispersed lipid crystal clefts and granulomatous lesions in the cerebellar hemispheres
4. Demyelination and perivascular accumulation of foamy macrophages in the globus pallidus
5. Demyelination, gliosis of the corticospinal tracts of the spinal cord
6. Nerve biopsy:
 - a. Primary axonal degeneration
 - b. Demyelination and remyelination

Laboratory Evaluation

1. Plasma cholestanol concentration five to 10 times normal (330 ± 30 ug/dl)
2. High urine bile alcohol concentration
3. Plasma bile alcohol concentration 500 to 1000 greater than normal
4. The differential laboratory features that distinguish CTX from other disorders with xanthomas include:
 - a. High plasma cholestanol concentration
 - b. Normal to low plasma cholesterol concentration
 - c. Decreased CDCA level
 - d. Increased levels of cholestanol and apolipoprotein B in the CSF
5. A biomarker for CTX is elevated 5-alpha-cholestanol concentration determined by gas chromatography-mass spectrometry (GC-MS)
6. Neuroimaging:
 - a. Brain MRI:
 - i. Cerebellar atrophy
 - ii. White matter hyperintensities
 - iii. Symmetric hyperintensities in the dentate nuclei
 - iv. Diffusely decreased gray and white matter volumes
 - b. Magnetic resonance spectroscopy:
 - i. Increased lactate and lipid peaks in FLAIR-hypointense lesions and diffuse decreases in N-acetyl aspartate (NAA) peaks
 - c. SPECT:
 - i. Regional cerebral blood flow changes
 - d. Positive VEP, SSEP, BAEP and NCV

Differential Diagnosis

1. Sitosterolemia:
 - a. A rare inherited sterol storage disease due to mutations in the adenosine triphosphate binding cassette (ABC) transporter genes ABCG5 and ABCG8 that map to chromosome 2p21
 - b. Increased absorption and decreased excretion of plant sterols are characteristic
 - c. Clinical manifestations:
 - i. Tuberous and tendinous xanthomas
 - ii. Premature atherosclerosis
 - iii. Hemolytic anemia
 - iv. Arthritis
 - v. Thrombocytopenic purpura
 - d. Laboratory evaluation:
 - i. High plasma phytosterol concentration
 - ii. Mildly elevated cholesterol concentrations
2. Dyslipidemia:
 - a. Familial hypercholesterolemia:
 - i. Is an AD disorder caused by a deficiency of low-density lipoprotein (LDL) receptor or in LDL related genes (ApoB and PCSK9):
 1. Elevated LDL cholesterol and triglyceride concentrations
 - b. Neuropathology:

- i. Decreased clearance of apolipoprotein B-containing lipoproteins which accumulate in different tissues
- c. Clinical manifestations:
 - i. Tendinous xanthomas on the backs of the hands, elbows, knees or xanthoma tuberosum
 - ii. Premature coronary artery disease
 - iii. Familial dysbetalipoproteinemia:
 1. Palmar crease xanthomas
 - iv. Familial hypercholesterolemia:
 1. Intertriginous xanthomas in children
 - v. Sitosterolemia and CTX:
 1. Tendinous xanthomas in adults
- d. Rare inborn errors of bile acid metabolism:
 - i. 7 alpha-hydroxylase deficiency
 - ii. 3 beta-hydroxy-C27-steroid oxidoreductase deficiency
 - iii. 2-methylacyl-CoA racemase deficiency

Differential Diagnosis of Recessive Syndromes with Prominent Ataxia

1. Cerebrotendinous xanthomatosis
2. Partial hypoxanthine guanine phosphoribosyl deficiency
3. Wilson's disease
4. Late-onset hexosaminidase deficiency
5. Refsum's disease
6. Adrenomyeloneuropathy
7. Mitochondrial DNA mutations

Autosomal Dominant Cerebellar Ataxia type 1*General Characteristics*

1. Type 1 autosomal dominant cerebellar ataxias are characterized by ataxia with additional neurologic signs that include:
 - a. Oculomotor dysfunction
 - b. Cognitive impairment
 - c. Pyramidal tract and extrapyramidal signs
 - d. Bulbar dysfunction
 - e. Spinal peripheral nerve abnormalities
2. The most prevalent type 1 ADCA is SCA3, followed by SCA2, SCA1 and SCA8. There is variable prevalence in different populations and ethnicities due to founder effects
3. The onset is in adulthood but presentation in childhood occurs. Gait, trunkal and limb ataxia are the most common cerebellar deficits and are often associated with nystagmus, saccadic abnormalities, and dysarthria
4. Clinical features are specific for each SCA type and the phenotype ranges from a pure cerebellar syndrome to spinal cord and peripheral nerve dysfunction, cognitive impairment, supranuclear ophthalmologic signs, and seizures
5. ADCAs can be divided into four subtypes according to their genetic pathomechanisms
 - a. Polyglutamine disorders due to expansion of CAG triplet repeats
 - b. Intronic disorders

- c. SCAs with the usual types of mutations
- d. SCAs with large duplications or deletions:
 - i. Polyglutamine disorders are more prevalent than the other types
 - ii. Polyglutamine disorders characteristic genetic features are:
 - 1. The translated protein of the expanded triplet gene has abnormally elongated glutamine repeats
 - 2. There is an inverse correlation between the size of the expansion and the onset, rate of progression, and clinical severity which is called anticipation. This feature is most striking in SCA7 and DRPLA (dentatorubral-pallidoluysian atrophy)
 - 3. In the CAG repeat disease, imprinting is frequent such that paternal transmission is more often associated with repeat expansions than maternal transmission of the expanded allele. The triplet repeat SCAs are 1, 2, 3, 6, 7, 17 and dentatorubral-pallidoluysian atrophy (DRPLA)
- 6. The most frequent intronic disease is exemplified by SCA8
 - a. It is caused by a bidirectional expansion of CTC/CAG which causes ribonucleic acid (RNA) mediated toxicity and polyglutamine tract formation
 - b. Imprinting of maternal transmission of the CTG repeat occurs in this disorder
 - c. Intronic disease occurs in SCA8, SCA12, SCA31 and SCA36
- 7. Conventional mutations in SCAs occur in SCA5, SCA11, SCA13, SCA14, SCA19/SCA23, SCA25, SCA26, SCA27, SCA28, SCA29 and SCA35
- 8. SCAs with large duplications or deletions occur in SCA15 and SCA20
- 9. The prevalence of ADCAs is approximately 1–5 people per 100,000 population worldwide

SCA1 ADCA1

General Characteristics

1. Is caused by mutations in the ATXN1 gene that maps to chromosome 6p22.3

Clinical Manifestations

1. Onset is usually in the 4th decade (4–74 years of age)
2. Dysarthria
3. Limb ataxia
4. Nystagmus and saccadic eye movement abnormalities
5. Upper motor neuron signs and Babinski sign are present
6. Involuntary choreiform movements
7. Spastic paraplegia is seen in some families

Neuropathology

1. Spinal cord demonstrates
 - a. Loss of anterior horn cells
 - b. Demyelination of spinocerebellar tracts; the dorsal columns

- c. Involvement of CN IX, X and XII
- d. Atrophy of the cerebellum, pons and olives
- e. Loss of Purkinje cells
- f. Atrophy of Clarke's column and the spinocerebellar pathways

Laboratory Evaluation

1. Genetic evaluation to demonstrate CAG repeat in ATXN1
2. MRI:
 - a. Cerebellar and brainstem atrophy
3. EMG:
 - a. Peripheral neuropathy

SCA2

General Characteristics

1. SCA2 is caused by mutations in the ATXN2 gene that maps to chromosome 12q24.2 that also demonstrates susceptibility for ALS

Clinical Manifestations

1. High inter- and intrafamily variability
2. Anticipation occurs
3. Onset is in the third or fourth decade
4. Slow saccades
5. Ophthalmoparesis
6. Chorea
7. Parkinsonism (some patients)
8. Myoclonus
9. Areflexia

Neuropathology

1. Affected patients have 32–79 repeats (normal is 13 to 31 CAG)
2. Cerebellar and olivary degeneration
3. Dying back axonopathy in some patients; dorsal root ganglion involvement in others
4. Sensorimotor cortex and frontal lobe atrophy

Laboratory Evaluation

1. MRI:
 - a. Cerebellar, pontine and olivary atrophy
 - b. fMRI:
 - i. Functional decrease in the cerebellar network and an increase in the default mode and frontoparietal networks
2. EMG:
 - a. Peripheral neuropathy
3. PET:
 - a. Decreased dopamine in the caudate and putamen of patients with Parkinsonism phenotype

SCA3

General Characteristics

1. Machado-Joseph disease is caused by CAG expansion of the ATXN3 gene that maps to chromosome 14q32.1

Clinical Manifestations

1. The most common SCA in some populations
2. Major phenotypes:
 - a. Type I
 - i. Ataxia, ophthalmoparesis
 - ii. Pyramidal signs
 - iii. Dystonia and other movement disorders that present in adolescence
 - b. Type II
 - i. Onset in middle adulthood
 - ii. Ataxia, spasticity and dystonia
 - c. Type III
 - i. Onset after 40 years of age
 - ii. Ophthalmoparesis
 - iii. Anterior horn cell disease with fasciculation, atrophy, and weakness
 - iv. Rare
 1. Parkinsonism and faciolingual myokymia
3. Some patients have impairment of temperature sensation that is generalized over the body
4. Bulging eyes; persistent stare

Neuropathology

1. The normal repeat length is 13–41; repeat lengths associated with disease are greater than 56
2. The SCA3 gene product is ataxin 3 which is a deubiquitinating enzyme; possible deficits of proteasomal degradation of ubiquitinated substrates
3. Ataxin-3 protein functions:
 - a. In the chaperone system
 - b. Ubiquitin-proteasome system
 - c. Aggregation-autophagy
 - i. These functions support its role in clearance of misfolded protein
 - ii. The pathogenic SCA3 (ataxin-3) impairs misfolded protein clearance that is dependent or independent of its deubiquitance activity which results in accumulation of misfolded proteins with progressive loss of neurons
4. Brain atrophy and neuronal loss occurs in:
 - a. Globus pallidus
 - b. Thalamic nuclei
 - c. Pontine nuclei
 - d. CN nuclei
 - e. Superior and middle cerebellar peduncles
 - f. Dentate nucleus
 - g. Clarke's column and spinocerebellar pathways
 - h. Anterior horn cells
 - i. Posterior column and DRGs
5. Relatively spared are:
 - a. The cerebral cortex
 - b. Corticospinal tracts
 - c. Cerebellar cortex
6. Diseased protein accumulates within inclusions inside the cell nuclei; they are ubiquitin positive spheres

Laboratory Evaluation

1. MRI:
 - a. Cerebellar and pontine atrophy
2. EMG:
 - a. Peripheral axonal neuropathy
3. Sleep studies:
 - a. REM sleep behavior disorder

SCA4*General Characteristics*

1. Most often referred to as hereditary ataxia with sensory neuronopathy
2. Kindreds are described in the USA of Scandinavian ethnicity
3. The mutation is unknown but is linked to chromosome 16q22.1. Anticipation has been seen in two kindreds

Clinical Manifestations

1. Onset is in middle-aged adults
2. Cerebellar ataxia at presentation
3. Pyramidal signs
4. Peripheral sensory loss (large fiber modalities)
5. Loss of deep tendon reflexes

Neuropathology

1. Not determined

Laboratory Evaluation

1. EMG
 - a. Absent sural sensory nerve action potentials

Spinocerebellar Ataxia 5 (SCA5)*General Characteristics*

1. Gene locus is xq25-q27.1

Clinical Manifestations

1. Norwegian ancestry
2. Cerebellar hypoplasia

SCA6*General Characteristics*

1. SCA6 is due to mutations in the CACNA1A gene that maps to chromosome 19p13.13
 - a. The gene encodes the pore forming $\alpha 1A$ subunit of P/Q type calcium channels (CaV2.1) that initiate synaptic transmission at fast synapses
 - b. It is due to a small repeat expansion in exon 47 in some of the isoforms of the CACNA1A gene as a polyglutamine sequence

Clinical Manifestations

1. Late onset
2. Primarily a pure cerebellar ataxia
3. The ataxia may be preceded by an episodic phase with dysarthria, nystagmus, and vertigo
4. Migraine is often associated
5. Usually a benign course

Neuropathology

1. The CACNA1A gene product is a membrane protein rather than a nuclear or cytoplasmic protein which is the norm for most polyglutamine disorders
2. Insoluble aggregates are rare and are located in the cytoplasm and rarely to the nucleus of Purkinje cells
3. The expanded alleles are usually 20 to 33 repeats (normal 4 to 8 repeats). The small repeats are more stable than in other polyglutamine disorders
4. A hypothesis for the pathogenesis of SCA6 disease is that a fragment of the CaV2.1 channel which is detected in cytosolic and nuclear areas may initiate the process

Laboratory Evaluation

1. MRI:
 - a. Minimal cerebellar atrophy
2. EMG:
 - a. Mixed axonal and demyelinating characteristics of a peripheral neuropathy in 22% of patients
 - b. SCA6 had less axonal damage than patients with SCA1 and 2

Spinocerebellar Ataxia 7 (SCA7)*General Characteristics*

1. SCA7 is caused by an expanded trinucleotide repeat in the ATXN7 gene that maps to chromosome 3p14.1. Anticipation occurs in some families
2. In the Harding classification this would be ADCA type II
3. In some families, there is more frequent paternal transmission
4. 34–36 CAG repeats are variably associated with disease manifestations (alleles with reduced penetrance). Approximately 75% of normal alleles have 10 CAG repeats

Clinical Manifestations

1. Progressive cerebellar ataxia
2. Dysarthria and dysphagia
3. Cone-rod and retinal dystrophy with central visual loss that may lead to blindness
4. Variable signs include:
 - a. Ophthalmoplegia
 - b. Pyramidal and extrapyramidal signs (brisk reflexes and spasticity)
 - c. Dementia
 - d. Large fiber modality sensory loss
5. The age at onset, degree of severity, and rate of progression vary among and between families
6. Infant and early childhood onset:
 - a. Muscle wasting, weakness and hypotonia
 - b. Rapid cerebellar and brainstem degeneration
 - c. Onset at or before adolescence causes retinal degeneration and blindness within a few years

Neuropathology

1. Neuronal loss, loss of myelinated fibers and gliosis in the cerebellum

2. Prominent Purkinje cell loss; neuronal loss in the inferior olive, dentate and pontine nuclei. Minimal neuronal loss in the cerebral cortex, basal ganglia and midbrain
3. Posterior column and spinocerebellar tract demyelination
4. Degeneration of photoreceptors, bipolar and granular retinal cells, especially in the foveal and parafoveal areas

Laboratory Evaluation

1. Molecular genetic testing; anticipation may be dramatic
2. Cone-rod retinal dystrophy that includes:
 - a. Abnormalities of rod and cone function by electroretinogram
 - b. Blue-yellow defect on color vision testing
 - c. Macular changes in late disease (fundoscopic evaluation)
3. MRI:
 - a. Cerebellar and pontine atrophy
4. EMG:
 - a. Sensorimotor peripheral neuropathy

Differential Diagnosis

1. Retinal degeneration is the distinguishing feature of SCA7
2. SCA1
 - a. A few patients have had visual loss
3. LHON can present with ataxia and visual loss
4. Infantile and childhood onset SCA7 may have features suggestive of lipid storage diseases and neuronal ceroid lipofuscinosis

SCA8*General Characteristics*

1. SCA8 is associated with mutations of the genes ATXN8 and ATXN80S that maps to chromosome 13q21
 - a. There is bidirectional transcription at the SCA8 locus that involves an expanded CTG trinucleotide/repeat in the ATXN80S gene and a complementary CAG repeat in the ATXN8 gene

Clinical Manifestations

1. Onset is in adulthood with cerebellar ataxia
2. Cognitive dysfunction occurs in approximately 70% of patients
3. Pyramidal and sensory signs occur in approximately 30% of patients
4. Dysexecutive and psychiatric deficits
5. Spastic and ataxic dysarthria
6. Diminished vibration sensibility
7. Nystagmus
8. Parkinsonism (rarely)

Neuropathology

1. Normal alleles contain 15–50 repeats; pathogenic alleles contain 71–1,300 repeats
2. Post-mortem evaluation (one patient)
 - a. Cerebellar atrophy with loss of Purkinje cells

- b. Loss of cells in the inferior olives
- c. Depigmentation of the substantia nigra
- 3. The expanded CTG repeat in the ATXN80S gene:
 - a. Is transcribed into an mRNA with an expanded CAG repeat that confers a toxic gain of function
- 4. The ATXN80S protein accumulates as ribonuclear inclusions (RNA foci) that colocalize with the RNA-binding protein MBNL1 in cerebellar cortical neurons
- 5. Loss of MBNL1 protein is suggested as contributing to SCA8 pathogenesis. Sequestration of MBNL1 in the abnormal RNA foci disrupts downstream splicing patterns

Laboratory Evaluation

- 1. MRI:
 - a. Atrophy of the vermis and cerebellar hemispheres
 - b. Cerebellar and pontine atrophy (some patients)

Rare Clinical Manifestation

- 1. Two patients have been described with a non-ataxic phenotype
 - a. Parkinsonism with dopaminergic responsiveness
 - b. ALS with cerebellar atrophy on brain MRI
- 2. Coexistence of ataxin 8 gene repeat expansion has been reported in MSA, HD, AD and SCA1, SCA2, SCA6, 16q-linked autosomal dominant cerebellar ataxia and Friedreich's ataxia
- 3. The SCA8 transcript protein has been reported to down-regulate Kelch-like protein by an antisense mechanism. KLHL is widely expressed in the brain but primarily in the Purkinje cell layer but also in the basal ganglia, spinal cord, hippocampus, and lateral entorhinal cortex
- 4. Kelch-like protein is postulated to be essential in these other CNS regions and its down regulation may underlie the non-ataxic phenotypes of SCA8

Spinocerebellar Ataxia 10 (SCA10)

General Characteristics

- 1. SCA10 is caused by a pentanucleotide repeat expansion (ATTCT) in the ATXN10 gene that maps to chromosome 22q13.31

Clinical Manifestations

- 1. Slow progressive cerebellar syndrome
- 2. Epilepsy (complex partial)
- 3. Mild pyramidal signs
- 4. The age of onset is between 18–45 years (mean 32.2 years)
- 5. Kindreds are primarily Mexican and Brazilian
- 6. Peripheral neuropathy
- 7. Psychological disorder

Neuropathology

- 1. The expanded ATTCT pentanucleotide repeat is in intron 9 of ATXN10 gene and ranges from 800 to 4500 repeats (normal is 10–29)

- 2. The translated RNA has been postulated to cause a gain of function mechanism that results in inactivation of proteins that are involved in RNA biogenesis
- 3. The spliced intron 9 RNA that contains the expanded AUUC repeat aggregates in CNS cells and sequesters RNP K. Sequestration of this protein triggers the translocation of protein kinase C delta (PKC δ) to mitochondria that leads to activation of caspase-3 and apoptosis

Laboratory Evaluation

- 1. EEG:
 - a. Complex partial seizure or generalized tonic/clonic seizure activity (approximately 80% of patients)
- 2. EMG:
 - a. Peripheral neuropathy (sensory in some patients)
- 3. MRI:
 - a. Mild cerebellar atrophy

Spinocerebellar Ataxia 12 (SCA12)

General Characteristics

- 1. SCA12 is caused by a CAG expansion at the 5' end of the gene encoding PP2R2B that maps to chromosome 5q31-5q32
- 2. PP2R2B encodes a brain-specific regulatory subunit of the protein phosphatase 2

Clinical Manifestations

- 1. Mild cerebellar tremor
- 2. Action tremor (hallmark)
- 3. Pyramidal and extrapyramidal signs
- 4. Dementia
- 5. The age at onset ranges from 8–55 years of age with most patients presenting in the fourth decade
- 6. Parkinsonian features (late)
- 7. Hyperreflexia (late)

Neuropathology

- 1. The CAG expansion is located within or slightly upstream from exon 7 at the 5' end of the gene
- 2. The number of repeats that cause the syndrome is between 55–78
- 3. The pathogenesis has been suggested to arise from a toxic effect of the RNA level
- 4. Autopsy (1 patient):
 - a. Atrophy of the cerebral cortex
 - b. Loss of Purkinje cells

Laboratory Evaluation

- 1. Targeted mutation analysis
- 2. MRI:
 - a. Cerebral and cerebellar atrophy
 - b. Cerebral cortex may be more involved than the cerebellar cortex (some patients)
 - c. Vermian atrophy is more prominent than that of the cerebellar cortex

Differential Diagnosis

1. SCA2, SCA3, SCA6 and DRPLA may have action tremors
2. Familial essential tremor
3. Ataxia with FGF 14 mutation has an action tremor but more severe cerebellar signs
4. Multiple system atrophy
5. Familial forms of Creutzfeldt-Jakob disease
6. SCA14 (has axial myoclonus)

Spinocerebellar Ataxia 13 (SCA13)*General Characteristics*

1. SCA13 is caused by two missense mutations in the KCN3 gene that maps to chromosome 19q13.3-q13.4
2. The gene encodes the K_v3.3 potassium channel

Clinical Manifestations

1. The phenotype is associated with an early onset ataxia that progresses slowly and may be associated with cognitive dysfunction and rare seizures
2. Adult onset progressive ataxia
3. Dysphagia, urinary urgency, and bradykinesia have been reported in patients older than 50 years of age

Neuropathology

1. Non-functional K_v3.3 channel
2. The mutant protein has reduced complex glycan adducts and is not trafficked correctly to the plasma membrane; it is retained in the Golgi apparatus

Laboratory Evaluation

1. Molecular genetic testing
2. MRI:
 - a. Mild to moderately severe cerebellar atrophy; most severe in the midline
 - b. The cerebral cortex and the brainstem are normal

Spinocerebellar Ataxia 14 (SCA14)*General Characteristics*

1. SCA14 is caused by missense mutations in the PRKCG gene that maps to chromosome 19q13.42
2. The gene encodes:
 - a. Protein kinase PKC γ (gamma) is a member of the PKC family of serine and threonine kinases. PKC γ (gamma) is expressed densely in Purkinje cells

Clinical Manifestations

1. Age of onset 10–70; mean 34 years
2. Slowly progressive cerebellar ataxia
3. Dysarthria
4. Nystagmus
5. Decrease of vibration sensibility
6. Cognitive impairment (some families)
7. Hyperreflexia

8. Parkinsonism characterized by rigidity and focal dystonia
9. Axial myoclonus
10. Facial myokymia
11. Choreic hand movements
12. Seizures
13. Sensory loss
14. Sensorineural hearing loss (2 patients)
15. Lifespan is normal

Neuropathology

1. PKC γ (gamma) is essential in signal transduction, cell differentiation, and synaptic transmission

Laboratory Evaluation

1. Molecular genetic testing
2. MRI:
 - a. Mild to moderately severe cerebellar atrophy that is primarily midline
 - b. There is no atrophy of the brainstem or cerebral cortex

Differential Diagnosis

1. Specific differential signs in this cerebellar ataxia are axial myoclonus and cognitive impairment
2. Progressive myoclonic epilepsy with ataxia from mutations in the PRICKLE1 gene
3. Myoclonus-dystonia from mutations in SGCE gene

Spinocerebellar Ataxia Type 15/16 (SCA15/16)*General Characteristics*

1. SCA15 is caused by heterozygous mutations and deletions in the inositol 4,5-triphosphate receptor (ITR1) gene that maps to chromosome 3p26.1

Clinical Manifestations

1. Slowly progressive ataxia
2. Postural and kinetic tremor
3. Mild hyperreflexia (without spasticity but rarely a Babinski sign). Additional features may include:
 - a. Gaze-evoked nystagmus in approximately 80% of patients
 - b. Approximately 50% of patients demonstrate an impaired vestibulo-ocular reflex that may produce movement induced oscillopsia
 - c. In less than 30% of patients, a postural head and/or truncal tremor
 - d. Upper limb postural tremor early in the course of the disorder
 - e. Orolingual dyskinesia, perioral myokymia and chorea may occur
 - f. Cognitive impairment

Neuropathology

1. Pure cerebellar atrophy: the brainstem is normal

Laboratory Evaluation

1. Atrophy of the rostral and dorsal vermis of the cerebellum; cerebellar hemispheres are normal or minimally atrophic
2. EMG:
 - a. Nerve conduction studies are most often normal; minor slowing of sural sensory and median motor conduction velocities have been detected in one Japanese kindred

Differential Diagnosis

1. The differential diagnosis is primarily that of a pure slowly progressive ataxia with an early tremor
2. The SCAs that are primarily cerebellar include SCA5, SCA6, SCA8, SCA11, SCA12, SCA14, SCA19/SCA22, SCA21, SCA23, SCA26, SCA27, SCA28 and SCA30
3. SCA8 and SCA30 are very similar to SCA15
4. Head tremor is suggestive of SCA15
5. SCA1, SCA2, SCA3 have a more rapidly progressive course
6. SCA2 has slow saccades that do not occur in SCA15, which has gaze-evoked nystagmus that is not seen in SCA2

Spinocerebellar Ataxia 17 (SCA17)*General Characteristics*

1. SCA17 is caused by a CAG/CAA repeat expansion in the TATA-box binding protein gene (TBP) that maps to chromosome 6q27
2. TBP encodes a general transcription initiation factor

Clinical Manifestations

1. Onset is from age 3 to 75 years (mean 34.6 years)
2. Ataxia is seen in 95% of patients
3. Dementia (approximately 90%)
4. Involuntary movements (approximately 70% of patients) that include:
 - a. Dystonia (blepharospasm, torticollis, writer's cramp, foot dystonia)
 - b. Chorea
 - c. Pyramidal signs
 - d. Rigidity
 - e. Patients with full penetrance develop neurologic and/or psychiatric signs and symptoms by age 50
 - f. Ataxia as well as psychiatric symptoms and disorders are early findings with the subsequent development of involuntary movements, Parkinsonism, dementia and pyramidal signs

Neuropathology

1. Atrophy of the stratum (most severe in the caudate nucleus) and the cerebellum
2. Neuronal loss in the Purkinje cell layer, striatum, and the cerebral cortex (some patients)
3. Diffuse labeling of polyglutamine (polyQ) tracts in the neuronal nucleoplasm

Laboratory Evaluation

1. MRI:
 - a. Variable atrophy of the cerebrum, brainstem, and cerebellum
2. Molecular genetic testing:
 - a. Penetrance of alleles of 41–44 repeats occurs in approximately 50% of patients; 45–48 repeats occur in greater than 80% of patients

Differential Diagnosis

1. DRPLA causes ataxia, choreoathetosis and dementia in adults
2. Huntington's disease
3. TBP alleles > than 45 CAG/CAA repeats occur in a HD-like phenotype (HDL-4)
4. One patient resembled MSA with ataxia, autonomic dysfunction, Parkinsonism, supranuclear palsy and cognitive impairment

Spinocerebellar Ataxia 18 (SCA18)*General Characteristics*

1. SCA18 is caused by mutations in the interferon related developmental regulator 1 gene (IFRD1) that maps to chromosome 7q22-q32

Clinical Manifestations

1. The disorder does not clearly fall into either the SCA or hereditary sensory neuropathy categories; it has also been designated sensory/motor neuropathy with ataxia (SMNA)
2. In the large five-generation American family studied, there was variable expressivity and severity of signs and symptoms
3. Peripheral sensory loss may be the initial symptom
4. Onset is usually in the second and third decades of life (13–27 years of age)
5. Gait difficulty
6. Dysmetria
7. Hyporeflexia
8. Muscle weakness and atrophy
9. Decreased large fiber sensory modality loss (proprioception and vibration sensibility)
10. Pes cavus

Neuropathology

1. Muscle biopsy:
 - a. Neurogenic atrophy
2. Axonal sensory neuropathy
3. High levels of IFRD1 are expressed in the brain, spinal cord, and dorsal root ganglia
4. In the nucleus the protein acts as a transcriptional corepressor and interacts with proteins of the SIN3 histone deacetylase complex
5. Genes in the NGF-IFRD1 pathway have roles in the neuropathy

Laboratory Evaluation

1. MRI
 - a. Mild cerebellar atrophy
2. EMG:
 - a. Axonal motor/sensory neuropathy

Spinocerebellar Ataxia 19/22*General Characteristics*

1. SCA19/22 is caused by loss of function in the KCND3 (potassium voltage-gated channel, shal-related subfamily, member 3) that maps to chromosome 1p13.2
2. KCND3 encodes the voltage-gated potassium channel Kv4.3, a membrane protein
3. The Kv4.3 is rapidly activated, and inactivates in response to membrane depolarization that generates the A-type potassium currents
4. The Kv4.3 channel controls action potential repolarization and frequency of firing

Clinical Manifestations

1. Onset is variable but most patients develop disease between 10–55 years of age
2. Mild cerebellar atrophy
3. Cognitive impairment
4. Myoclonus
5. Postural tremor
6. Seizures (one patient)
7. Peripheral neuropathy
8. Hyperreflexia
9. Cogwheel rigidity (1 family)

Neuropathology

1. Atrophy of the anterior vermis is greater than that of the cerebellar hemisphere
2. Loss of Purkinje cells
3. Degeneration and atrophy of both the molecular and internal granular layers
4. Purkinje cells stain for KCND

Laboratory Evaluation

1. MRI: Mild cerebellar atrophy

Spinocerebellar Ataxia 22*General Characteristics*

1. Studies of a four generation Han Chinese family with ataxia
2. Mutation is in chromosome 1p21-q23; thought to be the same locus as noted for SCA19

Clinical Manifestations

1. Mild cerebellar ataxia
2. Onset is between 35–40 years
3. Nystagmus
4. Decreased smooth pursuit extraocular movements
5. Decreased reflexes

Neuropathology

1. KNCA1 (encodes Kv1.1), KCNC3 (encodes Kv3.3) and KCND3 (encodes Kv4.3) (all are voltage-gated potassium channel genes) cause cerebellar degeneration and ataxia
2. Neuronal excitability appears to be important in the survival of cerebellar neurons

Laboratory Evaluation

1. MRI: Mild cerebellar atrophy

Spinocerebellar Ataxia 20 (SCA20)*General Characteristics*

1. The gene locus for SCA20 is within the pericentromeric region of chromosome 11q12
2. A 260-Kb duplication of 11q12.2-11q12.3 has been defined in the Australian index family

Clinical Manifestations

1. Onset between 19–64 years of age
2. Presents with dysarthria without ataxia, which may start abruptly or subacutely
3. It may be combined with adductor dysphonia
4. Palatal tremor (~66% of patients)
5. Hypermetric horizontal saccades (without nystagmus or vestibulo-ocular dysfunction)
6. Mild hyperreflexia
7. Postural arm tremor with or without head tremor
8. Portuguese families reported with spasmodic coughing episodes

Neuropathology

1. No autopsy material reported

Laboratory Evaluation

1. CT evaluation
 - a. Dentate calcification without pallidal calcification (<3 years from onset)
2. MRI:
 - a. Mild to moderate pancerebellar atrophy
 - b. Low dentate signal on T₁- and T₂-weighted sequences
 - c. Normal cortex and brainstem except for patients with palatal tremor who may demonstrate increased inferior olivary T₂ sequence signal
 - d. Axial proton density images demonstrate inferior olivary hypertrophy and low dentate nucleus signal
3. EMG: normal nerve conduction studies

Differential Diagnosis of Spinocerebellar Ataxia 20 (SCA20)

1. Distinctive features are early dentate calcification and palatal tremor
2. Dentate calcification affects .7% of the population >65 years if age; it is rarely seen in the absence of basal ganglia calcification. In SCA20 dentate calcification may appear in isolation

3. Hyperparathyroidism and pseudohypoparathyroidism have dentate and basal ganglia calcification. Hyperparathyroidism presents with proximal muscle aches, fatigue, tongue fibrillations and decreased reflexes (rarely increased)
4. Dentatorubral-pallidoluysian atrophy may have pallidal microcalcifications in the Haw river patient phenotype
5. Familial idiopathic basal ganglia calcification presents with cognitive function deficits and Parkinsonism rather than ataxia. Basal ganglia calcification, rather than that of the dentate nucleus, is predominant

Differential Diagnosis of Palatal Myoclonus

1. Vascular disease affecting Mollaret's triangle (acquired, not genetic)
2. In association with progressive ataxia in sporadic patients, possibly a unique syndrome
3. Multiple system atrophy of the cerebellar type (rare)
4. Early adult-onset Alexander disease, bulbar and spastic tetraparesis are associated
5. A dominant branchial myoclonus with ataxia (possibly a phenotypic variant of adult-onset Alexander disease)
6. There is overlap with spinocerebellar ataxia 5 (SCA5) and it is possible that they may be the same disease

Spinocerebellar Ataxia 21

General Characteristics

1. SCA21 is caused by a heterozygous mutation in the TMEM240 gene that maps to chromosome 1p36

Clinical Manifestations

1. The family studies are of a four generational French kindred (11 members)
2. Slowly progressive cerebellar ataxia
3. Mild cognitive impairment
4. Postural and/or resting tremor
5. Bradykinesia and rigidity
6. Parkinsonism was found to be not L-Dopa responsive
7. Age of onset is 17.4 years, earlier than for most ADCA Type I SCAs
8. Follow-up in the original French patients described and an addition of seven additional French families with SCA revealed:
 - a. Delayed psychomotor development from early childhood; frontal behavior symptom with later development
 - b. Mild to severe cognitive dysfunction
 - c. Gait ataxia and incoordination between 1–20 years of age
 - d. Additional signs include:
 - i. Dysarthria
 - ii. Dysgraphia
 - iii. Nystagmus
 - iv. Slow ocular saccades
 - v. Tremor
 - vi. Increased or decreased deep tendon reflexes and Babinski sign

Neuropathology (One Patient)

1. Mild loss of Purkinje cells in the cerebellar vermis
2. No intracellular inclusions

Laboratory Evaluation

1. MRI: Cerebellar atrophy (mild); some brainstem atrophy

Spinocerebellar Ataxia 23

General Characteristics

1. SCA23 is caused by missense mutations in the PDYN gene that maps to chromosome 20p13
2. The encoded protein is the precursor of dynorphin opioid peptides
3. PDYN mutations account for approximately .1% of European SCA patients

Clinical Manifestations

1. Late onset (43–56 years of age)
2. Gait ataxia
3. Limb ataxia
4. Dysarthria
5. Slow saccades
6. Ocular dysmetria
7. Decreased lower extremity vibration sensibility
8. Distal sensory neuropathy

Neuropathology (1 Patient)

1. Frontotemporal atrophy
2. Atrophy of the cerebellar vermis
3. Atrophy of the pons and spinal cord
4. Neuronal loss in the cerebellar vermis, dentate nuclei and inferior olives but not in the pons
5. Thinning of the cerebellopontine tracts
6. Demyelination of the posterior and lateral spinal cord columns

Laboratory Evaluation

1. MRI:
 - a. Generalized cerebral cortical and subcortical atrophy
 - b. Agenesis of the corpus callosum
 - c. Severe atrophy of the cerebellar vermis, pons and the inferior olivary nucleus

Spinocerebellar Ataxia 25

General Characteristics

1. SCA25 maps to chromosome 2p21-p13

Clinical Manifestations

1. Age at onset ranges from 17 months to 39 years (most are affected in childhood)
2. Cerebellar ataxia
3. Peripheral sensory neuropathy
4. Some patients suffered more cerebellar ataxia and less sensory neuropathy while the reverse occurred in other patients

5. Areflexia of the lower limbs
6. Variable manifestations include:
 - a. Gastrointestinal dysfunction with vomiting and abdominal pain; the digestive complaints are persistent in some patients
 - b. Scoliosis
 - c. Nocturia and urinary urgency

Neuropathology

1. Sural nerve biopsy: loss of myelinated fibers

Laboratory Evaluation

1. MRI: severe global cerebellar atrophy
2. EMG: sensory neuropathy

Spinocerebellar Ataxia 26

General Characteristics

1. SCA26 is caused by heterozygous mutations in the EEF2 gene that maps to chromosome 19p13.3
2. SCA26 is rare, with only one American family of Norwegian descent having been studied (23 affected members and 14 at-risk patients)

Clinical Manifestations

1. Age at onset is usually between 26–60 years (mean of 42 years) with no anticipation
2. Late-onset, slowly progressive cerebellar signs and symptoms
3. Impaired ocular pursuit and nystagmus

Neuropathology (Two Patients)

1. Significant loss of Purkinje cells with minimal or absent neuronal loss in other brain areas
2. Entire folia were seen with no Purkinje cells
3. It has been hypothesized that the mutation causes impaired translocation that causes an increased rate of –1 programmed ribosomal frameshift read-through during translation

Laboratory Evaluation

1. MRI
 - a. Moderately severe cerebellar atrophy with a normal pons and medulla

Spinocerebellar Ataxia 27

General Characteristics

1. SCA27 is caused by mutation of the fibroblast growth factor 14 (FGF14) gene that maps to chromosome 13q33.1
2. A reverse and frameshift mutation have been described

Clinical Manifestations

1. Onset in childhood
2. Tremor and incoordination of the hands begins at 15–20 years of age

3. Saccadic dysmetria
4. Psychiatric symptoms (depression and frontal lobe dyscontrol)
5. Severe limb and gait ataxia
6. Head tremor
7. Rare variants include:
 - a. Paroxysmal non-kinesigenic dyskinesia
 - b. Fever sensitivity
 - c. Pes cavus and mild axonal sensory neuropathy

Neuropathology

1. FGF14 regulates brain sodium channels including those in the cerebellum. Sodium channels may be functionally temperature-sensitive
2. Intracellular FGF14 “knock-down” (experimentally in mice) attenuates spontaneous and evoked action potentials of adult Purkinje cells and was associated with poor coordination and balance
3. Loss of IFGF causes a hyperpolarizing shift in the voltage dependence of steady-state inactivation of sodium current in adult Purkinje neurons which are essential for cerebellar function

Laboratory Evaluation

1. MRI:
 - a. Moderate cerebellar atrophy
2. EMG (one variant):
 - a. Mild axonal sensory neuropathy

Spinocerebellar Ataxia 28

General Characteristics

1. SCA28 is caused by heterozygous mutation in the AFG3L2 gene that maps to chromosome 18p11.21
2. Mutation in the AFG3L2 gene also causes autosomal recessive (AR) spastic ataxia 5
3. Missense mutations in the AFG3L2 proteolytic domain are approximately 1.5% of the European autosomal dominant cerebellar ataxias

Clinical Manifestations

1. Onset in early adulthood (24.4 ± 14.9 years); the range is 3 to 60 years of age
2. The course is slowly progressive over decades, with minimal functional impairment
3. Cerebellar ataxia is associated with dysarthria
4. Oculomotor signs (80% of patients) include:
 - a. Limited to spontaneous gaze (~50%)
 - b. Gaze-evoked nystagmus
5. Ptosis (~50% of patients)
6. Extrapyramidal signs (24% of patients) include:
 - a. Parkinsonism: primarily rigidity and bradykinesia
 - b. Dystonia
7. Cognitive and behavioral problems in ~20% of patients
8. Decreased vibration sensibility in the lower extremities occurs in approximately 20% of patients; superficial sensation is intact

- Reflexes are increased in the lower extremities in approximately 75% of patients, with associated Babinski signs in 25%

Neuropathology

- AFG3L2 is a component of the conserved matrix ATPase
- It is associated with pleiotropic cellular activity that is involved in the maintenance of the mitochondrial proteome that is expressed in Purkinje cells
- The mutation decreases cytochrome C activity and thus cellular generation of ATP

Laboratory Evaluation

- MRI:
 - Cerebellar atrophy most prominent in the superior vermis
 - Brainstem is normal
- EMG:
 - Conduction velocities were normal in seven patients; neurogenic abnormalities were observed in two

Differential Diagnosis of SCA28

- The SCA caused by polyglutamine-expressions: SCA1, SCA2, SCA3, SCA7, SCA17 and DRPLA usually have onset prior to age 30, are more rapidly progressive, and have brainstem involvement demonstrated by MRI
- SCA6 is an adult-onset, slowly progressive ataxia with gaze-evoked nystagmus that is phenotypically similar to SCA28
- The AR ataxias that include FA and Oculomotor apraxia type I and type II (AOA1 and AOA2) are:
 - More rapidly progressive
 - Most often have a childhood onset
- Mitochondrial disorders with ophthalmoparesis and ptosis should also be considered in the differential diagnosis

Spinocerebellar Ataxia 29

General Characteristics

- SCA29 is caused by a heterozygous mutation in the ITPR1 gene that maps to chromosome 3p26-p25
- ITPR1 encodes inositol 1,4,5-trisphosphate receptor type 1
 - It is a ligand-gated ion channel that mediates calcium release from the endoplasmic reticulum
- Deletions of ITPR1 cause SCA15 (adult onset)

Clinical Manifestations

- Onset in infancy
- Delayed motor development
- Cognitive dysfunction (some)
- A slowly progressive gait and limb ataxia
- Variable neurologic deficits include
 - Nystagmus (vertical in some kinbreds)
 - Dysarthria
 - Tremor

Neuropathology

- The missense mutations in ITPR1 are localized to its coupling domain. The coupling/regulatory domain contains protein phosphorylation and proteolytic cleavage sites, ATP binding sites, and binding sites for other proteins
- It is hypothesized that the neuropathologic deficits in SCA29 are due to abnormal ITPR1-mediated Ca^{2+} signaling pathways involved in multiple cellular processes. It has also been suggested that ITPR1 is important in embryonic development

Laboratory Evaluation

- MRI:
 - Mild cerebellar atrophy; in some patients it is more prominent in the vermis
 - It has been shown to be progressive in longitudinal studies in one patient

Differential Points Between SCA29, ITPR1, and SCA15

- ITPR1 and SCA29 are congenital non-progressive SCAs that remain static, while SCA15 progresses
- SCA15 is adult-onset, and has extracerebellar features that include cognitive impairment (variable), ophthalmoplegia, and pyramidal and extrapyramidal signs

Spinocerebellar Ataxia 30

General Characteristics

- SCA30 has been mapped to a 5-mb locus on chromosome 4q34.3-q35.1. The gene has not been defined

Clinical Manifestations

- Onset mean is 52 years (range 45–76 years)
- The onset is insidious
- A relatively pure, slowly progressive gait and appendicular ataxia with dysarthria
- Hypermetric saccadic eye movements with normal vestibulo-ocular reflex gain
- Gaze-evoked nystagmus (1 patient)
- Hyperreflexia in the lower extremities (some patients)
- Dystonia (one patient)

Neuropathology

- Not defined

Laboratory Evaluation

- MRI:
 - Isolated cerebellar atrophy, predominately in the superior and dorsal vermis

Spinocerebellar Ataxia 31

General Characteristics

- SCA31 is caused by a 2.5–3.8-Kb insertion that contains pentanucleotide repeats (TGGA) within the BEAN1 gene that maps to chromosome 16q21-q22

2. SCA31 is the fourth most common autosomal dominant cerebellar ataxia (ADCA) in Japan. Otherwise it is a rare ADCA

Clinical Manifestations

1. Symptomatic disease onset is between 8 and 83 years (mean of 58 years of age)
2. The usual disease duration is greater than 10 years, it has complete penetrance and has minimal or absent anticipation
3. Gait ataxia
4. Cerebellar type dysarthria
5. Limb ataxia
6. Decreased muscle tone
7. Oculomotor abnormalities
8. Horizontal gaze-evoked nystagmus and impaired pursuit eye movement
9. Variable neurologic signs:
 - a. Pyramidal signs
 - b. Sensorineural hearing loss
 - c. Downbeat nystagmus
 - d. Head tremor
 - e. Decreased vibration sensibility
 - f. Brisk deep tendon reflexes

Neuropathology (2 Autopsy Studies)

1. The pentanucleotide repeat contains (TGGA)n, (TAGAA)n, (TAAAA)n and (TAGAATAAAA) inserted into an intron shared by two different genes (BEAN1 and TK2) located in the long arm of chromosome 16, and shown to be the critical component of SCA31
2. Abnormal RNA structures ("RNA foci") are identified in Purkinje cell nuclei, indicating that BEAN1-gene-directed mutant transcripts are pathogenic. The RNA foci containing (UGGAA)n were found in the Purkinje cells of the two autopsied patients and are considered to be pathogenic. The mechanism of pathogenesis in Purkinje cell loss has not been defined
3. A hypothesis has been suggested for the mechanism of SCA30 sequestration of proteins that bind to these foci (RNA-mediated gain of function). In other non-coding repeat expansion disorders exemplified by DM1, DM2, FX-TAS, HDL2 and SCA8 the transcript repeats form aggregates in the nuclei of affected cells. The sequestration of proteins that bind to the foci dysregulate alternative splicing
4. Accentuated Purkinje cell loss was seen in the anterior vermis

Laboratory Evaluation

1. MRI:
 - a. Cerebellar atrophy starts from the upper vermis

DRPLA

General Characteristics

1. Dentatorubral-pallidoluysian atrophy is caused by an ex-

panded trinucleotide repeat in the ATN1 gene that maps to chromosome 12p13/31

2. Normal alleles contain 6–35 CAG repeats; full penetrance alleles have >48 CAG repeats
3. The prevalence of DRPLA in the Japanese population is approximately .48 per 100,000 of the population
4. European and North American patients also have DRPLA
5. The Haw River kindred of North Carolina is a large kindred that has been extensively studied and has clinical differences from the clinic DRPLA disorder but is generally thought to be a variant

Clinical Manifestations

1. The onset of DRPLA is from childhood to late adulthood (1–62 years; mean of 30 years of age)
2. The clinical presentation varies depending on the age of onset
3. Neurological manifestations in adults include:
 - a. Ataxia
 - b. Choreoathetosis
 - c. Dementia
4. Neurological manifestations in childhood include:
 - a. Ataxia
 - b. Cognitive difficulties
 - c. Behavioral disorders
 - d. Myoclonus
 - e. Epilepsy
5. Ataxia and dementia are cardinal characteristics irrespective of the age of onset
6. Seizures occur in all patients that have onset prior to 20 years of age
7. Seizures (types):
 - a. Generalized tonic-clonic, tonic, and clonic
 - b. Progressive myoclonic epilepsy that is associated with:
 - i. Myoclonus
 - ii. Seizures
 - iii. Ataxia
 - iv. Progressive intellectual impairment
8. Myoclonic epilepsy and absence or atonic seizures is rarely observed in patients prior to twenty years of age
9. Seizures are less common in patients between 20–40 years of age and are rare in patients >40 years of age
10. Patients with onset of DRPLA > 20 years of age have cerebellar ataxia, choreoathetosis, dementia and psychiatric disorders. Psychosis is a rare presenting manifestation
11. There is prominent anticipation

Neuropathology

1. Combined degeneration of the dentatorubral and pallidoluysian systems
2. There is accumulation of the mutant DRPLA protein (atrophin-1) in neuronal nuclei
3. There is a diffuse nuclear staining that detects expanded polyglutamine stretches

4. White matter involvement demonstrates:
 - a. Diffuse myelin pallor
 - b. Preservation of axons
 - c. Reactive astrogliosis
5. The transgenic mouse model demonstrates:
 - a. Reduction in the number and size of dendritic spines
 - b. Decreased neuronal perikarya and diameter of dendrites
6. Diffuse nuclear staining of mutant protein in neuronal nuclei is not limited to the dentatorubral-pallidoluysian systems

Laboratory Evaluation

1. MRI:
 - a. Atrophy of the cerebellum and brainstem
 - b. Pontine tegmental atrophy is severe
 - c. The age at MRI and the size of the expanded repeat correlate with the degree of atrophy
 - d. Diffuse white matter hyperintensities are noted on T₂-weighted MRI sequences in adult-onset patients

The Haw River Syndrome

General Characteristics

1. The Haw River kindred is a 5 generation kindred that lives in the region of the Haw River of North Carolina and has DRPLA; a second kindred has also been studied

Clinical Manifestations

1. Onset is between 15 and 30 years of age
2. Ataxia
3. Seizures
4. Choreiform movements
5. Progressive dementia
6. Death often after 15–25 years of illness

Neuropathology (2 Patients Autopsied)

1. Severe neuronal loss in the dentate nucleus, microcalcification of the globus pallidus, neuroaxonal dystrophy of the nucleus gracilis, and demyelination of the centrum semiovale

Laboratory Evaluation

1. MRI:
 - a. Mild cerebellar atrophy

Differential Diagnosis of DRPLA in Adult-Onset Disease (non-Progressive Myoclonic Epilepsy Phenotype; PME)

1. The adult onset form of DRPLA has the cardinal features of:
 - a. Ataxia
 - b. Dementia
 - c. Choreoathetosis
2. Huntington's disease, Huntington's disease-like 1 and Huntington's disease-like 2

- a. Ataxia is an important differential point in differentiating DRPLA from Huntington's disease. Some affected DRPLA patients in which the non-PME phenotype may present with severe involuntary movements and dementia that masks ataxia
- b. Atrophy of the cerebellum and tegmentum of the pons is prominent in DRPLA while caudate atrophy is cardinal for Huntington's disease
3. Pure cerebellar ataxia type III
 - a. Some patients with DRPLA have middle expanded CAG repeats, may have pure cerebellar signs and symptoms in their clinical course. These patients have to be distinguished from SCA2, Machado-Joseph disease, SCA6 and SCA17
 - b. If the major features are progressive myoclonic movement impairment and epilepsy i.e. early-onset DRPLA (<20 years of age) then the differential diagnosis includes:
 - i. Lafora type progressive myoclonic epilepsy
 - ii. Unverricht-Lundborg disease
 - iii. Neuronal Ceroid-lipofuscinosis
 - iv. Neuroferritinopathy
 - v. MERRF
 - vi. Sialidosis
 - vii. Galactosialidosis
 - viii. Gaucher's disease
 - ix. Pantothenate kinase deficiency
 - x. Benign adult familial myoclonus epilepsy (BAFME)

Spinocerebellar Ataxia 32

General Characteristics

1. SCA32 is an autosomal dominant disease that maps to chromosome 7q32-q33; the gene has not been defined

Clinical Manifestations

1. Age at onset varies widely particularly in female patients
2. If onset <40 years of age patients have intellectual disability
3. All affected males are infertile

Neuropathology

1. Biopsy of the testicle (one patient)
 - a. Azoospermia and testicular atrophy
 - b. Complete absence of germ cells and progenitor cells

Laboratory Evaluations

1. MRI:
 - a. Cerebellar atrophy

Spinocerebellar Ataxia 34

General Characteristics

1. SCA34 is caused by heterozygous mutation in the ELOV24 gene that maps to chromosome 6q14
2. The protein elongates very long chain fatty acids (at least 26 carbons)

Clinical Manifestations

1. Studied primarily in 625 patients in 5 generations of a French Canadian kindred as well as 2 Japanese families
2. Soon after birth there is a papulosquamous erythematous ichthyosiform plaque eruption. The skin lesions resemble those seen with erythrokeratoderma variabilis (EKVP) and are primarily located on the extremities
3. Skin lesions often disappear by age 25 but may reappear after 40 years of age
4. Pure form of cerebellar ataxia
5. In later stages of the illness:
 - a. Slowly progressive syndrome
 - b. Severe gait ataxia
 - c. Dysarthria
 - d. Nystagmus
 - e. Increased reflexes
 - f. No macular degeneration
 - g. Extraocular movement disorder
6. Patients with homozygous mutations have:
 - a. Ichthyosis
 - b. Spastic paraplegia
 - c. Severe neural developmental defects
7. A milder phenotype with SCA and EKV demonstrates:
 - a. Early-onset patches of erythema and hyperkeratosis
 - b. SCA that manifests in the fourth or fifth decade

Neuropathology

1. ELOVL4 protein localizes to the endoplasmic reticulum
2. It catalyzes the formation of very-long-chain (VLC) (C28–C40) fatty acids, that are saturated and polyunsaturated (PUFA)
3. The defective gene protein is truncated at the C terminus which causes mislocalization and aggregation in other organelles
4. It has been postulated that its toxic keto intermediates of fatty acid elongation are a mechanism of disease pathogenesis due to reduced VLC-PUFA synthesis. Fatty acids are essential for multiple physiologic functions that include skin barrier formation and peroxisome β -oxidation. How they cause cerebellar degeneration has not been defined

Laboratory Evaluation

1. MRI
 - a. Pontine midline linear hyperintensity (“hot cross bun” sign)
 - b. Cerebellar and pontine atrophy
 - c. High intensity signals in the middle cerebellar peduncle

Spinocerebellar Ataxia 35*General Characteristics*

1. Spinocerebellar ataxia 35 is caused by heterozygous mutation in the TGM6 gene (transglutaminase 6 gene) that maps to chromosome 20p13; missense mutation in the gene may also cause the disorder

Clinical Manifestations

1. The major study is that of a 4 generation Chinese kindred
2. The mean age at onset was 43.9 years (range of 40–48 years)
3. Initial features include: ataxia of gait, cerebellar dysarthria; upper limb incoordination occurs later in the course of the disorder; may become wheelchair-dependent 10 years after the start of the illness. Some patients had abnormal eye movements

Neuropathology

1. Transglutaminase 6 (TG6) catalyzes the formation of a covalent bond between a free amino group and the gamma-carboxamide group of proteins
2. The mutation decreases transglutaminase activity and stability:
 - a. Experimental overexpression of TG6 sensitizes cells to staurosporine induced apoptosis by increasing caspase activity

Laboratory Evaluation

1. MRI:
 - a. Diffuse cerebellar atrophy; no cerebral hemisphere or brainstem atrophy

Spinocerebellar Ataxia 36*General Characteristics*

1. SCA36 is caused by heterozygous expansion of an intronic GGCTG hexanucleotide repeat in the NOP56 gene that maps to chromosome 20p13
2. Normal alleles have 3 to 14 repeats whereas patients carry 650 to 2,500 repeats

Clinical Manifestations

1. Onset is between 40–60 years of age
2. Initial presentation is often a gait disorder
3. Dysarthria and appendicular ataxia follow the gait instability
4. Slowly progressive sensorineural hearing loss that manifests a few years after the cerebellar signs
5. Tongue atrophy with fasciculations
6. Swallowing is preserved
7. In advanced disease, patients may develop skeletal muscle atrophy and extremity fasciculation
8. Hyperreflexia
9. Variable clinical manifestations include:
 - a. Gaze-evoked nystagmus
 - b. Ptosis
 - c. Decreased vibration sensibility
 - d. Cognitive impairment

Neuropathology

1. Loss of Purkinje cells and dentate neurons
2. Anterior horn cell loss

- Immunohistochemical analysis (1) NOP56 is localized to neurons
- GGCCVG_n binds the RNA-binding protein SRSF2
- Transcription of MIR1292, an adjacent miRNA is decreased in lymphoblastoid cells from patients
- The major mechanism for cell death has been suggested to be RNA gain of function induced by the hexanucleotide expansion

Laboratory Evaluation

- MRI:
 - Early stages:
 - Atrophy of the superior vermis
 - Intermediate stage:
 - Involvement of the pons and medulla
 - Subcortical atrophy
 - Dilatation of the IVth ventricle similar to that seen in olivopontocerebellar atrophy; no "hot cross bun" sign
 - Cortical brain atrophy, primarily frontal lobe is seen late in the course of the disease
- Brainstem auditory evoked potentials:
 - Absence or reduced amplitude of waves I and II
- Pure tonal audiometry:
 - A drop of >40 dB in frequencies beyond 2500 Hz
- Normal motor and sensory nerve conduction velocities
- Somatosensory evoked potentials of the lower extremities are mildly abnormal
- Penetrance of NOP56 GGCCCTG hexanucleotide pathogenic allele is complete but depends on age

Spinocerebellar Ataxia 37

General Characteristics

- Studies have been done on only one large Spanish kindred
- SCA37 is an autosomal dominant disorder that maps to chromosome 1p32

Clinical Manifestations

- Onset is at a mean age of 44 (range 38 to 64)
- Initial presentation is gait instability with frequent falls
- Dysarthria
- Limb incoordination
- Clinical progression is slow
- Abnormal extraocular movements:
 - Deficits in vertical saccades and irregular vertical smooth pursuit
 - Later development of horizontal smooth pursuit deficits
 - Variable nystagmus

Neuropathology

- Not defined

Laboratory Evaluation

- MRI:
 - Cerebellar atrophy without brainstem involvement

Spinocerebellar Ataxia 38

General Characteristics

- Spinocerebellar ataxia 38 is caused by heterozygous mutation in the ELOVL5 gene that maps to chromosome 6p12.1

Clinical Manifestations

- Presentation is between 34 and 51 years of age
- Gait ataxia
- Nystagmus
- Slow saccades
- Dysarthria
- Distal sensory loss
- Normal cognition

Neuropathology

- Transfection of mutations into cell lines demonstrate:
 - Mutant proteins that have a less diffuse (ER endoplasmic reticulum) signal than wild-type
 - Mutant proteins accumulate in the golgi apparatus
 - Possible activation of the unfolded protein response that leads to apoptosis in affected neurons
 - ELOVL5 is a component of the synthesis of PUFA that contain more than 20 carbons; it is prominently expressed in adult brain. It is located in the soma and proximal portion of the dendritic tree in Purkinje cells

Laboratory Evaluation

- Arachidonic and docosahexaenoic acid are decreased in the serum
- MRI:
 - Cerebellar atrophy

Spinocerebellar Ataxia 40

General Characteristics

- SCA40 is caused by heterozygous mutation in the Ccdc88C gene that maps to chromosome 14q32

Clinical Manifestations

- Onset in the fourth decade
- Presentation is with unsteady gait
- Dysarthria
- Ocular dysmetria
- Intention tremor
- Hyperreflexia
- Impaired vertical gaze (one patient)
- Spastic paraparesis (one patient)

Neuropathology

- Functional studies demonstrate that mutant Ccdc88C protein activates JNK which triggers apoptosis
- A gain of function mutation

Laboratory Evaluation

- MRI (two patients)
 - Pontocerebellar atrophy

Autosomal Dominant Cerebellar Ataxia Type I (Summary)*Definition*

1. A type of Spinocerebellar ataxia that manifests ataxia that is associated with other neurologic signs and symptoms that include:
 - a. Extraocular motor deficits
 - b. Cognitive impairment
 - c. Pyramidal and extrapyramidal dysfunction
 - d. Bulbar abnormalities
 - e. Spinal cord involvement
 - f. Peripheral neuropathy
2. The most common ADCA type I is SCA3 followed by SCA27 > SCA1
3. The cerebellar deficits:
 - a. Involve any part of the body with prominent gait, trunk and limb ataxia; there is frequent associated supranuclear gaze deficits with saccadic dysmetria and hypometric and smooth pursuit deficits; nystagmus is common
 - b. Dysarthria and scanning speech are frequently seen
 - c. The ADCAI subtypes include:
 - i. SCA1, SCA2, SCA3, SCA4, SCA8, SCA10, SCA12, SCA13, SCA14, SCA15/SCA16, SCA17, SCA18, SCA19, SCA20, SCA21, SCA22, SCA23, SCA27, SCA28 and DRPLA
4. ADCA Type I by pathogenic mechanism
 - a. Subclass I:
 - i. CAG expression:
 1. SCA1, SCA2, SCA3
 2. SCA17
 3. DRPLA
 - b. Subclass II:
 - i. Trinucleotide repeat expressions that are outside of the protein coding regions of the causative gene
 1. SCA8
 2. SCA10
 3. SCA12
 - c. Subclass III:
 - i. Disorders caused by deletions, missense mutations and nonsense mutations in specific genes:
 1. SCA13, SCA14, SCA15/SCA16, SCA27 and SCA28

Pathogenic Mechanisms

1. Trinucleotide CAG repeat expansions
 - a. Encode large uninterrupted polyglutamine tracts which are toxic to cells at an RNA level
 - b. Toxicity may be mediated by:
 - i. Interference of protein aggregation and clearance
 - ii. Deficits in calcium homeostasis that causes apoptosis
 - iii. Transcriptional dysregulation
 - iv. Abnormalities in the ubiquitin-proteasome system
2. Trinucleotide repeat expansions outside of the protein coding region
 - a. SCA8, SCA10, SCA12

- b. Toxic reaction at the RNA level; the RNA repeat sequences interfere with gene expression in affected neurons
3. Specific gene deletions, missense mutations and nonsense mutations
 - a. SCA13, SCA14, SCA15/SCA16, SCA27 and SCA28
 - b. Mechanisms of cell death include:
 - i. Transcription dysregulation
 - ii. Mitochondrial dysfunction
 - iii. RNA toxicity
 - iv. Protein aggregation
 - v. Dysregulation of protein folding
 - vi. Bioenergetic failure
 - vii. Calcium homeostasis dysregulation
 - c. All mechanisms may lead to neuronal death by apoptosis during SCA disease progression

Autosomal Dominant Cerebellar Ataxia Type II*Definition*

1. ADCA Type II is composed of cerebellar syndromes associated with maculopathy. It is characterized by SCA7 that maps to chromosome 3p12-21.1 and the gene ATXN7. Approximately 75% of normal alleles have ten CAG repeats. Fully penetrant alleles in this disorder have greater than 36 CAG repeats and expansions as high as 460 CAG repeats. Paternal transmission increases anticipation

Clinical Manifestations

1. In adults progressive cerebellar signs and symptoms usually follow the onset of visual deterioration
2. The progression of the disorder causes severe dysarthria, dysphagia and inability to walk
3. Pigmentary maculopathy is the distinguishing feature:
 - a. Retinopathy includes the macula and leads to blindness
 - b. It extends to the peripheral fundus
 - c. There are early blue-yellow color discrimination deficits
4. Supranuclear ophthalmoplegia
5. Extrapyramidal features
6. The onset is between 2–65 years of age and a subset of patients is wheelchair bound by age 15
7. Adult onset patients usually have paternal transmission; there is reduced penetrance as obligate gene carriers do not manifest disease although they may live beyond 65 years of age
8. Myoclonus
9. Chorea
10. Personality change
11. In adult-onset patients, visual deficits from retinal degeneration may precede or follow cerebellar signs

Neuropathology

1. Loss of myelinated fibers and gliosis in the Purkinje cell layer are prominent

2. There is neuronal loss in the inferior olivary, dentate and pontine nuclei, cerebral cortex, basal ganglia, thalamus and midbrain
3. Biopsies of skeletal muscle and the liver have demonstrated abnormal mitochondria
4. Degeneration of the spinocerebellar tracts and dorsal column are evident in the spinal cord
5. There is degeneration of photoreceptors, bipolar and granular cells in the retina that is most evident in the fovea and parafoveal areas

Laboratory Evaluation

1. Electroretinogram:
 - a. Abnormal early in the disease course demonstrating a disorder of the photopic response initially. Over time there is a decrease in the scotopic (rod) response
2. Farnsworth dichotomous color vision testing reveals:
 - a. Difficulty with triton (blue-yellow) axis of color discrimination
3. MRI:
 - a. Cerebellar and pontine atrophy

Autosomal Dominant Cerebellar Ataxia Type III

General Characteristics

1. ADCA III manifests with cerebellar signs and symptoms but may also have pyramidal signs, ophthalmoplegia, and tremor
 - a. Most often disease onset is in adulthood although some patients are symptomatic in adolescence
2. The most common subtype is SCA6 with SCA5, SCA11, SCA26, SCA30 and SCA31 comprising the remainder of the group
 - a. There is variability of phenotype in between subtypes and within individual affected families
 - b. SCA5 and SCA11 are caused by missense, in-frame deletions and frameshift insertions or deletions
 - c. SCA6 is a trinucleotide CAG expression disorder, while SCA31 is caused by intronic repeat expansions
 - d. The specific genes for SCA26 and SCA30 have not been defined but the chromosome locus has been determined
3. ADCA Type III is compatible with a normal life span although dysphagia and falls cause considerable morbidity

Clinical Manifestations

1. In general, this is a benign and slowly progressive group of disorders
2. Primarily cerebellar signs and symptoms that include gait and limb ataxia with dysarthria
3. Oculomotor dysfunction includes nystagmus and impaired smooth pursuit
4. Rarely observed manifestations:
 - a. Pyramidal tract signs
 - b. Peripheral neuropathy
 - c. Involuntary movements

Neuropathology

1. The defined genes for ADCA III are:
 - a. Spectrin beta, non-erythrocyte 2 (SPTBN2) gene in SCA5
 - b. Calcium channel, voltage dependent P/Q type, alpha 1A subunit (CACNA1A) gene seen in SCA6
 - c. Tau-tubulin kinase – (TTBK2) for SCA11 (conventional mutations)
 - d. BEAN1 (brain expressed associated with NEDD4 1) gene seen in SCA31
 - e. Two gene loci have also been defined for SCA26 and SCA30
2. Present consensus of pathologic mechanisms underlying neurodegeneration in the spinocerebellar ataxias
 - a. Neurodegeneration in SCAs is multifactorial and progressive
 - b. Specific mechanisms include:
 - i. Dysregulation of protein folding
 - ii. Abnormal transcription
 - iii. Failure of bioenergetics
 - iv. Failure of calcium homeostasis
 - v. Cell death due to apoptosis
3. SCAs with clear degenerative patterns:
 - a. Retinal degeneration in SCA7
 - b. Tau aggregation in SCA11
 - c. Dentate calcification in SCA20
 - d. Protein deposition in the Purkinje cells of SCA31
 - e. Azoospermia in SCA32
 - f. Neurocutaneous pathology in SCA34

Laboratory Evaluation

1. Molecular genetic testing
2. Patterns of cerebellar and pontine atrophy delineated by MRI

Summary of Autosomal Recessive Cerebellar Ataxias

1. Hereditary ataxias with autosomal inheritance have been estimated at 3/100,000 of the population worldwide. There are now 75 disorders with this pattern of inheritance
2. The most common of the recessive ataxias are:
 - a. Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS)
 - b. POLG and related disorders
 - c. Ataxia telangiectasia
 - d. Cerebrotendinous xanthomatosis (CTX)
 - e. Refsum syndrome
 - f. AVED
3. Ataxia and/or cerebellar hypoplasia caused by biallelic pathogenic variants of related genes include:
 - a. Joubert syndrome
 - b. Congenital disorders of glycosylation
 - c. Pontocerebellar hypoplasia
 - d. Peroxisomal biogenesis disorders (Zellweger spectrum disorders)
 - e. Perrault syndrome

Summary of the Molecular Genetics and Clinical Features of X-Linked Cerebellar Ataxias

1. X-linked sideroblastic anemia and ataxia (XLSA/A);
 - a. ABCB7 Gene (Xq27.3)
 - b. Clinical manifestations
 - i. Childhood onset
 - ii. Anemia is asymptomatic
 - iii. Cognitive deficiency
 - iv. Microencephaly
2. CASK gene (XP11.4)
 - a. Clinical manifestations:
 - i. Hypotonia
 - b. Optic nerve hypoplasia
 - c. Growth retardation
3. FXTAS
4. FMRI gene (xq27.3)
 - a. Clinical manifestations
 - i. The most common of the x-linked ataxias
 - ii. Occurs in male and female permutation carriers
 - iii. Adult onset
 - iv. Expanded CGG sequences between 55 to 200 triplets are called permutations
 1. The alleles produce increased levels of messenger RNA
 2. These patients are cognitively normal
 3. They manifest progressive ataxia and tremor that is designated FXTAS
 4. Clinic Fragile X disease is the most common cause of genetically induced cognitive impairment
5. X-Linked mental retardation with cerebellar hypoplasia and facial dysmorphisms
 - a. General characteristics
 - i. The gene is OPHNIC
 - b. Clinical manifestations
 - i. Infantile onset
 - ii. Hypotonia
 - iii. Developmental delay
 - iv. Seizures
6. Syndromic X-linked mental retardation (Christianson type)
 - a. General characteristics
 - i. The gene is SLC9A6 (Xq26.3)
 - b. Clinical manifestations
 - i. Infantile onset
 - ii. Cognitive impairment
 - iii. Seizures
 - iv. Cognitive impairment in carrier females
 - v. May resemble Angelman syndrome

Episodic Ataxias

Overview

The episodic ataxias manifest unsteady gait often associated with nystagmus or dysarthria for minutes to hours. Associated signs and symptoms in specific types that include:

- a. Myokymia
- b. Vertigo
- c. Hearing loss

Episodic Ataxia Type 1 (EA1)

General Characteristics

1. Episodic ataxia type 1 is caused by a heterozygous mutation of the potassium channel gene KCNA1 that maps to chromosome 12p13.32

Clinical Manifestations

1. Constant myokymia
2. Episode of spastic contractions of skeletal muscles of the head and extremities that cause:
 - a. Loss of balance
 - b. Incoordination
3. Variable symptoms during attacks include:
 - a. Vertigo
 - b. Blurred vision
 - c. Nausea
 - d. Diplopia
 - e. Headache
 - f. Diaphoresis
 - g. Incoordination
 - h. Stiffening of the body
 - i. Dysarthria
 - j. Difficulty breathing
4. EA1 may be associated with epilepsy, delayed motor development, cognitive impairment, choreoathetosis and carpal spasm
5. Onset is in childhood or adolescence (average age is 8 years)
6. Duration of attacks is seconds to minutes
7. Occurrence is variable from up to 15 attacks/day to less than 1/month
8. Triggering events for attacks include:
 - a. Stress
 - b. Anxiety
 - c. Fatigue
 - d. Menstruation
 - e. Pregnancy
 - f. Temperature
 - g. Fever
 - h. Startle responses
 - i. Abrupt movement
 - j. Postural changes
 - k. Vestibular stimulation
 - l. Alcohol or caffeine
 - m. Exercise
9. Myokymia manifests both during and between attacks
10. Moderate muscle hypertrophy
11. Increased muscle tone may cause:
 - a. Hypercontracted posture
 - b. Contraction of the abdominal wall

- c. Elbow, hip and knee contractures
- d. Shortened Achilles tendon with toe walking
- 12. Difficulty in breathing during attacks
- 13. Skeletal abnormalities include:
 - a. Scoliosis and kyphoscoliosis
 - b. High arched palate
 - c. Mild craniofacial dysmorphism
- 14. Tonic-clonic and partial seizures

Neuropathology

The EA1 mutations affect fast inactivation of K^+ channels by a reduction in subunit surface expression or affinity for the inactivation domain.

Laboratory Evaluation

1. EEG:
 - a. Intermittent and generalized slow activity with intermittent spikes
2. MRI:
 - a. Usually normal; 1 patient has been reported with cerebellar atrophy
3. EMG:
 - a. Rhythmic or arrhythmic occurrence of singlets, duplets or multiplets
4. Molecular gene testing

Episodic Ataxia 2 (EA2)

General Characteristics

1. EA2 is caused by mutation in the calcium ion channel gene CACNA1A that maps to chromosome 19p13.2

Clinical Manifestations

1. Paroxysmal attacks of:
 - a. Ataxia
 - b. Vertigo and nausea
 - c. Attacks last for minutes to days
2. Neurologic signs and symptoms:
 - a. Dysarthria
 - b. Diplopia
 - c. Tinnitus
 - d. Dystonia
 - e. Hemiplegia
 - f. Migraine type headache
3. Onset is in childhood or early adolescence (range 2–32 years)
4. Frequency of occurrence varies widely from once or twice a year to three to four times/week
5. Triggering events include:
 - a. Stress
 - b. Exertion
 - c. Alcohol and caffeine
 - d. Heat and fever
 - e. Postural change
6. Patients are usually asymptomatic between attacks but gradually with time develop interictal nystagmus and ataxia

Neuropathology

1. Loss of function mutation of the CACNA1A that encodes a voltage dependent Ca^{2+} channel alpha-subunit (P/Q type; CaV 2.1)

Laboratory Evaluation

1. Molecular genetic testing
2. MRI:
 - a. Atrophy of the cerebellar vermis

Episodic Ataxia 3 (EA3)

General Characteristics

1. Described in a large Canadian kindred of Mennonite heritage (26 members are affected)
2. The locus is on chromosome 1q42

Clinical Manifestations

1. Adult onset
2. Vestibular ataxia
3. Tinnitus
4. Interictal myokymia
5. Acetazolamide responsive
6. Seizures (rare)

Neuropathology

1. Not defined

Laboratory Evaluation

1. MRI:
 - a. Not defined
2. Molecular genetic testing

Episodic Ataxia 4 (EA4)

General Characteristics

1. Also referred to as periodic vestibulocerebellar ataxia (PATX)
2. No chromosomal locus has been defined

Clinical Manifestations

1. Families described are from North Carolina of Northern European ancestry
2. Onset is early adulthood (3rd to 6th decade)
3. Recurrent attacks of vertigo, diplopia and ataxia
4. In a subgroup of patients, there is slowly progressive cerebellar ataxia
5. Abnormal eye movements that include:
 - a. Decreased smooth pursuit
 - b. Nystagmus (gaze-evoked)
 - c. Abnormal vestibular ocular reflexes
 - d. No response to acetazolamide

Neuropathology

1. Not defined

Laboratory Evaluation

1. Gene loss has not been defined

Episodic Ataxia 5 (EA5)*General Characteristics*

1. Heterozygous pathogenic variants in the CACNB4 gene that maps to chromosome 2q23 cause EA5
2. The gene encodes the beta-4 isoform of the regulatory beta-subunit of voltage-activated Ca²⁺ channels
3. EA5 is allelic with susceptibility to juvenile myoclonic epilepsy 6

Clinical Manifestations

1. Reported in a French Canadian family
2. Childhood to adolescent onset
3. Recurrent episodes of vertigo and ataxia that last for hours
4. Dysarthria
5. Imbalance
6. Acetazolamide responsive
7. Semiology of seizures is similar to EJM6
8. Downbeat and gaze-evoked nystagmus
9. Truncal ataxia

Neuropathology

1. Emerging evidence suggests a loss of intrinsic properties of Purkinje cells and synaptic dysfunction in calcium channel mutations

Laboratory Evaluation

1. Molecular genetics:
 - a. Missense mutation in the CACNB4 gene

Episodic Ataxia 6 (EA6)*General Characteristics*

1. EA6 is caused by mutation in the SL1A3 gene that maps to chromosome 5p13.2

Clinical Manifestations

1. Childhood onset
2. Slurred speech followed by headache (migraine)
3. Arm jerking with concomitant confusion
4. Episodes of ataxia precipitated by fever
5. Alternating hemiplegia
6. Interictal gaze-evoked nystagmus
7. Triggering events for ataxic attacks:
 - a. Stress
 - b. Fatigue
 - c. Caffeine
 - d. Alcohol

Neuropathology

1. Reduced glutamate uptake by mutant excitatory amino acid transporter-1 has been postulated as the major pathophysiological process of the disorder
2. The disease is associated with point mutation (P290R):
 - a. Reduces the number of excitatory amino acid transporter-1 proteins in the surface membrane

- b. Impairs excitatory amino acid transporter-1-mediated glutamate uptake
- c. Cells expressing the mutant P290R exhibit larger anion currents in the presence of external glutamate in the face of a lower number of mutant transporters in the surface membrane. These findings support a gain-of-function of excitatory amino acid transporter anion conduction as another mechanism that can cause episodic ataxia 6

Laboratory Evaluation

1. MRI:
 - a. Cerebellar atrophy
2. Molecular genetic testing

Episodic Ataxia 7 (EA7)*General Characteristics*

1. Episodic ataxia 7 is caused by an autosomal dominant mutation at locus rs1366444 and rs952108 that maps to chromosome 19q13
2. Described in a four generation family

Clinical Manifestations

1. Onset prior to age 20
2. Episodic attacks are associated with:
 - a. Weakness
 - b. Vertigo
 - c. Dysarthria
3. Attacks may last hours to days and are triggered by exercise and excitement
4. The frequency of attacks ranged from monthly to one per year; decreased with age

Neuropathology

1. Not defined

Laboratory Evaluation

1. Not defined

Episodic Ataxia 8 (EA8)*General Characteristics*

1. Autosomal dominant inheritance in a large 3-generation Irish family in which the locus was mapped
2. An 18.5 Mb locus that maps to chromosome 1p36.13-p34.3
 - a. A candidate gene is UBR4 which is a ubiquitin ligase protein that interacts with calmodulin

Clinical Manifestations

1. Onset in childhood as children learn to walk (~2 years of age)
2. Attacks are manifested by:
 - a. Unsteady gait
 - b. Generalized weakness

- c. Slurred speech
- d. Triggered by fatigue and stress
- e. Wide variation in the frequency of attacks; (2 attacks/day to months without an attack)
- f. Attack frequency may decrease with age
- g. There is no tinnitus or seizures
- h. Acetazolamide unresponsive
- i. Interictal impaired tandem gait and intention tremor
- j. Minimal gaze-evoked nystagmus (some family members)
- k. Response to clonazepam rather than acetazolamide
- l. Myokymia
- m. Mild dysarthria
- n. Twitching around the eyes

Neuropathology

1. The ubiquitin protein ligase encoded by UBR4 interacts in the nucleus with the retinoblastoma-associated protein and in the cytoplasm with the smooth endoplasmic reticulum
2. The protein interacts with calcium-bound calmodulin in the cytoplasm that suggests a role in calcium signaling
3. It has been postulated that UBR4 is a Ca^{2+} sensor, and that atypical binding of UBR4 with calmodulin and/or ITPR1 (inositol 1,4,5-triphosphate receptor) may alter the neuron's calcium sensor systems (disrupt calcium homeostasis) which is a regulator of the $\text{CaV}2.1$ channel

Laboratory Evaluation

1. MRI: (one patient)
 - a. Normal cerebellum; MRIs were taken at age 19 and 29
2. Molecular genetic testing

Differential Diagnosis of Episodic Ataxias

Sporadic Disorders

1. Multiple sclerosis
 - a. Optic nerve, spinal cord, and cognitive impairment
2. Arnold-Chiari malformations
 - a. Short neck and shallow posterior fossa
 - b. Severe C2 headache with valsalva maneuvers
 - c. Lower cranial nerve involvement
3. Vertebral basilar insufficiency:
 - a. Dizziness and diplopia
 - b. Focal motor weakness
 - c. Perioral numbness
4. Basilar migraine:
 - a. Upper extremity paresthesias
 - b. Severe vertigo
 - c. Occipital headache
 - d. Loss of consciousness
5. Labyrinthine disorders:
 - a. Severe dizziness and vertigo
 - b. Lateralizing nystagmus
 - c. Lateral pulsion
 - d. Nausea and vomiting

Hereditary Disorders

1. Disorders of mitochondrial oxidative metabolism
 - a. Pyruvate carboxylase deficiency

General Characteristics

1. Pyruvate carboxylase deficiency is caused by mutation in the pyruvate carboxylase gene that maps to chromosome 11q.32

Clinical Manifestations

1. There are 3 phenotypic subgroups:
 - a. Group A:
 - i. Patients from North America
 - ii. Psychomotor retardation
 - iii. Canadian Indian population:
 1. Seizures
 2. Respiratory distress
 3. Hypotonia
 4. Developmental delays
 5. One patient with Leigh's necrotizing encephalopathy
 - b. French form (Group B):
 - i. 2 familial cases of neonatal congenital lactic acidosis that was rapidly fatal
 - ii. Cognitive impairment
 - c. Benign type (Group C)
 - i. One patient with normal motor and cognitive ability
 - ii. A second patient with onset at 3 days of life:
 1. Psychomotor delay
 2. At age 9, cognitive impairment, dysarthria and dysgraphia

Neuropathology

1. Hypothesized that energy deprivation (bioenergetic failure) from pyruvate carboxylase (PC) deficiency decreases astrocytic buffering capacity against excitotoxicity
2. Cystic degeneration of periventricular white matter

Laboratory Evaluation

1. Primary lactic acidemia
2. In some patients there is hyperammonemia, citrullinemia, lysinemia and altered redox states
3. MRI:
 - a. General cerebral atrophy
 - b. Cystic periventricular leukomalacia

Pyruvate Dehydrogenase E1-Alpha Deficiency (PDHAD)

General Characteristics

1. PDHAD is caused by mutation in the PDHA1 gene of the pyruvate dehydrogenase complex that maps to chromosome xp221.12
2. Pyruvate dehydrogenase complex mutations are a common cause of lactic acidosis in children
3. Heterozygous females may be severely symptomatic

4. There is genetic heterogeneity of pyruvate dehydrogenase complex deficiency

Clinical Manifestations

1. The metabolic and neurologic manifestations of the disorder present with equal frequency
2. The metabolic form presents as severe lactic acidosis in newborns that is usually fatal
3. The neurologic form is characterized by:
 - a. Hypotonia
 - b. Lethargy
 - c. Cognitive impairment
 - d. Seizures
 - e. Spasticity
4. An intermediate form is characterized by:
 - a. Intermittent episodes of lactic acidosis with cerebellar ataxia
 - b. Many patients are phenotypically similar to Leigh's syndrome
5. Intermittent ataxia may be combined with choreoathetosis

Neuropathology

1. Regions surrounding the third ventricle and aqueduct demonstrate similar pathology to Wernicke's encephalopathy or Leigh's disease (some patients)
2. Cerebellar degeneration similar to olivopontocerebellar atrophy in some patients

Laboratory Evaluation

1. Elevated fasting levels of lactate and pyruvate
2. MRI:
 - a. Cerebral atrophy
 - b. Absence of the corpus callosum (some patients)
 - c. Lesions of the basal ganglia and brainstem similar to Leigh's syndrome

X-Linked Disorders That Cause Episodic Ataxia

Ornithine Transcarbamylase OTC Deficiency

General Characteristics

1. Ornithine transcarbamylase deficiency is caused by mutation in the OTC gene that maps to chromosome Xp11.4
2. In male hemizygotes clinical manifestations and age at onset depend on the mutation. In female heterozygotes, phenotypic expression depends on the extent of expression of the mutated gene

Clinical Manifestations

1. Milder mutations may be asymptomatic until the patient is exposed to high nitrogen loads
2. Age at onset varies widely (3 days to 49 years)
3. Episodic extreme irritability (100%)
4. Episodic vomiting and lethargy (100%)

5. Protein avoidance (92%)
6. Ataxia (77%)
7. Coma (46%)
8. Delayed growth (38%)
9. Developmental delay (38%)
10. Seizures (23%)

Neuropathology

1. Mutation in the gene that encodes the enzymes leads to:
 - a. Partial deficiency in heterozygous females and to complete deficiency in hemizygous males
2. Astrocytic transformation of astrocytes to Alzheimer type II glia due to the hyperammonemia
3. Cortical atrophy, widespread gliosis and atrophy in the internal granular layer of the cerebellum

Laboratory Evaluation

1. Intermittent episodes of hyperammonemia often precipitated by infection
2. Orotic acid excretion after protein loading (in the urine)
3. Citrullinemia in some patients
4. Increased plasma glutamine
5. MRI:
 - a. Cortical atrophy
 - b. Subcortical demyelination

Autosomal Recessive Ataxias Due to Urea Cycle Enzyme Deficiency

General Characteristics

1. The urea cycle enzyme deficiencies include:
 - a. Carbamoyl phosphate synthetase
 - b. Argininosuccinate synthetase (citrullinuria type 1)
 - c. Argininosuccinase
 - d. Arginase deficiency

Clinical Manifestations

1. Severe forms of hyperammonemia present in the first four days of life and manifest:
 - a. Lethargy
 - b. Focal and generalized seizures
 - c. Coma
2. Early childhood (less severe phenotype)
 - a. Intermittent ataxia
 - b. Confusion
 - c. Dysarthria
 - d. Vomiting
 - e. Headache
 - f. Ptosis
 - g. Involuntary movements
 - h. Seizures
3. Episodes are precipitated by increased protein ingestion and intercurrent infection

Neuropathology

1. Cortical atrophy

2. Alzheimer type II glia
3. Brainstem and subcortical gliosis and white matter changes

Laboratory Evaluation

1. Intermittent hyperammonemia
2. Increased citrullinemia

Intermittent Ataxia from Amino Acidurias

Hartnup Disease

General Characteristics

1. Hartnup disease is caused by homozygous or compound heterozygous mutation in the SLC6A19 gene that maps to chromosome 5p15.33
2. Incidence is approximately 1 in 15,000 of the population

Clinical Manifestations

1. Intermittent ataxia
2. Tremor
3. Chorea
4. Psychiatric disorders
5. Cognitive impairment
6. Pellagra-like skin rash
7. Triggers of attacks include:
 - a. Sunlight
 - b. Emotional stress
 - c. Sulfonamide drugs
8. Attacks may decrease with age
9. Attacks last approximately two weeks

Neuropathology

1. Defective renal and intestinal transport of monoamino monocarboxylic acids

Laboratory Evaluation

1. Multiple neutral amino acids are excreted in the urine
2. Monoamino monocarboxylic aciduria
3. Stool indoles and urinary indican may be increased after oral tryptophan loading

Intermittent Branched-Chain Ketoaciduria

General Characteristics

1. Maple syrup urine disease can be caused by homozygous or compound heterozygous mutations in 3 genes:
 - a. BCKDHA that maps to chromosome 19q13.2
 - b. BCKDHB that maps to chromosome 6q14.1
 - c. DBT that maps to chromosome 1p21.2

Clinical Manifestations

1. Intermittent ataxia
2. Cognitive impairment
3. Feeding difficulty
4. Thiamine responsive
5. Maple syrup odor of the urine

Neuropathology

1. Failure to catabolize the branched chain amino acids leucine, isoleucine and valine

Laboratory Evaluation

1. Elevation of branched-chain amino acids and ketoacids in the urine (leucine, isoleucine and valine)
2. MRI:
 - a. Demyelination of the cerebellum and middle cerebellar peduncle

Isovaleric Acidemia

General Characteristics

1. Isovaleric acidemia is caused by mutation of the isovaleryl CoA dehydrogenase gene that maps to chromosome 15q15.1

Clinical Manifestations

1. Acute neonatal type:
 - a. Massive metabolic acidosis from birth and rapid death
2. Chronic form:
 - a. Periodic attacks of severe ketoacidosis
 - b. Retarded cognitive function
 - c. Sweaty feet odor of the urine
 - d. An aversion to protein
 - e. Pernicious vomiting
 - f. Coma in severe attacks

Neuropathology

1. Branched-chain organic aciduria and isovaleric aciduria, propionic aciduria and methylmalonic aciduria may all cause ischemic stroke
2. Cerebellar hemorrhage may occur with isovaleric aciduria without acute metabolic episodes

Laboratory Evaluation

1. Isovaleric aciduria produces:
 - a. Increased hyperglycinemia
 - b. Leukopenia
 - c. Episodic ketoacidosis

Familial Paroxysmal Kinesigenic Dyskinesia (PKD)

General Characteristics

1. PKD is inherited as an autosomal dominant disorder from heterozygous mutations in the PRRT2 gene that maps to chromosome 16p11.2

Clinical Manifestations

1. The phenotype of PKD includes:
 - a. Benign familial infantile epilepsy (BFIE)
 - b. Infantile convulsions and choreoathetosis (ICCA)
 - c. Hemiplegic migraine
 - d. Migraine with and without aura
 - e. Episodic ataxia

2. The major clinical features of PKD are:
 - a. Unilateral or bilateral involuntary movements
 - b. Triggering events that include:
 - i. Standing from a sitting position
 - ii. Startle
 - iii. Stress
 - c. Manifestation of attacks include:
 - i. A combination of dystonia, ballism and choreoathetosis
 - ii. Attacks may be preceded by an aura
 - iii. There is no loss of consciousness
 - d. The frequency of attacks varies widely from up to 100/day to as few as one/month
 - e. Attacks usually last a few seconds to 5 minutes but occasionally for several hours
 - f. The age of onset is usually in childhood and adolescence
 - g. Familial PKD is usually seen in male patients

Familial Paroxysmal non-Kinesigenic Dyskinesia (PNKD1)

General Characteristics

1. PNKD1 is caused by mutation in the myofibrillogenesis regulator-1 (MRI) gene

Clinical Manifestations

1. Onset is in childhood or early adolescence
2. The attacks are characterized by unilateral or bilateral involuntary movements
3. Attacks may be spontaneous or triggered by alcohol, caffeine, excitement, stress, fatigue or chocolate
4. Clinical manifestations of an attack include:
 - a. An aura (some patients)
 - b. Dystonic posturing with choreic and ballistic movements
 - c. Not associated with seizures
 - d. The attack may last minutes to hours and may occur several times per day
 - e. The onset of the disorder may be as late as 50 years of age

Seizure Disorder

General Characteristics

1. Partial complex seizure disorders may retain consciousness to a degree during the manifestation of intermittent complex movements. These are most often generated from the frontal lobe
2. Complex automatisms from the temporal lobe are common and are characterized by altered consciousness. They may manifest as a continuation of the movement the patient was performing at its onset or the generation of a repetitive new movement
3. Epileptic seizures occur with both EA1 and EA2. Distinguishing features of these ataxias are:
 - a. Interictal myokymia occurs with EA1
 - b. Nystagmus and baseline nystagmus occurs with EA2

4. SCA10 has generalized and partial complex seizures

Migraine

General Characteristics

1. EA2 and FHM1 (familial hemiplegic migraine) are allelic disorders
2. Mutations in CACNA1A genes may be associated with other forms of migraine
3. Episodic vertigo is common with migraine and EA2

Differential Diagnosis of Autosomal Dominant Episodic Ataxia

EA1

1. Mutated gene is KCNA1
2. Maps to chromosome 12q13
3. Encoded protein Kv1.1
4. Age at onset 2–15 years of age
5. Attack duration is seconds to minutes
6. Myokymia is usual
7. No nystagmus
8. Seizures (occasional)
9. Tinnitus (rare)
10. Acetazolamide responsive (occasional)

EA2

1. Mutated gene – CACNA1A
2. Maps to chromosome – 19p13
3. Encoded protein – CaV 2.1
4. Age at onset – 2–20 years
5. Attack duration – hours
6. Myokymia – none
7. Nystagmus (usual)
8. Seizures – occasional
9. Tinnitus – usual
10. Acetazolamide responsive – usual

EA4/PATX (Periodic Vestibule Cerebellar Ataxia)

1. Mutated gene – not defined
2. Encoded protein – not defined
3. Age at onset – 23–60 years of age
4. Myokymia – none
5. Nystagmus – usual; gaze-evoked
6. Seizures – occasional
7. Not responsive to acetazolamide
8. Vertigo, diplopia combined with ataxia during attacks
9. Abnormal smooth pursuit
10. Abnormal vestibule-ocular reflexes
11. Attack duration – brief

EA5

1. Mutated gene – CACNB4
2. Maps to chromosome – 1q22-2q23

3. Encoded protein – CaV 2.1
4. Age of onset – 3 years to teens
5. Attack duration – hours
6. Dyokymia – none
7. Nystagmus – usual; downbeat
8. Seizures – usual; semiology similar to EJM6
9. Tinnitus – none
10. Acetazolamide – transient response
11. Dysarthria

EA6

1. Mutated gene is SLC1A3
2. Maps to chromosome 5p
3. Sporadic inheritance
4. Encoded protein – EAAT1
5. Age at onset – 5
6. Duration of attacks – hours to days
7. Myokymia – none
8. Nystagmus – interictal gaze-evoked nystagmus
9. Seizures – subclinical
10. Tinnitus – none
11. Not acetazolamide responsive
12. Slurred speech followed by headache
13. Alternating hemiplegia
14. Attacks are triggered by stress, fatigue, fever, caffeine and alcohol

EA7

1. Mutated gene – not defined
2. Loci maps to chromosome 19q13
3. Encoded protein – not defined
4. Age at onset – <20 years of age
5. Attacks are characterized by:
 - a. Weakness
 - b. Vertigo
 - c. Dysarthria
6. Duration of attacks – hours to days
7. Attacks are precipitated by exercise and excitement
8. The frequency of attacks varies widely from monthly to yearly
9. Attack frequency decreases over time

EA8

1. Mutated gene – not defined
2. Chromosome location is 1p36.13-p34.3
3. Encoded protein not defined
4. Age at onset – second year of life
5. Attacks manifest with unsteady gait, generalized weakness and slurred speech
6. Duration of attacks (minutes to hours)
7. Frequency of attacks varies from two attacks/day to two attacks per month
8. Variable clinical manifestations include:
 - a. Twitching around the eyes
 - b. Myokymia

- c. Dysarthria
- d. Intention tremor
- e. Migraine headache (two patients)
9. Clonazepam responsive

Spastic Ataxias**SPAX1***General Characteristics*

1. SPAX1 is caused by heterozygous mutation in the VAMP1 gene that maps to chromosome 12p13.31
2. The disorder is autosomal dominant

Clinical Manifestations

1. Age of onset is between 10–20 years of age
2. Initial presentation is with leg spasticity
3. Subsequently there is progressive
 - a. Head jerks
 - b. Dysarthria
 - c. Ocular movement abnormalities that include supranuclear gaze abnormalities
 - d. Pes cavus
 - e. Mild ptosis (some patients)
 - f. Decreased vibration sensibility in the lower extremities
 - g. Cognition is normal
 - h. Normal life span

Neuropathology

1. Degeneration of the corticospinal tracts and dorsal columns (Newfoundland families)
2. The mutation results in alternative splicing that produces an inactive isoform in neurons that causes decreased neurotransmitter exocytosis
3. VAMP1 is a member of a protein family that is involved in membrane-trafficking and axonal transport

Laboratory Evaluation

1. MRI:
 - a. Normal in a rural cohort studied from Newfoundland

SPAX2*General Characteristics*

1. SPAX2 is caused by homozygous mutation in the KIF1C gene that maps to chromosome 17q32; AR inheritance
2. Mutations in KIF1F5A and KIF1A encode motor proteins of the kinesin superfamily that cause spastic paraparesis and cerebellar abnormalities

Clinical Manifestations

1. Childhood onset
2. Dysarthria
3. Gait ataxia
4. Spasticity lower limb > than upper

5. Distal amyotrophy of the extremities
6. Babinski response (variable)
7. Palestinian kindred:
 - a. Tremor dysarthria, stance instability developing between age 6–10
 - b. Subsequent spasticity in the lower extremities
 - c. Head titubation, ataxia, dysmetria
 - d. Cerebellar ataxia was progressive while spasticity was static
 - e. Normal cognitive function
 - f. Fasciculations and nystagmus noted in Moroccan kindred (some patients)

Neuropathology

1. In the Palestinian kindred, cultured fibroblasts demonstrated absence of K1FC protein

Laboratory Evaluation

1. MRI:
 - a. Lesions varied widely among kindreds from no cerebellar atrophy to mild cerebral and cerebellar atrophy and white matter hyperintensities

SPAX3

General Characteristics

1. Autosomal recessive spastic ataxia type 3 is caused by homozygous or compound heterozygous complex genomic rearrangements that involve the MARS2 gene that maps to chromosome 2q33

Clinical Manifestations

1. 23 French Canadian patients from 17 families are reported
2. All patients of the cohort manifested:
 - a. Age of onset from 2–59 years (mean of 15 years of age)
 - b. Instability of gait
 - c. Spasticity
 - d. Hyperreflexia
3. Variable features include:
 - a. Urinary urgency (57%)
 - b. Dysarthria (74%)
 - c. Dystonic posturing (57%)
 - d. Horizontal nystagmus (44%)
 - e. Scoliosis (35%)
 - f. Sensorineural hearing loss (33%)
 - g. Cognitive impairment (44%)
 - h. 52% were wheelchair bound in their mid-thirties

Neuropathology – (Cultured Patient Cells Demonstrated)

1. Decreased complex I activity
2. Increased levels of reactive oxygen species
3. Decreased cell proliferation
4. Increased levels of MARS2 mRNA but a paradoxical decrease in protein levels hypothesized to occur from an RNAi-mediated decay mechanism
5. Cell expression techniques suggest a decrease in mitochondrial translation
6. Upregulated unfolded protein response

Laboratory Evaluation

1. MRI
 - a. Cerebellar atrophy in all patients
 - b. Cerebral atrophy in 43%
 - c. Periventricular white matter changes in approximately 50% of patients

SPAX4

General Characteristics

1. SPAX 4 is autosomal recessive and is caused by homozygous mutation in the MTPAP gene that maps to chromosome 10p11.23
2. The disorder has been described from a large consanguineous family of Old Order Amish ancestry

Clinical Manifestations

1. Early childhood onset
2. Slowly progressive
3. Ataxia
4. Spastic paraparesis
5. Dysarthria
6. Optic atrophy
7. Nystagmus (2 patients)
8. Developmental delay
9. Learning disabilities and emotional lability
10. No cognitive impairment

Neuropathology

1. Cultured fibroblast cell lines from patients with the p.N478D mutation (homozygous) revealed:
 - a. Loss of polyadenylation of all mitochondrial transcripts
 - b. Loss of oxidative phosphorylation complexes I and IV and decreased mitochondrial protein synthesis

Laboratory Evaluation

1. MRI:
 - a. Not defined

SPAX5

General Characteristics

SPAX5 is autosomal recessive and is caused by homozygous mutation in the AFG3L2 gene that maps to chromosome 18p11.21.

Clinical Manifestations

1. Childhood onset
2. Spastic gait
3. Progressive myoclonic epilepsy associated with generalized tonic-clonic seizures
4. Dysarthria and dysphagia
5. Lower extremity weakness with distal muscle atrophy
6. Oculomotor apraxia; ptosis
7. Dystonic movements
8. No cognitive impairment

Neuropathology

1. Muscle biopsy (electron microscopy)
 - a. Misplaced mitochondria associate with large lipid droplets
 - b. Decreased mtDNA copy number

Laboratory Evaluation

1. MRI:
 - a. Moderate cerebellar atrophy
2. EMG:
 - a. Axonal sensorimotor neuropathy

SPG7*General Characteristics*

1. SPG7 gene mutation that maps to chromosome 16q24.3
2. The gene encodes the protein paraplegin which is a component of the m-AAA protease
3. The m-AAA protease, a component of an ATP-dependent proteolytic complex, is located in the mitochondrial inner membrane
4. Degrades misfolded proteins and regulates ribosome assembly

Clinical Manifestations

1. Onset early adult life
2. Progressive weakness and spasticity of the lower legs
3. Decreased small and large fiber sensory modalities in the lower extremities
4. Urinary incontinence
5. Optic atrophy (variable)
6. Cerebellar dysarthria (variable) and ataxia
7. Supranuclear palsy (Turkish kindred)
8. Gait instability
9. Nystagmus

Neuropathology

1. Muscle biopsy:
 - a. Signs of OXPHOS deficiency
 - b. Ragged red fibers
 - c. Intense succinic dehydrogenase staining (SDH)
 - d. Cytochrome oxidase negative fibers
2. Experimental studies in mice lacking paraplegin
 - a. Axons contained abnormal mitochondria
 - b. Swollen axons with accumulated organelles and neurofilaments
 - c. Possible pathology due to defect of axonal transport

Laboratory Evaluation

1. MRI:
 - a. Some patients have normal spinal cord MRIs
 - b. White matter hyperintensities have been reported in the spinal cord, frontal lobe and midbrain

Differential Diagnosis of Ataxia with Mitochondrial Disorders

1. MERRF (myoclonic epilepsy with ragged red fibers)

2. NARP (neuropathy, ataxia, and retinitis pigmentosa)
3. Kearns-Sayre syndrome
4. MT-ATP6 (causes childhood and adult onset ataxia)
5. Leigh's syndrome

Cerebellar Subtype of Multiple System Atrophy*Overview*

Multiple system atrophy is a sporadic, progressive neurodegenerative disease that has basal ganglionic, autonomic, pyramidal and at times cortical dysfunction. It is subclassified into parkinsonian type MSA (MSA-P) and cerebellar-type MSA (MSA-C) that is dependent on predominant motor symptoms. Its prevalence is 1.9–4.9 patients per 100,000 people. Its incidence is 6/100,000 people. Approximately 65% of patients have the MSA-P form in Europe and the USA.

Clinical Manifestations

The mean age of onset of motor or autonomic symptoms is 56 years of age. MSA-C has never been reported in a patient younger than 30 years of age. It is extremely rare in patients older than 75 years of age. Autonomic signs and symptoms are manifested by erectile dysfunction, urinary incontinence and retention and other non-motor features that often precede motor symptoms. Reduced sweating and constipation are common while postural hypotension is a late complication.

The most common cerebellar signs at motor presentation are an ataxic unstable gait, dysarthria, limb ataxia and gaze-evoked nystagmus. In the early phase of the disorder there are defects in smooth pursuit (saccadic substitution), square wave jerks and dysmetric saccades. Hyperreflexia with Babinski signs are frequent concomitant with cerebellar signs.

Parkinsonism usually occurs approximately 5 years after cerebellar features and is of the akinetic-rigid form. In approximately 50% of patients it is L-DOPA responsive. Other motor signs include craniocervical dystonia that may induce camptocormia and Pisa syndrome.

Rarely there is dystonia of the face, hands and feet. Stridor, from laryngeal abductor palsy, usually occurs late in the disease course and has been suspected in sudden death. Poor autonomic control of extremity circulation causes the "cold hand sign". Approximately 30% of patients develop pain from musculoskeletal and dystonic posture generators.

A majority of patients develop REM sleep behavior disorder. Approximately 25% of patients experience excessive daytime sleepiness.

Cognitive impairment, primarily involving executive function and verbal learning as well as depression, anxiety and pathologic laughing and crying, affect a proportion of patients.

Neuropathology

1. Argrophilic filamentous aggregates in the cytoplasm of oligodendrocytes are seen in all MSA variants (glial cytoplasmic bodies)

2. Glial cytoplasmic bodies are associated with gliosis and neuronal loss in the:
 - a. Basal ganglia
 - b. Cerebellum
 - c. Pons
 - d. Inferior olivary nucleus
 - e. Spinal cord
3. Patients may demonstrate:
 - a. A striatonigral pattern
 - b. An olivopontocerebellar pattern (OPCA)
 - c. A balanced pattern of pathology in both systems
4. Degeneration of autonomic nuclei in the brainstem and spinal cord. Post-ganglionic denervation is also a major component of the autonomic failure. This is demonstrated by reduced sudomotor nerve density in sweat glands which may be seen prior to degeneration of ANS nuclei:
 - a. Alphasynuclein is the major component of glial cytoplasmic inclusions (GCIs). Other components of GCIs include:
 - i. Ubiquitin
 - ii. Tau
 - iii. p25-alpha
 - iv. Heat shock proteins
 - v. Dopamine
 - vi. DARPP-32
 - vii. Other proteins
5. Neuronal cytoplasmic inclusions (NCIs) and neuronal nuclear occlusions (NNIs) are also observed in MSA but GCIs are the most reliable criteria for the definitive diagnosis of MSA
6. GCIs:
 - a. May be facilitated by p25-alpha, a normal component of myelin
 - b. Cause oligodendrocyte death
 - c. There is evidence to support oligodendroglial dysfunction that leads to abnormal synthesis and release of trophic factors and other signaling molecules that triggers apoptosis as a major pathogenic mechanism in the disorder
 - d. Mitochondrial respiratory chain dysfunction may also be a factor in this degeneration due to:
 - i. COQ2 gene mutations that impair parahydroxybenzoate polyprenyltransferase (necessary for coenzyme Q10 synthesis) that have been associated with an increased risk of MSA
 - ii. Excessive generation of reactive oxygen species from mitochondrial dysfunction in activated microglia that also release:
 1. Nitrogen species
 2. Inflammatory cytokines
 - iii. An Increased risk of developing MSA has been demonstrated in:
 1. SNPs of genes that encode alpha-synuclein (the SNCA gene)
 2. SNPs in genes encoding prion protein

3. Loss of function mutations of the phenyl benzoate-polyprenyl transferase gene
- iv. There is evidence that proteosomal and autophagic degradation of alpha-synuclein is impaired in affected oligodendrocytes
- v. There may be increased uptake of alpha-synuclein from the cerebrospinal fluid that may be a component of mechanisms in the formation of GCIs

Laboratory Evaluation

1. MRI:
 - a. "Hot cross bun" sign in the ventral pons (possibly in 80% of patients); also seen in other pathologies but particularly in SCA2
 - b. Striated dopaminergic denervation or glucose hypometabolism demonstrated by SPECT or PET in patients with cerebellar symptomatology

Differential Diagnosis of MSA-C

1. Secondary cerebellar disorders are caused by:
 - a. Toxins
 - b. Infections
 - c. Vitamin deficiency
 - d. Tumors
 - e. Autoimmune demyelination
 - f. Paraneoplastic syndromes
 - g. Drugs
 - h. Superficial siderosis
 - i. Endocrine disorders
 - j. Vascular disease
 - k. Congenital defects that decompensate in middle age
2. Late onset autosomal dominant SCAs that resemble MSA-C:
 - a. SCA6 is the most common
 - b. SCA2 and SCA3
 - i. In Asian and African patients
 - ii. There is associated L-Dopa responsive Parkinsonism
3. Permutation of the FMR1 Gene
 - a. Causes FXTAS which manifests:
 - i. Cerebellar ataxia
 - ii. Postural and intention tremor
 - iii. Psychiatric disorders
 - iv. Neuropathy
 - v. Cognitive impairment
4. Sporadic adult onset ataxia:
 - a. Age at onset is approximately 50 years of age (similar to MSA-C)
 - b. Much longer survival in sporadic late onset ataxia
 - c. Approximately 50% of patients can walk after 12 years of disease whereas MSA-C are wheelchair bound after approximately 5 years
 - d. Autonomic dysfunction is severe in MSA-C
 - e. Nystagmus, gaze paralysis, decreased or absent ankle deep tendon reflexes are more commonly seen with sporadic late onset ataxia

- f. MRI demonstrates the “hot cross bun” sign in the ventral pons in MSA-C
- g. Proton MR spectroscopy
 - i. Lower levels of lactate in the pons in MSA-C
- h. Cerebral blood flow is lower in the pons in MSA-C than sporadic late onset cerebellar ataxia
- i. MSA-C
 - i. Denervation of the external anal sphincter and urethral sphincter which can be demonstrated by EMG
 - ii. Degeneration of Onuf’s nucleus in MSA-C may not occur early in MSA-C
- j. CSF biomarkers are being evaluated:
 - i. Combined neurofilament light chains, 3-methoxy-4-hydroxyphenyl ethylene glycol (MHPG) and dopamine metabolites homovanillic acid and dihydroxyphenylacetic acids are being evaluated for differentiation of MSA-C from late onset cerebellar ataxias

Congenital Defects of the Cerebellum

General Characteristics

1. There is an extended period of ontogenesis which may make the cerebellum more vulnerable to environmental factors
2. Neuroblast migration from the external granular layer lasts for one year
3. Cerebellar development occurs from 32 days of gestation to one year
4. The cerebellar cortex is susceptible to the toxic effects of drugs, chemicals, viral infections, ischemia and hypoxia

Hypoplasia or Aplasia of the Vermis

General Characteristics

1. Possible X-linked dominant inheritance

Clinical Manifestations

1. Hypotonia at birth
2. Delayed milestones
3. Mild cerebellar ataxia
4. Non-progressive course
5. Slight cognitive impairment
6. Nystagmus occasional

Neuropathology

1. Associated cerebellar hemispheric hypoplasia (many patients)
2. Enlarged posterior fossa with elevation of the torcula
3. Cerebellar hemispheres have an abnormal folial pattern with wide separation of the hemispheres and shallow sulci, thinned white matter
4. MRI:
 - a. Large posterior fossa with elevated torcula
 - b. Vermian hypoplasia
 - c. Widely separated cerebellar hemisphere, shallow sulci, thinned white matter

- d. Retrocerebellar CSF collection (some patients)
- e. Some patients demonstrate isolated vermian atrophy
- f. Associated supratentorial anomalies:
 - i. Agenesis of the corpus callosum
 - ii. Hydrocephalus
 - iii. Patients with callosum agenesis may also have the Dandy-Walker malformation
- g. Small pons (some patients)

Joubert Syndrome

General Characteristics

1. Joubert syndrome is caused by homozygous mutation in the INPP5E gene that maps to chromosome 9q34
2. There is great genetic heterogeneity in the disorder (at present mutations in 19 genes)

Clinical Manifestations

1. Developmental delay
2. Dysregulation of breathing pattern
3. Hypotonia
4. Tremor
5. Cognitive impairment
6. Facial dysmorphisms:
 - a. Large head
 - b. Prominent forehead
 - c. High rounded eyebrows
 - d. Triangular mouth
 - e. Tongue protrusion (with tremor)
 - f. Prognathism
7. Hyperpnea intermixed with central apnea
8. Behavioral problems/autism (some)
9. Oculomotor apraxia (Italian kindred)
10. Variable signs:
 - a. Retinal dystrophy
 - b. Renal abnormalities (often cysts)
 - c. Speech apraxia
11. Joubert syndrome and clinical subtypes of related disorders:
 - a. Retinal disease:
 - i. Pigmentary retinopathy similar to retinitis pigmentosa
 - ii. Coloboma
 - 1. Chorioretinal dysplasia
 - 2. Associated with hepatic fibrosis
 - b. Ocular abnormalities:
 - i. Ptosis, strabismus and/or amblyopia
 - ii. Third nerve palsy (rare)
 - c. Renal disease:
 - i. Nephronophthisis (tubulointerstitial nephropathy)
 - ii. Cystic dysplasia (corticomedullary function)
 - iii. Prevalence of renal disease is 23–30% of patients
 - d. Oculorenal disease:
 - i. Retinal and renal disease in the same patient
 - e. Hepatic disease

- i. Congenital hepatic fibrosis (ductal plate malformation)
- ii. May be associated with chorioretinal coloboma
- iii. The COACH syndrome includes:
 - 1. Coloboma
 - 2. Cognitive impairment
 - 3. Oligophrenia
 - 4. Ataxia
 - 5. Cerebellar vermis hypoplasia
 - 6. Hepatic fibrosis
- f. Orofacial digital dysmorphism:
 - i. Polydactyly occurs in approximately 8% of patients. It can be unilateral or bilateral and is postaxial; mesoaxial polydactyly (rare)
 - ii. Preaxial polydactyly of the toes
 - iii. Facial dysmorphisms:
 - 1. Broad forehead
 - 2. Arched eye brows
 - 3. Strabismus
 - 4. Ptosis
- g. Classic facial dysmorphisms:
 - i. Long face with bitemporal narrowing
 - ii. High arched eyebrows
 - iii. Ptosis
 - iv. Prominent nasal bridge
 - v. Triangular mouth
 - vi. Prognathism
 - vii. Tongue hypertrophy (due to chronic tongue movements)
- h. Musculoskeletal abnormalities:
 - i. Cone-shaped epiphyses
 - ii. Scoliosis
- i. Endocrine abnormalities:
 - i. Pituitary hormone deficiency of isolated growth hormone, or hypothyroidism to panhypopituitarism
- j. Obesity
- k. Laterality defects:
 - i. Situs inversus
- l. Rare Hirschprung's disease
- m. Rare congenital heart disease

Neuropathology

- 1. Vermal agenesis
- 2. Malformation of multiple brainstem structures
- 3. Lack of superior cerebellar commissural fibers
- 4. All of the genes associated with the disorder encode proteins that are associated with the assembly and biology of cilia
- 5. The WNT and SHH pathways as well as the WNT-planar cell polarity pathway (PCP) are putative in the pathogenesis of the disorder
- 6. Kallmann syndrome has been described with partial cerebellar vermis hypoplasia possibly related to fibroblast growth factor deficiency which is essential for cerebellar development

Laboratory Evaluation

- 1. MRI:
 - a. The "molar tooth" sign:
 - i. Deep interpeduncular fossa
 - ii. Thick and elongated superior cerebellar peduncles
 - iii. Hypoplastic or aplastic superior cerebellar vermis
 - b. Cerebellar heterotopias and cerebellar folial disorganization
 - c. Cerebrospinal fluid in the fourth ventricle or the posterior fossa that is similar to the Dandy-Walker malformation
 - d. Occipital encephalocele or meningocele (some patients)
 - e. Brainstem and hypothalamic hamartomas (most prominent in patients with oral-facial digital syndrome type VI)
 - f. Ventriculomegaly or hydrocephalus
 - g. Agenesis of the corpus callosum
 - h. Hippocampal malformations
 - i. Cortical anomalies that include:
 - i. Heterotopias
 - ii. Dysplasia
 - iii. Polymicrogyria
 - iv. Neuroepithelial cysts
- 2. Diffusion tensor imaging:
 - a. Absence of delineation of the corticospinal and superior cerebellar tracts
- 3. Functional MRI:
 - a. Abnormal activation patterns during motor tasks

Dandy-Walker Syndrome (DWM)

General Characteristics

- 1. Dandy-Walker malformation is caused by deletions of Z1C1
- 2. Zinc finger protein of the cerebellum and Z1C4
- 3. Zinc finger of the cerebellum 4 that maps to chromosome 3q24
- 4. The recurrent risk of 1–2% for non-syndromic form of the Dandy-Walker malformation is against Mendelian inheritance

Clinical Manifestations

- 1. Onset at birth with bulging occiput
- 2. Early hypocephalus
- 3. Cranial nerve palsies
- 4. Nystagmus
- 5. Truncal ataxia
- 6. Cognitive impairment (in approximately 50% of patients)
- 7. Hypotonia
- 8. Large posterior occiput in adults

Neuropathology

- 1. Decreased postnatal granule cell progenitor proliferation
- 2. Z1C1 and Z1C4 have been shown to have SHH-dependent and independent functions during cerebellar development (in genetically manipulated models)

Laboratory Evaluation

1. MRI:
 - a. Partial or complete absence of the cerebellar vermis
 - b. Posterior fossa cyst contiguous with the fourth ventricle
 - c. Elevated transverse sinuses
 - d. Thinning and bulging of the bones of the posterior fossa
 - e. Atresia of the foramina of Magendie and Luschka (some)
 - f. Associated conditions include:
 - i. Congenital heart disease
 - ii. Cleft lip and/or palate
 - iii. Neural tube defects
 - iv. Warburg syndrome
 - v. Meckel syndrome
 - vi. New association:
 1. Diabetes insipidus, central hypothyroidism, renal tubular acidosis

Pontocerebellar Hypoplasia (PcH)*General Characteristics*

1. PcH is a heterogeneous group of disorders associated with chromosomal defects, metabolic disorders and congenital muscular dystrophies
 - a. Subunits of the tRNA splicing endonuclease complex, TSEN54, TSEN34 and TSEN2 are involved in PcH2, PcH4, PcH5 and 1 patient with PcH1
 - b. Some patients with PcH1 as well as PcH6 have mutations in the mitochondrial arginyl tRNA synthetase RARS2 gene
 - c. Large deletions and mutations of the ULDLR gene as in Reelin associated lissencephaly have been reported with PcH
 - d. CASK mutations have recently been described as a new phenotype

Clinical Manifestations

1. There are seven described types
2. Severe developmental delay
3. Poor feeding, lethargy, hypotonia and apneic spells
4. Seizures (variable)
 - a. Respiratory difficulty

Neuropathology

1. Abnormally small cerebellum and brainstem
2. Type 6 demonstrates homozygous or compound heterozygous mutation in the RARS2 gene that maps to chromosome 6q15
3. The gene encodes the mitochondrial protein arginyl tRNA synthetase
4. One kindred demonstrates deficient mitochondrial activity of complexes I, II and IV
5. Patient derived lymphoblastoid cell lines demonstrate:
 - a. Reduced proliferation and increased expression of the cell cycle inhibitor INK4A (cyclin-dependent kinase inhibitor 2A p161 INK4A)

Laboratory Evaluation

1. MRI:
 - a. Progressive atrophy of the cerebellum, pons and cerebral cortex
 - b. Particular thinning of the pons and atrophy of the cerebellar hemisphere
 - c. Cerebellar vermis hypoplasia

Chiari Malformation*General Characteristics*

1. Chiari I
 - a. The vermis of the cerebellum protrudes through the foramen magnum > 5 mm
2. Chiari II
 - a. Vermis herniation
 - b. Downward displacement of the medulla with nuclear dysplasia
 - c. Occurs with a meningocele
 - d. Associated syringomyelia
3. Chiari III
 - a. Cervical spina bifida
 - b. Cerebellar encephalocele
 - c. And elongated medulla
4. Chiari IV
 - a. The attributes of malformations I–III with additional absence of the cerebellum

Clinical Manifestations

1. Short neck, low hairline and some restriction of movement to all planes
2. Shallow posterior fossa
3. Associated expected signs and symptoms of a cervical syrinx with Chiari II
4. Severe C2 headache associated with coughing or any form of valsalva maneuver
5. Sudden gait ataxia after age 30
6. Hoarseness and deficits of lower cranial nerves which may be insidious or has an acute onset
7. Increased reflexes; pyramidal signs
8. Downbeat nystagmus if there is compression of the cerebellar floccular nodular lobe
 - a. Late onset hydrocephalus

Neuropathology

1. Herniated cerebellar tissue shows:
 - a. Purkinje and granule cell loss
 - b. Shrinkage and gliosis of folia and myelin depletion
 - c. Distortion of the brainstem tracts and nuclei
 - d. Heterotopias in the cerebellar hemispheric white matter
 - e. Pontomedullary junction may be ill defined
 - f. The upper four to six cervical roots are angled upward towards their intervertebral canals
 - g. Variably there may be hypoplasia or agenesis of cranial nerve, olivary and pontine nuclei

- h. Associated anomalies include:
 - i. Subependymal nodular heterotopias in the walls of the lateral ventricles
 - ii. Thickening of the massa intermedia
 - iii. Spina bifida
 - iv. Myelomeningocele > meningocele and is located in lumbosacral segments
 - v. Hydromyelia (C8)
 - vi. Diastematomyelia
 - vii. Diplomyelia
 - viii. Aqueductal forking, forking and gliosis
 - ix. Cerebral hemisphere may demonstrate polygria

Laboratory Evaluation

1. MRI:
 - a. Chiari type I
 - i. The cerebellar tonsils are at least 5 mm below the foramen magnum
 - ii. They are usually pointed and fibrotic
 - b. Chiari type II
 - i. The vermis is herniated through the foramen magnum
 - ii. Downward displacement of the medulla
 - iii. Associated syringomyelia which is usually at the cervical medullary function
 - iv. Associated meningocele
 - c. Chiari type III
 - i. Cervical spina bifida
 - ii. Cerebellar encephalocele
 - iii. Elongated medulla
 - iv. "Beaked" collicular plate of the midbrain
 - v. Widening of the angles of the petrous pyramid
 - d. Chiari IV
 - i. Above features of the other types with absence or hypoplasia of the cerebellum

Rhombencephalosynapsis

General Characteristics

1. A developmental midline defect primarily affecting the vermis
2. Many associated anomalies

Clinical Manifestations

1. Cognition may be normal
2. Hydrocephalus may be present and is most often due to aqueductal stenosis
3. Medical associations include:
 - a. Vertebral anomalies
 - b. Anal atresia
 - c. Cardiovascular anomalies
 - d. Trachea-esophageal fistulas
 - e. Renal anomalies
 - f. Ataxia is the most common neurologic finding in non-syndromic patients

Neuropathology

1. Absence of the vermis; remnants of the nodulus may remain
2. Other midline associated anomalies include:
 - a. Atresia of the septum pellucidum
 - b. Fusion of the fornices
 - c. Holoprosencephaly
 - d. Fusion of the colliculi
 - e. Forking or atresia of the aqueduct
 - f. Fusion of the thalami
 - g. Agenesis of the corpus callosum
 - h. Neural tube defects
3. Associated syndromes:
 - a. Gómez-López-Hernández syndrome:
 - i. Cerebellotrigeminal dermal dysplasia
 - ii. Parietal skin alopecia
 - iii. Trigeminal anesthesia
 - iv. Keratitis
 - v. Corneal opacity
 - vi. Low-set ears
 - vii. Brachy-turricephaly (due to craniosynostosis); abnormal vertical height of the skull

Laboratory Evaluation

1. MRI:
 - a. A spectrum of severity, the gradient ranged between total absence of the vermis and retained parts of the anterior and posterior vermis including the nodulus
 - b. Hydrocephalus due to aqueductal stenosis
 - c. Rare findings include:
 - i. Fusion of the dentate nuclei
 - ii. Fusion of the cerebral peduncles
 - iii. Septo-optic dysplasia

Cerebellar Dysplasias

Lissencephaly with Cerebellar Dysplasia

General Characteristics

1. An autosomal recessive form of lissencephaly is associated with cerebellar, hippocampal and brainstem malformation
2. Two mutations in the reelin gene (RELN) that maps to chromosome 7q22 are causative

Clinical Manifestations

1. Varied phenotype
 - a. Microcephaly
 - b. Cognitive impairment
 - c. Spasticity
 - d. Congenital lymphedema (some)
 - e. Myopia and nystagmus (some)
 - f. Seizure (some)
 - g. Craniofacial dysmorphism

Neuropathology

1. Mutations disrupt RELN cDNA that cause low or absent reelin protein
2. The secreted protein binds to the very low density lipoprotein receptors (VLDLR) the apolipoprotein-E-receptor-2 (ApoER2), $\alpha 3\beta$ -integrin and protocadherin
3. Reelin mutations cause abnormalities of the cerebellum, hippocampus and brainstem
4. Associated cortical lissencephaly (parietal lobe) with thickened cortex and 4 rather than 6 layers

Laboratory Evaluation

1. MRI:
 - a. Small size of the vermis and cerebellar hemisphere
 - b. Smooth appearing cerebellar cortex
 - c. No folds, no fissures and no cerebellar lobulation
 - d. Small pons
 - e. Prominent agyria of the cerebral cortex (in some patients)

Differential Diagnosis of Diffuse Cerebellar Dysplasia

1. Lissencephaly with cerebellar dysplasia
2. Congenital muscle dystrophy
 - a. Fukuyama and muscle-eye-brain disease have:
 - i. Cortical or subcortical cerebellar cysts
 - ii. Multiple small cortical folia (cerebellar polymicrogyria)
 - iii. The dysplasia is most severe in the superior cerebellum
 - iv. Fukuyama has cobblestone cortex
3. Merosin deficient muscular dystrophy
 - a. Diffuse and delayed myelination of deep cerebral and cerebellar white matter
 - b. Inferior vermian hypoplasia
 - c. Normal cerebellar cortex
4. Walker-Warburg and muscle-eye-brain disease
 - a. Pontine hypoplasia with a midline longitudinal cleft
5. Congenital cytomegalovirus infection
 - a. Cerebellar hemispheres pathology parallels that of the cerebral hemispheres
 - b. Small cerebellar hemispheres with decreased foliation, shallow sulci
 - c. Rare cerebellar cortical calcification
 - d. Pontine shrinkage is dependent on the extent of cerebral cortex and cerebellar involvement
6. Diffuse cerebellar dysplasia
 - a. Bizarre, thick folia with abnormal orientation
 - b. Slight reduction of cerebellar white matter

Differential Diagnosis of Focal Cerebellar Dysplasia

1. Rhombencephalosynapsis:
 - a. Absence of the cerebellar vermis
 - b. Midline fusion of the two cerebellar hemispheres
2. Joubert syndrome
 - a. "Molar tooth" malformation

3. Lhermitte-Duclos disease

- a. Sharply defined non-enhancing cerebellar hemispheric mass
- b. An outer layer of radial and superficial parallel myelinated fibers with an inner layer of dysplastic neurons

Cerebellar Ataxic Syndromes***Ramsay Hunt Syndrome I****General Characteristics*

1. A very heterogeneous syndrome
2. A recent description of a mutation in the GOSR2 gene that maps to chromosome 17q21

Clinical Characteristics

1. Early onset ataxia
2. Action myoclonus by age 6
3. Scoliosis
4. Seizures (tonic-clonic)
 - a. Syndactyly

Neuropathology (1 Autopsied Patient)

1. Mild cerebral atrophy
2. Minor Purkinje cell loss and gliosis in the vermis
3. GOSR2 protein is a member of the SNARE family of vesicle docking proteins
4. The protein has a role in protein transport from the endoplasmic reticulum into the Golgi apparatus

Laboratory Evaluation

1. EEG:
 - a. Generalized spike-and-wave often posterior predominant
 - b. Polyspike
2. Borderline or mildly elevated CK
3. MRI:
 - a. Normal in 5/6 patients. One patient had mild cerebellar atrophy
4. Muscle biopsy and EMG may be normal

Chediak-Higashi Disease (CHS)*General Characteristics*

1. CHS is caused by homozygous or compound heterozygous mutation of the lysosomal trafficking regulator gene (LYST) that maps to chromosome 1q42; autosomal recessive deletion

Clinical Manifestations

1. Decreased hair and eye pigmentation (partial albinism)
2. Photophobia
3. Nystagmus
4. Spinocerebellar phenotype
5. Bleeding diathesis
6. Frequent infections

7. An accelerated phase:
 - a. Pancytopenia
 - b. High fever
8. Ataxia
9. Peripheral neuropathy
10. Cognitive impairment (some patients)

Neuropathology

1. Giant azurophilic granules in the peripheral blood (white cells)
2. Huge lysosomes and cytoplasmic inclusions within tissue
3. Lymphoproliferative stage:
 - a. Generalized lymphohistiocytic infiltrates, hepatosplenomegaly, lymphadenopathy, pancytopenia and often bleeding

Laboratory Evaluation

1. MRI:
 - a. Cerebellar atrophy
 - b. Hemorrhage from coagulopathy
2. Deficiency of cathepsin G and elastase
3. In cells from patients with CHS:
 - a. Peptide loading onto major histocompatibility complex class II molecules and antigen presentation are defective
4. EMG (some kindreds):
 - a. Sensorimotor axonal neuropathy

Clinical Variants of Olivopontocerebellar Atrophy (Older Classification)

1. Type I – Menzel variant
 - a. Cerebellar ataxia
 - b. Dorsal column involvement
2. Fick-Hamacher – Type II
 - a. Prominent cranial nerve involvement
 - b. Cerebellar ataxia
3. Type III
 - a. AD
 - b. Pure Cerebellar ataxia
4. Type IV
 - a. Retinitis pigmentosa
 - b. Cerebellar ataxia
5. Marie-Foix-Alajouanine syndrome
 - a. General characteristics
 - i. Primarily a slowly progressive late onset cortical cerebellar atrophy
 - b. Clinical manifestations:
 - i. Onset in the fifth and sixth decades
 - ii. Gait ataxia > appendicular in some patients
 - iii. Minimal or absent dysarthria
 - iv. Cognitive impairment may occur
 - c. Neuropathology
 - i. Loss of Purkinje cells throughout the cerebellum
 - ii. Rarefaction of the granular cell layer in areas where Purkinje cell loss is severe

- iii. Vermian involvement can be predominant
- iv. Neuronal loss in the inferior olivary nucleus occurs concomitantly with granular cell and molecular layer degeneration
- d. Laboratory evaluation
 - i. MRI:
 1. Cortical and olivary nuclear atrophy in the cerebellum and brainstem

Pelizaeus-Merzbacher Disease (PMD)

General Characteristics

1. PMD is a rare leukodystrophy caused by mutation in the PLP1 gene that maps to the Xq22.2 chromosome
2. There are a great number of PLP1 gene mutations that include duplications, point mutations and deletions that may be responsible for the wide clinical spectrum of the disorder

Clinical Manifestations

1. There are 3 types of PMD
 - a. Classic type:
 - i. Onset in infancy and death in late adolescence or young adulthood
 - ii. Initial rotary and nystagmoid eye movements
 - iii. Jerking and rolling head movements
 - iv. Nystagmus lessens as the patient matures
 - v. Ataxia, spasticity and involuntary movements sequentially appear
 - vi. Optic atrophy
 - b. Connatal type:
 - i. Rapid progression
 - ii. Fatal in infancy and childhood
 - c. The transitional form:
 - i. Onset in childhood
 - ii. Stridor occurs in some patients
 - iii. Rotary nystagmus
 - iv. Abnormal head movements
 - v. Sequential development of spasticity of the legs and arms
 - vi. Cerebellar ataxia
 - vii. Cognitive impairment
 - viii. Parkinsonian features

Neuropathology

1. Proton magnetic resonance spectroscopy
 - a. Affected white matter demonstrates increased N-acetyl aspartate, glutamine, myo-inositol, creatine and phosphocreatine
 - b. Decreased concentration of choline-containing compounds
 - c. Pattern supports enhanced neuroaxonal density, astrogliosis that supports dys- and hypomyelination
2. Absence of proteolipid apoprotein (lipophilin) in the brain

3. Possible involvement of the unfolded protein response, a stress induced signaling cascade that regulates the secretory pathway through the endoplasmic reticulum as a major pathogenic mechanism of the disorder
4. PLP1-duplications may be causative in the classic and transitional forms; lead to defective CNS myelination
5. Missense mutations may give rise to more severe forms of the disease while deletions and null mutations to mild PMD. The most common mutations are duplications that cause the classical intermediate form of the disease

Laboratory Evaluation

1. MRI:
 - a. Bilateral and multiple regions of signal hyperintensity in the periventricular and subcortical white matter
 - b. Abnormal brainstem auditory evoked potentials; waves III, IV and V (generated in the pons and midbrain) are primarily affected
 - c. Visual and somatosensory evoked potentials may demonstrate conduction delay

Seminal Features of Some Named Cerebellar Syndromes

1. Marie Sanger Brown
 - a. Cranial nerve involvement
2. Marinesco-Sjögren
 - a. Cataracts
3. Friedreich's ataxia
 - a. Dilated cardiomyopathy
 - b. Scoliosis
4. Marie-Foix-Alajouanine
 - a. Pure cerebellar cortical deficit
 - b. Late onset
5. Gordon Holmes
 - a. Cortical cerebellar atrophy
 - b. Hypogonadism
6. Ramsay Hunt type I
 - a. Progressive myoclonus
7. Madame Louis-Bar
 - a. Ataxia telangiectasia (ATM)
 - b. Involuntary movements
 - c. Lymphoma
8. Fahr's disease
 - a. Calcification of the dentate nucleus and basal ganglia
9. Menzel variant of OPCA
 - a. Posterior column involvement
10. Fick-Hamacher variant of OPCA (cranial nerve involvement)
11. Leigh's disease (m.8993T)
 - a. Optic atrophy
12. Gerstmann-Sträussler-Scheinker variant of CJ disease
 - a. Dementia (rapidly progressive)
13. Pelizaeus-Merzbacher disease
 - a. Nystagmus
14. Russell syndrome (DRPLA); SCA7

- a. Myoclonus
- b. Basal ganglia involvement
15. Adult Krabbe's disease
 - a. Increased protein in the CSF
 - b. Peripheral neuropathy
16. Behr disease
 - a. Optic atrophy
17. SCA3/Machado-Joseph disease
 - a. Bulging eyes
 - b. Distal amyotrophy
18. Spastic ataxia
 - a. HSP4
 - b. Spasticity
19. Gillespie syndrome
 - a. Aniridia
 - b. Congenital ataxia
 - c. Cognitive impairment
20. Granule cell hypoplasia
 - a. Congenital ataxia
 - b. Cognitive impairment
21. Tay-Sachs disease
 - a. Cherry red spot
 - b. Intention tremor
 - c. Neurogenic features
22. Fabry's disease
 - a. Stroke
 - b. Angiokeratomas
23. Refsum's disease
 - a. Intermittent neuropathy
 - b. Ichthyosis
 - c. Cataracts and hearing loss
24. Bassen-Kornzweig disease
 - a. Abetalipoproteinemia
 - b. Peripheral neuropathy
25. Hartnup disease
 - a. Rash on exterior surfaces
26. Joubert disease
 - a. Vermian atrophy
 - b. Episodic hyperpnea

Distinguishing Clinical Manifestations of Abnormal Dominant Cerebellar Ataxias

1. SCA1
 - a. Pyramidal signs
 - b. Peripheral neuropathy
2. SCA2
 - a. Slow saccades
 - b. Myoclonus
 - c. Areflexia
3. SCA3
 - a. Slow saccades
 - b. Extraparamidal signs
 - c. Bulging eyes
 - d. Peripheral neuropathy

- e. Amyotrophy
4. SCA4
 - a. Sensory neuropathy
5. SCA5
 - a. Early onset with slow progression
6. SCA6
 - a. Late onset
 - b. May have no family history
 - c. Nystagmus
 - d. Minimal ataxia
7. SCA7
 - a. Macular degeneration
8. SCA8
 - a. Minimal ataxia
9. SCA9
 - a. Adult onset of ataxia
 - b. Ophthalmoplegia (some patients)
 - c. Pyramidal tract signs
 - d. Dysarthria
10. SCA10
 - a. Generalized or complex partial seizures
11. SCA11
 - a. Mild
 - b. Pyramidal signs
 - c. Abnormal extraocular movements (some)
12. SCA12
 - a. Tremor
 - b. Dementia
13. SCA13
 - a. Cognitive impairment
14. SCA14
 - a. Early onset disease has intermittent myoclonus
15. SCA15/SCA16
 - a. Slowly progressive
 - b. Action and postural tremor
 - c. Pyramidal tract (some patients)
16. SCA17
 - a. Gait ataxia
 - b. Dementia
17. SCA18
 - a. Pyramidal tract signs
 - b. Extremity weakness
 - c. Sensory axonal neuropathy
18. SCA19/SCA22
 - a. Cerebellar syndrome
 - b. Myoclonus (rare)
 - c. Cognitive impairment (occasional)
19. SCA20
 - a. Palatal tremor
 - b. Dysphonia
20. SCA21
 - a. Extrapyramidal signs
21. SCA23
 - a. Distal extremity sensory loss
22. SCA24
 - a. Redesignated as autosomal recessive SCAR4
 - b. Late onset (3rd decade)
 - c. Gait, trunk, limb ataxia
 - d. Horizontal macrosaccadic oscillations of high velocity
 - e. Myoclonic jerks and fasciculations
 - f. Pes cavus
23. SCA25
 - a. Sensory neuropathy
 - b. Facial tics
 - c. Gastrointestinal symptoms
24. SCA26
 - a. Pancerebellar syndrome
25. SCA27
 - a. Cognitive impairment
 - b. Poor ocular pursuit
 - c. Gaze-evoked nystagmus
26. SCA28
 - a. Ophthalmoparesis
 - b. Ptosis
27. SCA29
 - a. Early onset and new progressive ataxia
 - b. Allelic variant of SCA15
28. SCA30
 - a. Slowly progressive
 - b. Pure ataxia
29. SCA31
 - a. Late onset
 - b. Decreased muscle tone
30. SCA32
 - a. Cognitive deficits
 - b. Azoospermia and testicular atrophy
31. SCA33
 - a. Not unique
32. SCA34
 - a. Papulosquamous erythematous ichthyosiform plaques
33. SCA35
 - a. Late onset
 - b. Slowly progressive gait and limb ataxia
34. SCA36
 - a. Late onset
 - b. Truncal ataxia
 - c. Dysarthria
 - d. Variable motor neuron disease
 - e. Sensorineural hearing loss
35. SCA37
 - a. Late onset
 - b. Dysarthria
 - c. Abnormal vertical eye movements
36. SCA38
 - a. Adult onset
 - b. Axonal neuropathy
37. SCA40
 - a. Adult onset
 - b. Brisk reflexes
 - c. Spasticity

Differential Diagnosis of Autosomal Recessive Hereditary Ataxias

1. Friedreich's ataxia
2. AOA1
3. AOA2
4. Ataxia telangiectasia (ATM)
5. Cerebrotendinous xanthomatosis (CTX)
6. Refsum syndrome
7. Vitamin E deficiency
8. ARSACS

Differential Diagnosis of Autosomal Recessive Disorders Associated with Ataxia and/or Cerebellar Hypoplasia That Are Caused by Biallelic Pathogenic Variants in Related Genes

1. Joubert syndrome
2. Congenital disorder of glycosylation
3. Pontocerebellar hypoplasia
4. Peroxisomal biogenesis disorders (Zellweger spectrum diseases)
5. Perrault syndrome

Differential Diagnosis of X-Linked Hereditary Ataxias

1. X-linked sideroblastic anemia and ataxia
2. CASK-related disorders
3. FXTAS
4. X-linked mental retardation with cerebellar hypoplasia and distinctive facial appearance
5. Systemic X-linked mental retardation (Christianson type)
6. X-linked spinocerebellar ataxia 5

Genetic Differential Diagnosis

1. More than one family member is affected
 - a. Autosomal dominant
 - i. The family history supports male and female probands in multiple generations
 - ii. The most common autosomal dominant ataxias are; SCA1, SCA2, SCA3, SCA6 and SCA7
 1. All are trinucleotide repeat expansions
 - b. Autosomal recessive
 - i. The family history shows that only siblings are affected in one generation of the family
 - ii. The parents are consanguineous
 - iii. Friedreich's ataxia, ataxia-telangiectasia, AOA1, AOA2, vitamin E deficiency, Refsum's disease and cerebrotendinous xanthomatosis are the most common
 - c. X-linked inheritance;
 - i. The family history shows that the affected members are male and are related to each other by females
 - d. Simplex patient
 - i. Only one family member is affected
 1. An acquired rather than genetic etiology for the disorder

2. A de novo mutation associated with an autosomal dominant ataxia
3. Decreased penetrance of a pathogenic variant associated with autosomal dominant ataxia
4. A single occurrence of an autosomal recessive X-linked disease in the family
5. An incorrect history with alternate paternity
- ii. If the cause is not a secondary cerebellar disorder
 1. There is an approximately 13% probability that the patient has:
 - a. SCA1, SCA2, SCA3, SCA6, SCA8 or SCA17
 - b. Friedreich's ataxia, AOA1 or AOA2

Differential Diagnosis of Intermittent Metabolic Ataxia

1. Defects of urea cycle enzymes:
 - a. Ornithine transcarboxylase (X-linked)
 - b. Argininosuccinate synthetase
 - c. Arginase deficiency
 - d. Hyperornithinemia (not a urea acid cycle enzyme)
 - e. All with hyperammonemia
2. Amino acidurias:
 - a. Branch chain ketoaciduria
 - b. Isovaleric acidemia
 - c. Hartnup disease
 - d. Without hyperammonemia
3. Pyruvate dehydrogenase deficiency (PDH)
4. Multiple biotin-dependent carboxylase deficiency

Differential Diagnosis of Progressive Ataxia Due to Enzyme Deficiencies

1. Metachromatic leukodystrophy (arylsulfatase)
2. Niemann-Pick disease (sphingomyelinase)
3. Krabbe's disease (galactosylceramide)
4. Tay-Sachs disease (hexose aminodase)
5. Deficiency of mitochondrial sterol 27 hydroxylase
6. Phenylketonuria (phenylalanine dehydrogenase)
7. Hyperornithinemia (transcarboxylase)
8. Fabry's disease (galactosylcerebrosidase)
9. Mannosidosis (alpha-D-mannosidase)
10. Fucosidosis (alpha-fucosidase)
11. 3-methyl-glutaconic aciduria (3-methyl-glutaconyl CoA hydrolase)
12. Gamma-glutamyl-cysteine synthetase deficiency
13. Triosephosphate isomerase deficiency

Differential Diagnosis of Congenital Anomalies and Structural Defects with Significant Cerebellar Symptomatology

1. Platybasia
2. Basilar impression
3. Chiari malformation
4. Craniocervical defects
 - a. Atlanto-occipital fusion

- b. Odontoid process anomalies
- 5. Dandy-Walker syndrome
- 6. Joubert syndrome
- 7. Pontocerebellar hypoplasia
- 8. Lhermitte-Duclos (gliocytoma)
- 9. Diffuse dysplasia
- 10. Focal cerebellar dysplasia
- 11. Congenital muscular dystrophy
 - a. Fukuyama type
 - b. Absent merosin
- 12. Walker-Warburg disease
- 13. Muscle-Eye-Brain disease (MEB)

Differential Diagnosis of Ataxic Disorders with Known Metabolic Causes

1. Metabolic disorder:
 - a. With hyperammonemia:
 - i. Ornithine transcarboxylase deficiency
 - ii. Argininosuccinate synthetase deficiency
 - iii. Argininosuccinase deficiency
 - iv. Arginase deficiency
 - v. Hyperornithinemia
 - b. Amino acidurias without hyperammonemia
 - i. Intermittent branch chain ketoaciduria
 - ii. Isovaleric acidemia
 - iii. Hartnup disease
 - c. Disorders of pyruvate and lactate metabolism
 - i. Pyruvate dehydrogenase deficiency (complex IV)
 - ii. Pyruvate decarboxylase deficiency (complex IV)
 - iii. Multiple carboxylase deficiencies

Differential Diagnosis of Unrelenting Ataxia Syndromes

1. Abetalipoproteinemia
2. Hexosaminidase-A deficiency
3. Cerebrotendinous xanthomatosis (CTX)
4. Mitochondrial diseases
5. Glutamate dehydrogenase deficiency
6. Partial hypoxanthine guanine phosphoribosyl transferase deficiency (Lesch-Nyhan disease)

Differential Diagnosis of Episodic Ataxia

1. Autosomal episodic ataxia Type 1-8
 - a. EA1 (KCNA1)
 - i. Attacks last seconds to minutes
 - ii. Startle or exercise induced
 - iii. Myokymia
 - b. EA2 (CACNA1A)
 - i. Attacks last minutes to hours
 - ii. Posture change induced
 - iii. Vertigo
 - c. EA3 (1q42)
 - i. Adult onset
 - ii. Vertigo and tinnitus

- d. EA4 (not defined)
 - i. Adult onset
- e. EA5 (CACNB4)
 - i. Childhood to adolescent onset
- f. EA6 (SLC1A13)
 - i. Childhood onset
 - ii. Migraine
 - iii. Associated seizures
- g. EA7 (19q13)
 - i. Childhood to adolescent onset
 - ii. Seizures
 - iii. Vertigo
2. Paroxysmal kinesigenic choreoathetosis
 - a. Induced by initiation of movement
 - b. Associated dystonia
 - c. Attacks are short-lived (minutes)
3. Spinocerebellar ataxia 6
 - a. Associated nystagmus
4. Familial hemiplegic migraine:
 - a. Associated CACN genes on chromosome 19
 - b. Most often hemiplegia rather than migraine headaches
 - c. Hemiplegia is on the same side in all affected family members
5. Basilar artery migraine (Bickerstaff)
 - a. A disease of young women
 - b. Associated paresthesia of the hands may be an initial symptom
 - c. Dysarthria and dysphagia
 - d. Brief loss of consciousness in some patients
6. Post-ictal ataxia
 - a. Associated psychiatric phenomena
7. Hartnup disease
 - a. Most often seen in alcoholic patients
 - b. Associated erythematous rash on extensor surfaces
8. Hypoglycemia
9. Hyperammonemia
10. Organic acidurias
11. Refsum's disease:
 - a. Cataracts
 - b. Deafness
 - c. Intermittent neuropathy
 - d. Ichthyosis
12. Acute intermittent porphyria
 - a. Dominated by abdominal pain
 - b. Psychosis
 - c. Peripheral neuropathy (motor)

The Differential Diagnosis of Secondary Cerebellar Disease

Overview

The major drug groups that affect the cerebellum are the anti-convulsants. Characteristic of all taken in excess are lethargy,

nystagmus (usually gaze-evoked but may be spontaneous) due to interference with “hold neurons” of the visual system that foveate the target. Dilantin has been noted to cause ophthalmoplegia as well as a slowly progressive peripheral neuropathy often limited to depressed ankle jerks. Phenobarbital, in addition to nystagmus, may cause severe dysarthria and reversible decortication and decerebration. Patients lying in coma from phenobarbital overdose may develop skin blisters.

5-fluorouracil is the usual anti-neoplastic agent that causes a mild cerebellar cortical deficit. Notably is absence of a peripheral neuropathy which is characteristic of most of the other CNS toxic and anti-neoplastic agents. Cytarabine (Ara-C) has primarily cerebellar toxicity when administered in high doses. It may also have cerebral manifestations that include headache, somnolence, seizures and altered personality. Symptoms usually start within three to eight days after beginning treatment. Cerebral toxicity rarely occurs without cerebellar involvement. Ifosfamide causes neurotoxicity in approximately 30% of patients. It is associated with depressed consciousness, ataxia, myoclonus, seizures and coma. Risk factors may include low albumin, elevated creatinine and kidney disease as well as high serum chloroacetaldehyde.

Cisplatin toxicity may be confused with cerebellar ataxia. Cisplatin affects the dorsal root ganglia with loss of large proprioceptive neurons and consequent posterior column deficits. The intention tremor is throughout all thirds of movement (cerebellar intention tremor is the last 1/3 of a movement) and patients are dramatically affected unless they have visual compensation. The neuropathy is usually severe.

Cyclosporine and lithium cause cerebellar features and render patients ataxic but their seminal features are myoclonus, impaired cognition and hyperreflexia. Hypnotic sedatives cause ataxia both of gait and limb, but dysarthria, lethargy, depressed reflexes and psychiatric problems predominate.

The primary deficiency states with cerebellar dysfunction as a core symptom are B12 and vitamin E deficiency. The former is dominated by spasticity, an active peripheral neuropathy (parasthesias), an ebullient mental status, optic atrophy and cranial nerve I dysfunction. Vitamin E deficiency from either alpha-tocopherol transporter or alimentary deficiency has very prominent dorsal column signs and symptoms. Acute B12 deficiency may be induced by nitrous oxide anesthesia. Pantothenic acid deficiency is commonly associated with chronic alcoholism and may be partly responsible for its associated ataxia.

Alcohol is by far the most serious cerebellar toxin worldwide. Its pattern of expression is appendicular in the lower extremities with imbalance and anterior vermis deterioration. The patients have a stiff legged gait (“Martinet” gait) without the usual cerebellar modulation of both the stance and swing phase. There is minimal dysarthria, nystagmus or upper extremity dysmetria.

The usual pattern of toxic agents that affect CNS and the cerebellum are:

1. Optic neuritis (always occurs with methyl alcohol poisoning by ingestion); centrocecal scotoma
2. Dorsal column dysfunction with acute vibratory and position sense impairment (the longest myelinated fibers are involved first)
3. Spasticity as a late consequence
4. Frontal lobe cognitive impairment

This pattern is seen with toluene (n-ethyl toluene) and paint solvents. Glue sniffing affects the frontal lobes and causes euphoria and then lethargy. Huffer’s syndrome (gasoline sniffing) induces prominent frontal lobe depression. Paint sniffing (usually silver paint in the Southwest USA) causes cerebellar deficits that are overshadowed by pronounced mental status alterations. Thallium is recognized by euphoria, ataxia and hair loss, while mercury poisoning is distinguished by mental status changes, dystonia and choreoathetosis in addition to ataxia. Rarely, lead, manganese and benzene derivatives have prominent ataxia. Heroin and cocaine abuse may cause severe ataxia with MRI evidence of cerebellar and middle cerebellar peduncle demyelination.

Endocrine induced ataxia is usually secondary to hypothyroidism. This is minimal and is most often accompanied by VIIIth nerve deficits, proximal myopathy (pseudohypertrophy or Hoffman’s syndrome) bilateral carpal or tarsal tunnel syndrome and failure to make ear wax or sweat normally.

Severe liver disease is associated with ataxia which is often due to degeneration of the anterior vermis (lingual, culmen and centralis) from alcohol abuse. The caudate and putamen may be hyperintense on T2-weighted sequences. Patients may demonstrate acquired hepatolenticular degeneration (usually following several episodes of delirium tremens). This syndrome manifests as subcortical dementia, severe dysarthria, extrapyramidal signs and falling backwards.

In general, tumors of the cerebellum are age specific. Children and young adults may have an ependymoma of the fourth ventricle. This tumor is suggested by vertigo with change of head position, nystagmus and papilledema. Projectile vomiting (pressure on the vomit center on the floor of the IVth ventricle) is common upon awakening. There is no preceding nausea. Ataxia, headache and hydrocephalus are prominent. The origin of medulloblastomas is the superior medullary velum of the IVth ventricle. The symptoms and signs are similar to those of an ependymoma but the spinal cord is seeded with the tumor. Cystic and solid astrocytomas may be hemispheric or vermian. In the latter, axial symptoms are more prominent than appendicular. These tumors frequently distort the IVth ventricle and put pressure on the pons and medulla. Headache, vomiting and unilateral or bilateral VIth nerve palsy may occur if there is increased intracranial pressure from hydrocephalus (the VIth nerve is trapped under the petroclinoid ligament in Dorello’s canal). Any mass in the IVth ventricle or posterior fossa may cause downbeat nystagmus accentuated by lateral gaze. Tumors involving the floccular nodular lobe cause hypermetric saccades and rotary nystagmus with a contralateral torsional component. Rarely,

oligodendrogliomas are found in the cerebellum. Most of the tumor is benign, but there is usually one section that is malignant. Hemangioblastomas are most common in the cerebellar hemispheres in adults and are midline in younger patients. They bleed intermittently. This is evident by new blood (4–8 days after the original bleed) noted by increased signal on T2-weighted MRI sequences in the center of the lesion with a surrounding hemosiderin ring (old bleed). They cause symptoms by destruction of tissue in specific locations and by pressure on contiguous structures. There are three major tumors of the cerebellopontine angle that often involve the cerebellum by pressure. A Schwannoma presents with tinnitus, ipsilateral sensorineural hearing loss and ipsilateral ataxia. Meningiomas may compress the Vth nerve and present with facial pain. Epidermoids have high signal on T2-weighted sequences (keratin) and may present with pain radiating to the inner ear (as do tumors that distort the tentorium), ipsilateral ataxia or cranial nerve involvement. A ganglioneuroma is benign and may present with vermian or hemispheric symptoms and signs. It does not enhance strongly with gadolinium.

The cerebellum is a major destination for metastatic lesions in adults (high relative cerebellar blood flow). The hemispheres are more frequently involved than the vermis. Squamous cell carcinoma of the lung is the most frequent, followed by breast and the GI tract. Prostate metastases reach the posterior fossa by means of the valveless paravertebral veins (Batson's plexus). This tumor may specifically metastasize to the petrous apex (may involve cranial nerves V and VI). Lymphomas in HIV patients are often neurotic and occasionally involve the cerebellum (they are much more frequently encountered in the corpus callosum). A cholesterol granuloma (very bright on T2-weighted sequences) at the petrous apex occasionally compresses the cerebellum. Meningiomas of the tentorium (angiographically demonstrate an enlarged feeding vessel from the meningohypophyseal trunk – the artery of Bernasconi-Cassinari) may produce headache, referred pain to the inner ear, (IX nerve) and ipsilateral ataxia. Rarely a cerebrotendinous xanthoma or amyloidoma may compress the cerebellar from the tentorium.

There are twelve paraneoplastic autoantibodies associated with autoimmune mediated cerebellar ataxia. They include:

1. Anti-Yo
2. Z1C
3. CARP VIII
4. Tr
5. R1
6. Hu
7. Ma
8. CRMP-5
9. ANNA-3
10. PCA-2
11. VGCC
12. mGlu antibodies

Anti-GAD, thyroid and gliadin antibodies are found in non-paraneoplastic cerebellar ataxia. Some of these anti-neural

autoantibodies target nuclear antigens that are widely expressed in CNS neurons (anti-Hu and anti-Ri) others target antigens present in the cytoplasm or plasma membrane of Purkinje cells. These 12 most common Purkinje cell (PC) autoantibodies are often referred to as “Medusa” head antibodies due to their characteristic somatodendritic immunohistochemical binding pattern. Most of these antibodies target antigens involved in the mGluR1/calcium pathway that is essential for Purkinje cell (PC) function and maintenance. At the present time there are approximately 30 different autoantibodies targeting brain antigens in patients with autoimmune cerebellar ataxia. Most of the “Medusa” head antibodies are involved in regulating calcium homeostasis in PCs.

Anti-Yo antibodies are one of the most common paraneoplastic antibodies. Most patients present with a subacute and severe pancerebellar syndrome that manifests truncal and appendicular ataxia, dysarthria and often downbeat nystagmus. Other associated signs include long tract involvement, peripheral neuropathy, diplopia, vertigo, dysphagia and cognitive impairment. Almost all reported patients are female with a median age at onset of 61 years. MRI reveals cerebellar atrophy. The CSF may demonstrate a lymphocytic pleocytosis and elevated protein. Anti-Yo antibodies are usually associated with malignant gynecological tumors (ovary, breast, mesovarium, fallopian tube, uterus and very rarely cervical).

In the majority of patients the paraneoplastic cerebellar degeneration precedes the tumor diagnosis. Anti-Yo positive sera recognizes CDR2 (cerebellar degeneration-related 2) antigen. The antibody stains the PC cytoplasm and some of the dendritic arbor. Anti-Yo positive paraneoplastic cerebellar degeneration demonstrates massive Purkinje cell loss. Immune cell infiltrates are positive in some patients.

Anti-Nb/AP3B2 (beta-NAP) is a PC antibody that has been described in one 35 year old female patient. She presented with a subacute pancerebellar syndrome similar to that seen with anti-Yo-positive patients. She had associated diffuse hyperreflexia with Babinski signs. Brain and spinal cord MRI studies were normal as was the CSF. The target antigen is a neuron-specific vesicle coat protein (neuronal adaptin-like protein) beta-NAP which is now termed AP3B2. Experimental work suggests that the protein is involved in the formation of neurosecretory vesicles.

PCA-2 has been reported in 9 patients whose age ranged from 43–73 years. Three of the nine patients had predominant cerebellar ataxia. Patients demonstrated a wide-based gait, limb ataxia, dysarthria and loss of fine motor control. The other 6 patients had limbic or brainstem encephalitis, autonomic neuropathy, and inappropriate ADH (one patient). MRI was normal at presentation of two patients. Most patients had a mild lymphocytic pleocytosis in the CSF. This syndrome has been primarily reported in patients with small cell lung cancer. The antigen is unknown.

Anti-Tr/DNER paraneoplastic autoantibody disorder causes a subacute pancerebellar syndrome with truncal and limb ataxia and downbeat nystagmus. Extracerebellar symp-

toms have been reported in two patients, one with a Babinski sign and the other with optic atrophy. Brain MRI demonstrates cerebellar atrophy and the CSF shows a moderate lymphocytic pleocytosis. Hodgkin's disease is the underlying tumor. The Tr antigen is the delta/notch epidermal growth factor related receptor. The cerebellar degeneration precedes the diagnosis of Hodgkin's disease in most patients.

Anti-Ri antibodies are found in association with breast, gynecological and small cell lung cancer. Their distinguishing feature is opsoclonus, Anti-Ma antibodies are seen with testicular germ cell tumors and cause limbic and brainstem encephalitis in addition to cerebellar degeneration. Anti-CV2/CRMP5 also causes encephalomyelitis with cerebellar degeneration. The antibody attack may be predominantly directed against glial cells. The most common antibodies directed against ion channels are those targeting P/Q or N-type voltage-gated calcium channels. Anti-mGluR1 antibodies have been demonstrated in patients with paraneoplastic cerebellar degeneration. They are produced intrathecally and their concentration is much higher in the CSF than the serum. Anti-mGluR5 antibodies have been detected in the CSF and serum of a few patients with Hodgkin's lymphoma and produce limbic encephalopathy (Ophelia syndrome) rather than ataxia.

Hyperosmolar syndromes from sodium excess (dehydration) or diabetes (glucose > 3000 mg/dl) may cause severe ataxia. Most often segmental myoclonus predominates. The rapid correction of low serum sodium (usually between 100–120 mg/dl) at greater than 12 mm/hr may cause pontine and extrapontine myelinolysis. The ataxia occurs from destruction of the pontine fibers that constitute the majority of the axons in the middle cerebellar peduncle.

Autoimmune induced cerebellar dysfunction is most prominent with demyelinating disease such as MS. In general, it is accompanied by frontal lobe mental changes, intranuclear ophthalmoplegia, spasticity and optic nerve inflammation. In Devic's disease there is a clear association with antibodies to aquaporin-4 antigen. The antibody attack is primarily target to the optic nerves and a long length of the spinal cord (3 vertebral segments). Acute disseminated encephalomyelitis may be associated with severe ataxia and frequently evolves into MS. A distinguishing feature is that cell lesions are of the same age on MRI. In acute hemorrhagic leukoencephalitis which may involve the cerebellum, lesions tend to selectively involve the left side of the CNS. Post-viral and -vaccination syndromes have an autoimmune component that can cause a cerebellar hemispheric or vermillion syndrome. They occur 10–14 days following the infection or vaccination. There may be periventricular MRI lesions in post-viral patients and large lesions of the centrum semiovale after vaccination. The latter may be accompanied by transverse myelitis. The white matter lesions most suggestive of MS are in the corpus callosum (Dawson's finger), optic nerve and periventricular areas.

There is an overlap between central and peripheral myelin (as regards antigen epitopes). Thus patients with GBS or

CIDP may have central inflammatory white matter lesions that involve cerebellar tracts.

Anoxic lesions of the cerebellum affect both gray and white matter. This pathology is suggested by metronomic eye movements. These are oscillations in which the eyes remain at the end of their complete excursion prior to oscillating to the opposite extreme.

Viral infections most often present with the sudden onset of headaches and stiff neck with preserved consciousness. Herpes simplex, Coxsackie and Herpes Zoster are the most severe. HS predominately affects the temporal and frontal lobes and causes seizures with loss of consciousness. Herpes Zoster encephalitis is often associated with V1 infection. There is large vessel MCA or carotid stroke 12–14 days after onset. The cerebellum may be involved but ataxia is rarely the predominant symptom. In children post-viral acute panencephalitis most often occurs 14 days after an upper respiratory or gastrointestinal infection. Bacterial cerebellar abscesses were common following chronic middle ear infection in the pre-antibiotic era. They are often accompanied by lateral sinus thrombosis, altered consciousness, a head tilt to the side of the lesion and ipsilateral ataxia.

Brainstem encephalitis (rhombencephalitis) may also affect the cerebellum. HZ, listeria monocytogenes (dorsal pons) herpes simplex (medial temporal lobe) and paraneoplastic involvement (anti-Hu) in association with limbic encephalitis are the most common etiologies. Delirium and nystagmus are prominent.

Differential Diagnosis of Acute Ataxia from Cerebellar Lesions

1. Vascular:
 - a. PICA infarction
 - i. Inability to walk
 - ii. Nausea and vomiting
 - iii. Cranial nerve IX and X involvement
 - b. AICA infarction
 - i. VIIIth nerve deficit
 - ii. Ataxia of the arm > leg
 - iii. Peripheral VIIth nerve palsy (the peripheral blood supply of the nerve is from AICA)
 - c. Superior cerebellar artery infarction:
 - i. Arm and leg have ipsilateral ataxia
 - ii. Prominent dysarthria
2. Cerebellar hemorrhage:
 - a. Severe posterior occipital headache
 - b. Closure of the ipsilateral eye
 - c. Head tilt to the side of the lesion
 - d. Nystagmus
 - e. Ipsilateral ataxia (hemispheric); severe gait instability (vermian)
 - f. Quadriparesis not quadriplegia (pontine pressure)
 - g. Small reactive pupils (pontine pressure)
 - h. Central neurogenic hyperventilation

3. Large cerebellar infarcts:
 - a. Pseudotumoral presentation on the third to fourth day from swelling
4. Cerebellar tumor:
 - a. Focal neurologic signs depending on location
 - b. Sudden exacerbation of signs from hemorrhage
 - c. Posterior occipital headache; pressure on the tentorium is associated with headache radiation to the inner ear; C2 irritation (meningeal involvement of the posterior fossa) there may be brow radiation
5. Demyelinating disease
 - a. There are associated intranuclear ophthalmoplegia, afferent pupillary defects, spasticity and cognitive impairment
6. GBS and other dis-immune processes that affect large proprioceptive dorsal root ganglia neurons (DRG) that cause ataxia from dorsal column demyelination (Richter's variant of GBS)
 - a. In sensory ataxia the intention tremor is throughout all components of a movement
 - b. In cerebellar tremor the ataxic movement is in the terminal 1/3 of a movement
 - c. In a cerebellar outflow tremor, there is an increase of tremor amplitude as the target is approached
 - i. A tremor of the proximal muscles occurs with fixation
 - ii. Abnormal finger movements ('piano playing') are seen in the outstretched upper extremities with the eyes closed. If the ataxia is cerebellar, the outstretched upper extremity rises (eyes closed) and the hand has a 'spoon' posture due to imbalance of the extensor and flexor intrinsic hand muscles
 - d. Acute proprioceptive loss from damage to the dorsal column nuclei cause ballistic rather than ataxic movements
7. Tick paralysis causes ataxia out of proportion to weakness. The attacks are similar to those seen with labyrinthine disorders. Ticks are found on the cold parts of the body
 - d. Seizures if there is an acute drop of the serum sodium (usually between 120–130 mg%)
3. Hyperammoninemia:
 - a. Related to protein intake
 - b. Altered consciousness
 - c. Increased reflexes
4. Wernicke's encephalopathy:
 - a. Primarily appendicular ataxia
 - b. Altered consciousness
 - c. Ophthalmoplegia (caucasian > black patients)
 - d. Areflexia
 - e. Mammillary body hemorrhages
5. Multiple carboxylase deficiency
6. Branch-chained amino acidurias

Differential Diagnosis of Metabolic Disorders in which Ataxia Occurs as a Minor Feature

1. Sphingomyelinase deficiency
2. Metachromatic leukodystrophy
3. Multiple sulphate deficiency
4. Adrenoleukodystrophy
5. Late onset globoid cell leukodystrophy (Krabbe's disease)
6. Ceroid lipofuscinosis
7. Sialidosis type 1

Further Reading

Further Reading on Brainstem and Cranial Nerves

Extraocular Muscles

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SAL-LIKE 4

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Differential Diagnosis of Acute Metabolic Ataxia

1. Hypoglycemia
 - a. The CSF sugar usually is less than 30–40 mg% (CSF sugar is 2/3 of serum sugar)
 - b. As the sugar decreases there is sympathetic overactivity with jitteriness, goose bumps, agitation and hunger
 - c. At a serum level of 30–40 mg% the symptoms are primarily parasympathomimetic with a one degree drop in temperature, hypersalivation and encephalopathy with or without seizure activity. Ataxia may occur throughout the process
2. Hyponatremia (Na level 110 mg/dl):
 - a. Lethargy
 - b. Absent reflexes
 - c. Mild ataxia and weakness

SALL4

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Chapter 11

Basal Ganglia and Movement Disorders

Overview

The basal ganglia are components of cortical-subcortical circuits that originate in specific cortical regions. Most movement disorders result from abnormalities of the basal ganglia thalamocortical circuit which originates from the pre- and post-central sensorimotor regions which include M1 (area 4), the supplementary motor cortex (SMA), the premotor cortex (PMC), the cingulate motor area (CMA), and primarily S1 of the sensory cortex. These areas project to the motor components of the striatum, the post-commissural putamen, the dorsal lateral subthalamic nucleus (STN) and the ventral posterolateral portion of the globus pallidus (GPi). The GPi in turn projects to the ventrolateral nucleus of the thalamus (VL) that in turn projects back to M1 and premotor areas. The striatum and STN are the initial primary projection zones for cortical and thalamic afferents to the basal ganglia. The GPi, the substantia nigra and pars reticulata are the primary basal ganglia efferents to the thalamus and brainstem.

Two primarily anatomically distinct pathways, the “direct” and “indirect” link the striatum and GPi/SNr which can rapidly modulate the GABA-ergic output of the basal ganglia to the VL thalamic motor nuclei. The “direct” pathway, from striatal medium spiny neurons, projects to GPi and SNr. The “indirect” pathway originates from striatal neurons that project to the external segment of GPe that projects to GPi and SNr directly or after synapsing in STN. The STN is glutamatergic and also receives afferent projections from cortical motor and non-motor areas as well as the centromedian (CM) and parafascicular thalamic nuclei (Pfc). Cortical projections to the STN and its subsequent modulation of GPi and SNr constitute the “hyperdirect” pathway. Collateral projections from the globus pallidus and substantia nigra (SNr) synapse in the CM and parafascicular nuclei are posited to be components of a thalamostriatal feedback circuit. The centromedian afference from the basal ganglion and its projections to the putamen and STN are motor. Input and output from the parafascicular nucleus is related to associative and limbic modulation of basal gangliar nuclei.

The basal ganglia also project by collaterals to the superior colliculus and the pedunculopontine nucleus (PPN) which is important for the regulation and initiation of gait and balance. There are projections from the PPN to the basal ganglia, thalamus and basal forebrain. The basal ganglia projection to the superior colliculus arises from the SNr and is involved in the control of saccadic eye, head and neck movements. Recent experimental work has demonstrated that the motor thalamocortical loops and the cerebellum are interconnected. The cerebellum modulates the basal ganglia through a bisynaptic pathway that involves the thalamus and synapses in the striatum.

In turn, the basal ganglia may influence the cerebellum from projections to the STN that projects to pontine nuclei whose afferents synapse in the cerebellar cortex. Abnormalities of specific movement disorders are caused by neuronal dysfunction within basal ganglia-thalamocortical circuits.

A basic approach to understanding and diagnosing movement disorders is to fit them into specific clinically useful major symptom complexes. A proposed classification is one in which a patient is moving too much, too little and at times hardly at all.

1. Conditions that are characterized by an excess of movement:
 - a. Hyperkinesia
 - b. Dyskinesia
 - c. Combinations of the two
2. Decrease of movement:
 - a. Akinesia
 - b. Bradykinesia
 - c. Decreased autonomic movement
 - d. Not associated with weakness or spasticity
3. The planning of a movement is called an engram. Planning for simple movements (one-step) has been associated with the premotor cortex and the supplementary motor area (SMA). The engram of tasks that require sequential movements are associated with the posterior parietal lobe
4. Inability to sustain a sequence of movements is “motor” impersistence that is often seen with right parietal lobe pathologies. Inability to progress from one movement to the next to perform a specific task is perseveration and is most often seen with left frontal lesions
5. Areas that are associated with movements induced by emotional triggers (fear, curiosity, joy) employ a distributed “limbic” cortical loop in which the caudate nucleus and anterior cingulate gyrus are pivotal
6. Horizontal and vertical eye movements have complicated connections that originate from multiple cortical visual areas (supranuclear ocular system) with projections to:
 - a. Midbrain ocular motor areas
 - b. Brainstem nuclei
 - c. The medial longitudinal fasciculus, multiple areas of the reticular formation, the parapontine reticular formation (PPRF, the brainstem center for horizontal gaze), the superior colliculus and the vestibular nuclei
7. Self-paced internal movements (tapping a finger to a pre-set pattern) are associated with the supplementary motor area (SMA)
8. Overlearned movements such as walking, turning over in bed, and reflex defensive movements (nocifensor movements) are initiated and coordinated in the basal ganglia

Specific Correlation of Lesions and Movement Disorders

1. Cortex:
 - a. Area 4 (M1) primary motor cortex:

- i. Pyramidal dysfunction; primarily the loss of distal extremity fine motor control and fractional digital movement
 - b. Area 6 (PMC):
 - i. Ideomotor apraxia:
 1. An apraxia is the inability to perform an individual or sequential task with normal motor, sensory and coordinative function
 2. An ideomotor apraxia (the engram for the movement is encoded in area 6) is the inability to perform a single command such as a salute or the use of a comb
 3. A limb-kinetic apraxia may also be seen in area 6 lesions. This type of apraxia is a lack of facility in performing the motor components of the task
 - ii. The inhibitory strip of Marion Hines. If this component of area 6 is stimulated (usually by a seizure), there is inhibition of area 4
 - c. Engrams, persistence, impersistence, apraxias, as well as grasp and avoidance responses occur with specific cortical lesions
 - d. Parietal lesions may cause a "loathness to move" (superior parietal lobe projection via the superior longitudinal fasciculus) are involved; these innervate areas 4 and 6
 - e. Hand-eye coordination may be affected with lesions of the superior parietal cortex (area 5) that disconnect the superior longitudinal fasciculus from the hand area of area 4. These connections are most important for the use of stereoscopic vision for fine finger movement
 - f. Corticoreticular myoclonus may be seen with diffuse lesions of the cortex
2. Putamen:
 - a. Parkinson's disease; disruption of the cortically initiated striatal-thalamocortical circuit
 - b. Dystonia
 3. Caudate nucleus:
 - a. Chorea
 - b. Emotional aspects of movement
 4. Globus pallidus:
 - a. A unilateral lesion may cause contralateral dystonia, hemiparkinsonism or tremor
 - b. Bilateral lesions may cause a flexed posture, rigidity, dystonia
 5. Red nucleus:
 - a. Fibers of passage from the dentate nucleus are involved in this area and may cause a "rubral tremor":
 - i. The oscillation of the extremities increases (at right angle) on the trajectory to the target
 - ii. An associated postural kinetic tremor
 6. Substantia nigra:
 - a. Bradykinesia; akinesia
 - b. Parkinson's disease
 7. Subthalamic nucleus (STN):
 - a. If 85% of the nucleus is affected, there is contralateral hemiballismus
 - b. The proximal musculature is more affected than distal musculature
 8. Reticular formation:
 - a. Myoclonus (nucleus gigantocellularis)
 9. Palatal myoclonus:
 - a. Lesions that affect Mollaret's triangle, that is composed of:
 - i. Fibers from the parvocellular red nucleus that project to the ipsilateral inferior olivary nucleus via the central tegmental tract
 - ii. Inferior olivary projections to Purkinje cells of the contralateral cerebellar cortex via the inferior cerebellar peduncle
 - iii. Dentate nuclear projections via the superior cerebellar peduncle to the contralateral red nucleus
 10. Pallidal putaminal lesions:
 - a. Sudden falling contralaterally while sitting, standing or walking:
 - i. Slower than falls from lack of tone, that occurs with medial reticular formation lesions
 - ii. Deficit of postural corrective reflexes
 11. Lesions of the putamen and internal capsule:
 - a. Contralateral hemiplegic-Parkinsonism
 12. Locomotor centers (gait):
 - a. The nucleus cuneiformis of the midbrain is activated by the pedunculopontine nucleus and the globus pallidus to initiate gait
 - b. The parietal lobe, cerebellum, and brainstem areas modulate spinal step generators that form the basic oscillatory circuits between flexor and extensor spinal cord motor neurons

Summary

The Direct and Indirect Systems

Recurrent collaterals from basal ganglia projections make distinct separation of the direct and indirect loops impossible. Despite earlier histological studies that demonstrated a distinct patch and matrix organization of the basal ganglia, they have been found to have a more complex physiology that cannot be easily compartmentalized. Results of surgical procedures and deep brain stimulation do not support this distinct-systems hypothesis in every instance.

The Direct System

The putamen and caudate nuclei receive excitatory input from the pars compacta of the substantia nigra (D2 receptors). Their medium spiny neurons project to and inhibit the medial globus pallidus and pars reticularis of the substantia nigra. Both the striatal neurons and the GPi and SNr release

GABA. Thus the GABA-ergic projection to the GPi and SNpr inhibits their firing and consequent release of GABA onto the motor neurons of VA and VL of the thalamus. The thalamic motor neurons are glutamatergic and excitatory to the motor cortex. The more intense the GABA-ergic outflow to the motor thalamus, the greater its inhibition and the less glutamatergic input to the motor cortex. This results in bradykinesia and the inability to sustain movement.

The Indirect System

The putamen and caudate neurons receive dopaminergic (D1 receptors) from the SNpc. They project GABA-ergic afferents to the external segment of the GPe. In turn, GPe projects inhibitory GABA-ergic afferents to the STN. The STN utilizes glutamate and projects to and stimulates GPi and SNpr the GABA-ergic outflow of the basal ganglia to the motor thalamus (VA/VL). Stimulation of GPi and SNpr lessens the firing of excitatory VA and VL neuronal projections that decreases cortical motor neuron discharge. Activation of the indirect pathway striatal neurons inhibit GPe neurons which disinhibits the STN (less GABA-ergic afference) that leads to increased GPi and SNpr GABA-ergic output to the motor thalamus. In essence, in akinetic rigid syndromes there is less inhibition of GABA-ergic output from GPi and SNpr with consequent less excitation of the motor cortex from glutamatergic VA/VL thalamic motor neurons.

Bradykinetic Disorders

Parkinson's Disease (PD)

General Characteristics

1. In PD both animal and human studies have demonstrated dysfunction in both the direct and indirect pathways that support:
 - a. Decreased neuronal discharge in GPe
 - b. Increased neuronal firing in STN, GPi and SNr from lack of dopaminergic projections from SNpc to the striatum. This leads to activation of striatal neurons of the indirect pathway which leads to inhibition of GPe with consequent disinhibition of GPi, SNpr and STN as well as decreased activation of the direct pathway
2. Recent studies have demonstrated abnormalities of neuronal firing patterns that include:
 - a. Increased basal ganglia neurons that discharge in bursts
 - b. Oscillatory firing patterns
 - c. Increased synchrony
 - d. Particularly important for the disease are synchronized neuronal oscillations in the beta frequency range, and the failure to generate gamma-band oscillations before and during movement
3. Incidence of 4/1000 of the population over the age of 40
4. Affects both sexes approximately equally
5. Prevalence rates vary worldwide, possibly due to exposure to different environmental toxins

6. Prevalence rate increases exponentially with age; at 65 possibly 1% of the population in the USA may be affected
7. Risk factors:
 - a. Age is the most important
 - b. Rural living
 - c. Herbicides
 - d. Well water (weak correlation)
 - e. Industrial or chemical exposure:
 - i. MPTP (overheated demerol) drug addicts
 - ii. Carbon disulfide (dry cleaning)
 - iii. Carbon monoxide (mechanics)
 - iv. Manganese (welders)
 - f. Smoking may reduce the risk
 - g. Family history of essential tremor (increased risk 2.1–2.4×)
 - h. Minor head trauma (3.1–4.2× increased risk)
 - i. Relative risk of PD in relatives of the proband:
 - i. Siblings – 6.7× (increased risk)
 - ii. Offspring – 3.2× (increased risk)
 - iii. Nieces and nephews – 2.2× (increased risk)

Clinical Manifestations (Idiopathic PD)

1. In general there is a 60–70% loss of dopaminergic neurons of the SNpc to effect clinical signs
2. The earliest ventral tier dopaminergic neurons of the SNpc that are lost project to the lateral putamen
3. Lewy body formation is seen in affected dopaminergic neurons
4. Cardinal features:
 - a. Bradykinesia–akinesia
 - b. Tremor at rest (4–6 Hz)
 - c. Rigidity (cogwheel in type; Negri sign)
 - d. Autonomic dysfunction
 - e. Loss of postural control
 - f. Cognitive decline in a significant proportion of patients

Bradykinesia

1. This is the most distressing symptom for patients with PD. The patient has difficulty initiating and sustaining movements. Movement is slow and performed without facility. When this aspect of PD is severe the patient is frozen – akinesia
2. Brady- and akinetic patients (usually after at least 5 years of disease) suffer “freezing” episodes; they are unable to change motor programs rapidly and freeze when turning or going through a doorway
3. Patients at the end of effective therapy with L-dopa and other D2 agonists experience “off” periods during which bradykinesia, akinesia and fatigue make any form of movement difficult
4. An akinetic patient may initiate movement rapidly if startled or frightened

Tremor

1. Occurs at rest (4–6 Hz); almost pathognomonic for idiopathic Parkinson's disease

2. The tremor occurs in the hand at rest that demonstrates metacarpophalangeal flexion; it then progresses to involve the entire arm and becomes bilateral. The hand frequently moves up and down concurrently with the “pill-rolling” nature of the finger tremors. The leg frequently becomes involved, as does the head with disease progression. The tremor in the head is “up and down”. That of essential tremor of the head is side-to-side. If severe, the tremor may persist during movement as well as at rest
3. The tremor responds well in early stages to L-dopa and trihexyphenidyl treatment

Rigidity

1. Is more in the extremities than in the axial musculature
2. “Catching” or cogwheel character (Negri sign)
3. Patients may have stiffness throughout the range of motion of the affected extremity
4. The rigidity contributes to the patient’s flexed stooped posture

Loss of Postural Reflexes

1. Frequent falls with characteristic hip and humeral fractures due to inability to extend the arms
2. Falling backwards is common. Patients are unable to control the last portion of a posturally induced movement

Autonomic Dysfunction

1. Autonomic dysfunction starts to become evident with moderately advanced disease
2. Difficulty initiating micturition
3. Severe constipation may be seen early in the disease course
4. Sexual dysfunction
5. Seborrheic dermatitis
6. Postural hypotension increases as the disease progresses

Associated Motor Deficits in Parkinson’s Disease

1. Decreased spontaneous blink and all subconscious movement (decreased turning in sleep)
2. Gait ignition failure
3. Shuffling gait with decreased swing phase and decreased associated arm swing
4. Once the patient is in motion he cannot position his body over its center of gravity so that he festinates and is unable to control the speed and stability of his gait
5. Failure of upgaze and poor smooth pursuit eye movements; the patient utilizes saccadic substitution to compensate
6. Hypomimia and hypoxemia
7. Swallowing dysfunction due to failure of the posterior pharyngeal striated muscles to deliver the bolus to the esophagus. There may be concomitant slow opening of the extremal esophageal sphincter that is the function of the cricopharyngeus muscle (cranial nerve IX)
8. Micrographia during writing (failure to maintain movements once they are initiated)
9. Sialorrhea (less spontaneous swallowing)
10. Anosmia

Non-Motor Signs and Symptoms of Parkinson’s Disease

Autonomic Dysfunction

1. Gastric hypomotility with constipation is often the most troubling feature:
 - a. Loss of weight as the disease progresses which has a central disturbance as well as peripheral components
2. Micturition difficulty
3. Sexual dysfunction
4. Orthostatic hypotension
5. Hyperhidrosis

Psychiatric Disorders

1. Depression
2. Anxiety
3. Hallucinations
4. Impulse control disorders (pounding)
5. Apathy

Cognitive Impairment

1. Mild cognitive impairment occurs in approximately 15% of PD patients at presentation
2. Executive dysfunction is the core symptom of the cognitive deficits in PD and includes:
 - a. Rigidity of thought
 - b. Inability to change mental focus
 - c. Slow cognitive processing
 - d. Inability to plan, organize and execute intellectually driven tasks
3. Memory deficits
4. Visuospatial deficits
5. Social cognitive deficits

Sleep Disorder

1. The frequency of REM sleep behavior disorder (RBD) ranges between 20–75% of PD patients
2. RBD may precede, follow or be concomitant with PD
3. RBD may be associated with hallucinations and dementia
4. Factors associated with RBD in Parkinson’s disease include:
 - a. Male gender
 - b. A non-tremor motor phenotype
 - c. Longer disease duration
 - d. Autonomic dysfunction
5. RBD is most commonly seen in PD, dementia with Lewy bodies and multiple system atrophy (the synucleinopathies)

Neuropathology

1. Parkinson’s disease is overwhelmingly a non-Mendelian disorder that occurs as a simplex condition (a single affected individual in a family)
2. The cardinal pathologic feature of non-Mendelian Parkinson’s disease is the loss of dopaminergic neurons in the substantia nigra pars compacta (the ventral tier neurons may be affected initially)
3. Intracytoplasmic inclusions (Lewy bodies) are seen in the surviving intact nigral dopaminergic neurons

4. Lewy bodies consist of the protein alpha-synuclein associated with ubiquitin, neurofilament protein, and alpha B crystallin. Rarely tau proteins are associated and Lewy bodies that rarely are surrounded by neurofibrillary tangles. Lewy neurites are also seen in PD disease and are the abnormal neurites of affected neurons. They contain granular material and α -synuclein filaments. They are also found in dementia with Lewy bodies, multiple system atrophy and in the CA2–3 areas of the hippocampus in Alzheimer's disease. Histologic evaluation of a classic Lewy body demonstrates an eosinophilic cytoplasmic inclusion that consists of a dense core surrounded by a halo of 10-nm wide radiating fibrils. The primary structural component is alpha-synuclein. A cortical Lewy body lacks a halo and is less well-defined. In addition to the substantia nigra, Lewy bodies occur in the locus coeruleus, nucleus basalis of Meynert, cranial nerve motor nuclei, central and peripheral divisions of the autonomic nervous system, hypothalamus, and the cerebral cortex. In the genetic forms of Parkinson's disease, nigral pathology may occur in the absence of Lewy bodies, as exemplified by mutation of PARK 2

Heritable Causes of Parkinson's Disease

1. Mendelian forms of PD in which mutation of a single gene is causative of the disorder may be inherited in an autosomal dominant, recessive and in an X-linked manner

PARK 1

General Characteristics

1. PARK 1 is caused by mutations of the alpha-synuclein gene (SNCA) that maps to chromosome 4q21 and is autosomal dominant
2. Pathogenic variants include single nucleotide variants as well as gene duplications and triplications

Clinical Manifestations (Contursi Kindred)

1. Patients carry the A53T mutation:
 - a. Mean age of onset is 45.6 years
 - b. Rare tremor at rest
 - c. Cortical type of dementia occurs in 20% of patients
 - d. Patients with triplication mutations (100% overexpression of alpha-synuclein) – age of onset is 34 years
 - e. Patients with the duplication mutation (50% overexpression of alpha-synuclein) – age of onset ranges between 39–65 years of age
 - f. The clinical features and response to L-dopa were typical for PD (Contursi kindred)
 - g. In the kindred reported from Greece, additional features included central hypoventilation, postural hypotension, urinary incontinence and myoclonus

Neuropathology (Seidel Kindred)

1. Neuronal dopaminergic loss in the substantia nigra

2. Neuronal loss in the locus coeruleus and dorsal motor vagal nucleus
3. Widespread SNCA-positive Lewy bodies, Lewy neuritis and glial aggregates in the cerebral cortex, brainstem, hypothalamus and cerebellum in an X-linked pattern
4. There are inherited factors that predispose to PD in families without a Mendelian pattern of inheritance
5. Approximately 10–20% of PD patients report a positive family history with 5–10% demonstrating a monogenic form of the disease

Laboratory Evaluation

1. MRI of the brain: Both MRI and CT are usually normal
2. Identification of disease-causing mutations

PARK 2

General Characteristics

1. PARK 2 is caused by mutation in the Parkin gene (PARK2) that maps to chromosome 6q25.2-q27
2. It is an autosomal recessive form of familial juvenile Parkinsonism
3. The gene product is an E3 ubiquitin ligase
4. It is the most common form of familial PD and has a worldwide distribution

Clinical Manifestations

1. The onset in general is in patients less than 21 years of age; some patients have had onset after age 40
2. Retropulsion
3. Dystonia of the feet
4. Hyperreflexia
5. Some patients have a symmetrical presentation
6. In patients with an earlier onset:
 - a. Psychiatric features
 - b. Early dyskinesia
 - c. Increased reflexes
7. Excellent response to L-dopa
8. Diurnal fluctuation
9. Sleep benefit
10. Early susceptibility to levodopa induced dyskinesia

Neuropathology

1. Moderate loss of neurons in the SNpc; the greatest loss is in the ventrolateral and medial regions
2. No Lewy bodies (in general)
3. Some loss of neurons in the locus coeruleus
4. Parkin binds and ubiquitinates target depolarized mitochondria for autophagy

Laboratory Evaluation

1. PET scan:
 - a. Decreased fluorodopa uptake in the caudate, putamen, ventral and dorsal midbrain
2. Fibroblasts from PD patients with biallelic mutations in PARK2

- a. Decreased mitochondrial complex I activity
- b. Mitochondrial morphological changes that include increased mitochondrial branching

PARK 3*General Characteristics*

1. The gene locus maps to a locus on chromosome 2p13
2. Inheritance is autosomal dominant

Clinical Manifestations

1. Similar to sporadic PD
2. Mean age of onset is 59 years of age
3. Cognitive impairment (some)
4. Excellent response to levodopa

Neuropathology

1. SNpc degeneration
2. Positive for Lewy bodies

Laboratory Evaluations

1. Genetic analysis

PARK 4*General Characteristics*

1. PARK 4 is caused by triplication of the alpha-synuclein gene (SNCA) that maps to chromosome 4q22.1
2. Lewy body dementia is also caused by mutation on the SNCA gene and has some overlapping clinical features with PARK 4

Clinical Manifestations

1. Iowa kindred (4 generations):
 - a. Onset in the thirties
 - b. Rapid progression to death in 10–12 years after onset
 - c. Early weight loss
 - d. Dopa-responsive Parkinsonism
 - e. Cognitive impairment to dementia; early memory loss and visual spatial impairment
 - f. Dysautonomia a prominent feature

Neuropathology

1. Neuronal loss in the substantia nigra and locus coeruleus
2. Widespread Lewy bodies that are especially prominent in the cerebral cortex
3. Vacuolation of the temporal cortex neuronal loss and gliosis in the CA 2/3 of the hippocampus
4. Neuronal loss in the nucleus basalis of Meynert
5. Spongiosis and gliosis of the cortex (proband of the Iowa kindred)

Laboratory Evaluation

1. Alterations in gene dosage due to duplications and triplications from rearrangements are more common than point mutations
2. PET (3 patients from Iowa kindred)
 - a. Decreased striatal uptake of fluorodopa

PARK 5*General Characteristics*

1. Autosomal dominant Parkinson's disease 5 is caused by heterozygous mutation in the VCHL1 gene that maps to chromosome 4p13
2. The gene codes for ubiquitin carboxy-terminal hydrolase L1 (deubiquitin enzyme) that is involved in the ubiquitin-proteasome degradation pathway
3. Inheritance is AD with incomplete penetrance

Clinical Manifestations

1. Reported in 2 family members (brother and sister; paternal uncle affected; father not affected)
 - a. Onset 49–51 years of age
 - b. Rigidity bradykinesia and postural instability supervene with disease progression
 - c. L-dopamine responsive

Neuropathology

1. Not defined

Laboratory Evaluation

1. Molecular genetic evaluation

PARK 6*General Characteristics*

1. PARK 6 is caused by homozygous mutations in the PINK 1 gene. Heterozygous mutation of the gene as well as mutation in the DJ1 gene combined with mutations in the PINK 1 gene have also been described
2. PINK 1 gene maps to chromosome 1p36.12; PTEN-induced kinase 1
3. Inheritance is autosomal recessive

Clinical Manifestations

1. Age at onset is between 18–56 years; most have onset in the third or fourth decade
2. The onset is asymmetric
3. Postural instability, rigidity, bradykinesia
4. Variable signs include:
 - a. Resting tremor
 - b. Sleep benefit
 - c. Dystonia at onset (some patients)
 - d. Hyperreflexia
 - e. Excellent response to levodopa but with early onset of dyskinesia
 - f. Slow disease progression
 - g. Most patients with PARK 6 have a clinical phenotype that resembles idiopathic PD, a minority has clinical features similar to PARK 2

Neuropathology

1. Reported from one autopsy:
 - a. Neuronal loss in the substantia nigra with astrocytic gliosis

- b. Lewy bodies occur in surviving neurons; the amygdala and locus coeruleus showed neither cell loss or Lewy bodies
- c. Cell culture studies suggest:
 - i. PINK 1 is located in mitochondria and may be important in the mitochondrial stress response

Laboratory Evaluation

1. Molecular genetics (evaluation)
 - a. Homozygous mutations in the PINK 1 gene
 - b. Heterozygous mutations
 - c. Digenic form of the disorder from a mutation in the DJ1 gene and mutations in the PINK 1 gene

PARK 7 (DJ1)

General Characteristics

1. PARK 7 is caused by homozygous or compound heterozygous mutations in the DJ1 gene that maps to chromosome 1p36
2. Inheritance is AR
3. As noted earlier, a digenic form of the disorder occurs from mutation in the DJ1 and PINK 1 genes

Clinical Manifestations

1. Onset of symptoms prior to age 40
2. Resting and postural tremor
3. Bradykinesia
4. Loss of postural reflexes
5. Psychiatric episodes
6. Disease progression is slow
7. One patient has been reported with classical manifestations of ALS
8. In three patients with double homozygosity for 2 mutations in the DJ1 gene there was:
 - a. Early onset parkinsonism
 - b. Amyotrophic lateral sclerosis
 - c. Cognitive impairment

Neuropathology

1. DJ1 protein is phenotropic and plays a protective role against oxidative stress-induced cell death
2. DJ1 is a stress sensor and is upregulated during oxidative stress
3. The oxidative status of C106 of DJ1 determines its functional capacity
4. Excess oxidation of C106 inactivates DJ1 protein. Highly oxidized DJ1 occurs in PARK 7
5. DJ1 has been studied in regard to its role in its mitochondria-specific autophagy (mitophagy). If mitochondrial membrane potential is decreased, DJ1 is translocated into the mitochondria that induces mitophagy which clears the damaged mitochondria

Laboratory Evaluation

1. Molecular genetic determination of mutations in the DJ1 gene

2. EMG evaluation of patients with evidence of an ALS phenotype

PARK 8

General Characteristics

1. PARK 8 is caused by heterozygous mutation of the LRRK2 gene (leucine rich repeat kinase 2) that maps to chromosome 12q12
2. Inheritance is autosomal dominant
3. The LRRK2 gene encodes a complicated protein with several domains that include:
 - a. Armadillo repeat CARM region
 - b. An ankyrin repeat (ANK)
 - c. A leucine-rich repeat (LRR) domain
 - d. A kinase domain
 - e. A RAS domain
 - f. GTPase domain
 - g. WD40 domain
4. LRRK2 is primarily in the cytoplasm but may also locate to the outer mitochondrial membrane
5. The gly2019 S mutation is a common cause of familial Parkinson's disease and also predisposes to the sporadic form of the disorder

Clinical Manifestations

1. Onset is the fourth to fifth decade
2. Bradykinesia, rigidity, postural instability
3. Resting tremor
4. Levodopa responsive
5. Patients with the G 2019S mutation manifest:
 - a. Hyposomnia
 - b. Tremor postural instability
 - c. Gait disorder
 - d. Impaired color discrimination
 - e. Frontal temporal dementia (2 patients)

Neuropathology

1. There is a wide spectrum of neuropathological findings
2. The most common neuropathology includes:
 - a. Alpha-synuclein positive Lewy bodies and Lewy neuritis
 - b. Tau (MAPT) and ubiquitin (UBB) immunoreactive inclusions are less common
 - c. LRRK2 (G2019S mutation):
 - i. Extensive loss of dopaminergic neurons in the SNpc and cell loss in the locus coeruleus
 - ii. Lewy bodies were demonstrated (2 patients)
 - iii. Autopsy of 8 patients with LRRK2 (G2019S) mutation:
 1. Lewy bodies in the brain stem to the cortex

Laboratory Evaluation

1. CSF may show decreased levels of amyloid-beta 42, total tau (MAPT) and phosphorylated tau (G2019S)
2. PET scanning:
 - a. Decreased striated dopamine

PARK 9*General Characteristics*

1. Parkinson's disease 9 is caused by homozygous or compound heterozygous mutation in the ATP13A2 gene that maps to chromosome 1p36.13
2. The gene encodes a lysosomal type 5 ATPase
3. One family with homozygous mutation in the ATP13A gene has been reported to have neuronal ceroid lipofuscinosis-12

Clinical Manifestations

1. Juvenile onset
2. Rapid progression of signs and symptoms
3. Rigidity and bradykinesia
4. Supranuclear vertical gaze palsy
5. Spasticity
6. Cognitive impairment
7. Variable features:
 - a. Facial and finger mini myoclonus
 - b. Visual hallucinations
 - c. Oculogyric dystonic spasms
 - d. Aggressive behavior
 - e. Cognition may remain relatively intact

Neuropathology

1. The P-type ATPase pump PARK9/ATP13A2 decreases L-synuclein toxicity in primary neurons
2. ATP13A2 encodes a zinc pump which confers zinc resistance in neurons
3. ATP13A2 facilitates transport of zinc into membrane bound vesicles
4. Dysfunction in endogenous ATP13A2 in multivesicular granules (MVBs) causes:
 - a. Lysosomal dysfunction
 - b. Impaired delivery of endocytosed proteins/autophagy cargo to the liposome
5. MVBs (multivesicular bodies) are also the source of intraluminal nanovesicles:
 - a. That are released extracellularly as exosomes
 - b. Contain alpha-synuclein and cause its externalization in exosomes
6. It has been proposed that ATP13A2 modulates zinc levels in MVBs that regulate the biogenesis of exosomes that contain alpha-synuclein
7. After expression of the gene due to mutation may cause:
 - a. Lysosomal impairment
 - b. Alpha-synuclein accumulation
 - c. Lysosomal and mitochondrial dysfunction

Laboratory Evaluation

1. MRI:
 - a. Loss of gray matter in the motor cortex, caudate, thalamus, PFC, and cerebellum
 - b. Diffuse brain atrophy
 - c. Iron deposition in the basal ganglia

PARK 10*General Characteristics*

1. The PARK 10 locus contains four genes: TCEANC2, TMEM58, MiR-4781 and LDLRAD1
2. The locus maps to chromosome 1p32

Clinical Manifestations

1. Mean age at onset of 65.8 years of classic Parkinson's disease
2. Controversial evidence for the risk and age of onset of Parkinson's disease with this chromosomal locus

Neuropathology

1. Not defined

Laboratory Evaluation

1. Molecular genetic analysis

PARK 11*General Characteristics*

1. Susceptibility to Parkinson's disease may be conferred with heterozygous mutation in the GIGYF2 gene that maps to chromosome 2q37.1
2. Recent studies have not replicated the association with PD in disparate populations
3. Alternate splicing causes multiple transcript variants

Clinical Manifestations

1. Classic Parkinson's disease

Neuropathology

1. Not defined

Laboratory Evaluation

1. Genetic determination of the mutation

Autosomal Dominant Parkinson's Disease

1. PARK 1 and PARK 2:
 - a. Mutation in or triplication of the SCNA gene that maps to chromosome 4q22
2. PARK 5:
 - a. Mutation of the VCHL1 gene on chromosome 4p14
3. PARK 8
 - a. Mutation of the LRRK2 gene on 12q12
4. PARK 11
 - a. Mutation in the GIGYF2 gene on chromosome 2q37
5. PARK 13
 - a. Mutation in the HTRA2 gene on chromosome 2p12
6. PARK 17
 - a. Mutation in the VPS35 gene in chromosome 16q12
7. PARK 18
 - a. Mutation in the EIF4G1 gene on chromosome 3q27
8. PARK 21
 - a. Mutation in the DNAJC13 gene on chromosome 3q22
9. PARK 3 – mapped to chromosome 2p13

Autosomal Recessive Early Onset Parkinson's Disease

1. PARK 2
 - a. Mutation in the Parkinson gene that maps to 6q25.2-q27
2. PARK 6
 - a. Mutation in the PINK 1 gene that maps to chromosome 1p36
3. PARK 7
 - a. Mutation in the DJ1 gene that maps to chromosome 1p36
4. PARK 14
 - a. Mutation in the PLA2G6 gene that maps to chromosome 22q13
5. PARK 15
 - a. Mutation in the FBX07 gene that maps to chromosome 22q12-q13
6. PARK 19
 - a. Mutation in the DNAJC6 gene that maps to 1p32
7. PARK 20
 - a. Mutation in the SYNJ1 gene that maps to chromosome 21q22

Other Parkinson's Disease Loci

1. PARK 3
 - a. Mapped to chromosome 2p13
2. PARK 10
 - a. Mapped to chromosome 1p34-32
3. PARK 12
 - a. Mapped to a locus on the X chromosome
4. Mitochondrial mutations may cause or be associated with Parkinson's disease

Susceptibility Genes for the Development of Parkinson's Disease

1. Susceptibility genes for the development of late-onset PD have been associated with mutations or polymorphisms in:
 - a. GBA – 1q22
 - b. ADH1C – 4q23
 - c. TBP – 6q27
 - d. ATXN2 – 12q24.12
 - e. MAPT – 17q21.31
 - f. HLA locus genes
2. It is postulated that each gene confers an independent risk of disease development that is small but in aggregate may have a substantial effect
3. Expanded Trinucleotide repeat gene disorder may increase susceptibility to develop PD. These genes are usually associated with spinocerebellar diseases and include:
 - a. ATXN2
 - b. ATXN3
 - c. TBP
 - d. ATXN80S

Familial Parkinson's Disease

1. An Icelandic study of patients diagnosed with PD over 50 years (772 patients). Detailed genealogic database for the study comprised 610,920 people over 11 centuries
 - a. The study revealed a genetic component to PD that included 560 patients with late onset disease (>50 years of age)
 - b. The study demonstrated:
 - i. No highly penetrant Mendelian pattern
 - ii. Both early and late-onset disease skipped generations
 - iii. The risk ratios for the development of PD in this large generation-spanning study was:
 1. 6.7 increased risk for siblings
 2. 3.2 increased risk for offspring
 3. 2.7 increased risk for nephews and nieces of patients with late-onset

The Differential Diagnosis of Parkinson's Disease**Tau-Associated Parkinsonism***General Characteristics*

1. Neurofibrillary tangles consist of insoluble fibular aggregates of hyperphosphorylated tau

Clinical Manifestations

1. Tau H1 haplotype of the tau gene is associated with progressive supranuclear palsy and corticodorsal degeneration
2. A probably risk factor for Parkinson's disease

Frontal Temporal Dementia Parkinsonism Mapped to Chromosome 17*General Characteristics*

1. Mutations in the gene encoding microtubule associated protein tau (MAPT) cause familial FTD with Parkinsonism linked to chromosome 17q21 (FTDP-17)
2. Inheritance is autosomal dominant
3. Parkinsonism is associated with exon 10 missense mutations that affect exon10 splicing

Clinical Manifestations

1. Parkinsonism with frontotemporal dementia

Neuropathology

1. Coding mutations cause decreased binding of the tau proteins to microtubules
2. Splice site mutations destabilize a stem-loop structure that regulates alternate splicing of exon 10 that increases the four repeat isoform
3. PSP and corticobasal ganglia degeneration also have the excess four repeat tau isoform

4. Patients with defined MAPT mutations have cytoplasmic neurofibrillary inclusions composed of hyperphosphorylated tau
5. Multiple FTD families:
 - a. Lack MAPT mutations
 - b. Demonstrate progranulin PGRN mutations that map to chromosome 17q21.31 and encode a growth factor involved in pleiotropic processes including development and inflammation as well as microglial activation

Clinical Variants of FTD-17 PD

Disinhibition-Dementia-Parkinsonism-Amyotrophy-Complex (DDPAC)

General Characteristics

1. Maps to 17q21-22

Clinical Manifestations

1. Presents with personality and behavioral changes
2. Rigidity, bradykinesia, loss of postural reflexes
3. Amyotrophy of the extremities
4. Rapidly progressive (mean survival of 13 years)

Neuropathology

1. Atrophy and spongiform degeneration in the frontotemporal cortex
2. Neuronal loss and gliosis in the amygdala (SNpc) and anterior horn cells of the spinal cord
3. No Lewy bodies

Pallido-Ponto-Nigral Degeneration (PPND)

General Characteristics

1. PPND is caused by an N279K mutation of the MAPT gene linked to chromosome 17
2. The disorder is autosomal dominant

Clinical Manifestations

1. Dystonia
2. Dementia
3. Ocular motility deficits
4. Pyramidal tract dysfunction
5. Frontal lobe release signs
6. Urinary incontinence
7. Severe sleep disturbance

Neuropathology

1. Degeneration of the globus pallidus and substantia nigra
2. Ballooned neurons in neocortical and subcortical areas
3. Tau inclusions in the cytoplasm of neurons and oligodendroglia similar to those found in CBD and PSP
4. Morphologic and biochemical deficits overlap with sporadic CBD and PSP
5. Tau inclusions are formed from aggregated filaments and hyperphosphorylated tau proteins

Laboratory Evaluation

1. PET:
 - a. Decreased fluorodopa uptake in the caudate and putamen
 - b. Cerebral glucose metabolism is globally reduced (maximally in the frontal cortex)

Familial Progressive Subcortical Gliosis

General Characteristics

1. Autosomal dominant inheritance
2. Tau mutation linked to chromosome 17q21-22

Clinical Manifestations

1. Onset is in the fourth to fifth decades
2. Initial personality change, depression and psychotic episodes
3. Later in the course, speech impairment and components of the Klüver-Bucy syndrome (some patients)
4. Dementia
5. Parkinsonism

Neuropathology

1. Generalized cerebral atrophy
2. Predominant involvement of the white matter of the frontal and temporal lobe
3. Microscopic evaluation:
 - a. Fibrillary astrocytosis of the subcortical white matter and at the subpial and deep layers of the overlying cerebral cortex. Severe gliosis was noted in the cingulate gyrus and insular cortex
4. Severe astrocytosis and degenerative changes occur in the substantia nigra
5. The PSG-1 mutation has a tau mutation at position +16 of the intron after exon 10 that:
 - a. Destabilizes a stem loop structure that causes overexpression of the soluble four-repeat tau isoform that results in neuronal and glial tau pathology

Laboratory Evaluation

1. MRI: (one patient)
 - a. Involvement of the frontal and temporal lobes with atrophy
 - b. Increased signal of subcortical white matter on T2-weighted sequences

Atypical Parkinsonism of the Kii Peninsula of Japan (Muro Disease)

General Characteristics

1. Atypical Parkinsonism of the Kii Peninsula of Japan is also known as Muro disease
2. There are four subtypes:
 - a. Sporadic ALS
 - b. Kii ALS/PDC with tauopathy
 - c. ALS with C9 or 672 gene mutation
 - d. ALS with the optineurin gene mutation
3. Recent epidemiological studies have shown that ALS has declined over the past 50 years while that of PDC (*Parkinsonism-dementia complex*) has risen

Clinical Manifestations

1. All patients have cognitive dysfunction that includes:
 - a. Abulia, apathy
 - b. Bradyphrenia
 - c. Hallucination
 - d. Disorientation
 - e. Delayed reaction
2. Progressive Parkinsonism
3. Late severe dementia
4. ALS
5. Levodopa unresponsive Parkinsonism

Neuropathology

1. Abundant neurofibrillary tangles in the temporal lobe, frontal lobe and brain stem
2. Motor neuron loss in the spinal cord
3. No senile plaques

Laboratory Evaluation

1. MRI:
 - a. Most have frontotemporal lobe atrophy (some patients are negative)
 - b. Hypometabolism of the frontal lobes
 - c. SPECT evaluation demonstrates decreased blood flow to the anterior cingulate gyrus

Amyotrophic Lateral Sclerosis – Parkinsonism-Dementia Complex 1 of Guam

General Characteristics

1. Mutation of the TRPM7 gene that maps to chromosome 15q21.2 confers susceptibility to the disorder (some patients)
2. A similar phenotype is seen from a double homogeneous mutation in the DJ1 gene associated with PARK7
3. There is a high incidence of the disorder among the Chamorro people of Guam
4. There is evidence by segregation analysis that the disorder is autosomal dominant with complete penetrance in males and approximately 50% penetrance in females
5. Polymorphisms in MAPT may increase risk but no mutation in MAPT or other genes have been found to be causative of the disorder
6. Some linkage analytic studies support a locus on chromosome 12

Clinical Manifestations

1. Gradual onset and progression of primary Parkinsonism and dementia
2. Signs and symptoms may follow Parkinsonian features or appear concomitantly
3. The onset is usually in the fifth to seventh decade

Neuropathology

1. Severe cortical atrophy with neuronal loss
2. Widespread neurofibrillary tangles, severe in the isocortex and hippocampal formation

3. NFTs are preferentially distributed within layers II–III in the isocortex of ALS/PDC; in Alzheimer's disease they are sparser in layers II–III but denser in layers V–VI
4. A tau triplet repeat is found in ALS/PDC in both cortical and subcortical areas

Laboratory Evaluation

1. MRI:
 - a. Atrophy of frontal and temporal lobes
2. SPECT:
 - i. Decreased blood flow to the frontal and temporal lobes

Fragile X-Mental Retardation Tremor Ataxia Disorder

General Characteristics

1. FXTAS is caused by an expanded trinucleotide repeat that maps to Xq27.3
2. Patients with the fragile X permutation express 55–200 CGG expanded repeats and elevated FMR1 messenger RNA levels
3. Full expansion of repeats, >200, cause fragile X mental retardation syndrome

Clinical Manifestations

1. Affects older male patients primarily in the sixth decade
2. Intention tremor
3. Parkinsonism
4. Cognitive dysfunction
5. Autonomic dysfunction
6. Penetrance in male carriers >50 years of age is 33%; in female carriers it is 5–10%

Neuropathology

1. Cerebral and cerebellar white matter disease
2. Enlarged astrocytes with inclusions; intranuclear inclusions in the brain and spinal cord
3. Spongiosis of the middle cerebellar peduncle
4. The intranuclear inclusions contain FMR1 mRNA, lamin A/C, neurofilaments and ubiquitin
5. Postulated that FXTAS is caused by a toxic gain of function of FMR1 RNA

Laboratory Evaluation

1. MRI:
 - a. Cerebral and cerebellar volume loss
 - b. Increased signal intensity on T2-weighted sequences in the middle cerebellar peduncles

Parkinsonism in Autosomal Dominant Spinocerebellar Ataxia

1. SCA2 Parkinsonian signs and symptoms are more common in Chinese than Caucasian patients
2. SCA3 Parkinsonism may be severe
3. 18F-dopa PET scans demonstrate basal ganglia decrease of dopamine
4. Patients may be minimally responsive to L-dopa

*Parkinsonism in Huntington's Disease***General Characteristics**

1. The gene is IT15 (expanded CAG repeats) that maps to chromosome 4p16.3

Clinical Manifestations

1. The age of onset is related to the number of repeats; juvenile onset patients have > than 50 CAG repeats
2. Patients present with neurological or psychiatric features rarely with both simultaneously
3. Extremity chorea
4. Impersistence of sustained movements (inability to hold the tongue out; milkmaids hand)
5. Lurching gait
6. Slow and hypometric saccades (vertical > horizontal); convergence paresis; inability to initiate saccades; late in the disorder choreatic eye movements
7. Parkinsonism (bradykinesia predominant)
8. Orolingual apraxia
9. Increased reflexes and clonus
10. Juvenile Variant (Westphal)
 - a. Presents in the teens
 - b. Akinetic rigid syndrome
 - c. 90% of patients are of paternal lineage
 - d. Seizures

*X-Linked Dystonia Parkinsonism***General Characteristics**

1. Primarily found in Filipino patients from the Panay Islands; known as Lubag
2. X-linked missense mutation; mutation in the TAF1 gene (Xq13.1)

Clinical Manifestations

1. Onset in adulthood (mean 39 years of age)
2. Most often the presentation is Parkinsonism
3. Focal dystonia primarily affects the jaw, neck, eyes and trunk; within 2–5 years after onset, 50% of patients develop generalized dystonia
4. Parkinsonism manifests as bradykinesia, rigidity and postural instability
5. Blepharospasm
6. Poorly responsive to L-dopa

*Rapid-Onset Dystonia Parkinsonism***General Characteristics**

1. Mutation of the ATP1A3 gene that maps to chromosome 19q13.2

Clinical Manifestations

1. Rapid onset of symptoms; progress over hours
2. Signs are initiated by physical and emotional stress
3. Presents with cranial and limb dystonia
4. Dysarthria and dysphagia
5. Parkinsonism that is not L-dopa responsive

*Parkinsonism in Dentato-Rubro-Pallido-Luysian Atrophy (DRPLA)***General Characteristics**

1. AD; a trinucleotide repeat in the ATN1 gene that maps to chromosome 12p13.31

Clinical Manifestations

1. Cerebellar ataxia
2. Parkinsonism
3. Myoclonus
4. Dystonia
5. Seizures

*Parkinsonism in Wilson's Disease***General Characteristics**

1. Wilson's disease is AR and is caused by mutation of the ATP7B gene that maps to chromosome 13q14.3

Clinical Manifestations

1. Onset is between 6–40 years of age
2. Neurologic symptomatology manifests in the patients' early twenties
3. The presentation may be psychiatric, neurologic or as liver disease
4. Usually severe dysarthria
5. Wing beating tremor (postural kinetic)
6. Postural instability
7. Dystonia
8. Parkinsonism
9. Kayser-Fleischer ring in the cornea (the copper accumulation is in Descemet's membrane)
 - a. Present in all patients with neurologic disease
10. Rare chorea
11. No sensory symptoms
12. Depression, personality change, emotional lability
13. Cognitive decline with disease progression

Differential Diagnosis of Parkinson's Disease***Lewy Body Dementia*****General Characteristics**

1. Associated with mutation of the G1GYF2 gene that maps to chromosome 2q37.1

Clinical Manifestations

1. The onset is the sixth to seventh decade; average age is 68
2. Visuospatial, attentional deficits in problem solving abilities are seen early
3. Fluctuations in cognitive abilities from day to day are striking
4. Visual hallucinations are a seminal feature
5. Variable clinical manifestations include:
 - a. Repeated falls

- b. Syncope
- c. Sensitivity to neuroleptic medications
- d. Auditory and tactile delusions
- e. Transient ischemic-like episodes
- f. Rest tremors, Parkinsonian rigidity and bradykinesia occur but not to the same degree that is seen with idiopathic Parkinson's disease

Multiple System Atrophy (MSA)

General Characteristics

1. In the past MSA has been thought to be a sporadic disorder but recently:
 - a. Small familial aggregates have been reported
 - b. Familial aggregates of alpha-synucleinopathy with PD and MSA occur in the same kindreds
2. The diagnostic criteria require:
 - a. Definite MSA has CNS alpha-synuclein positive glial cytoplasmic inclusions with neurodegenerative changes in striatonigral or olivopontocerebellar structures
 - b. Probable MSA:
 - i. Is a sporadic, progressive adult-onset disorder with autonomic failure, Parkinsonism that is not responsive to levodopa or cerebellar ataxia
 - c. Possible MSA:
 - i. A sporadic progressive adult-onset disorder with Parkinsonism or cerebellar ataxia with one feature of autonomic dysfunction plus one other clinical or neuroimaging abnormality
3. MSA core features are dysautonomia with combinations of Parkinsonism (poorly or not responsive to L-dopa), cerebellar ataxia, and pyramidal signs
4. The new criteria retain the major diagnostic categories of MSA with Parkinsonism (MSA-P) or predominant cerebellar ataxia (MSA-C)

Clinical Manifestations

1. Distribution of signs:
 - a. Approximately 28% have all four major manifestations (autonomic dysfunction, Parkinsonism, cerebellar ataxia and cognitive impairment)
 - b. 18% have Parkinsonism, corticospinal and autonomic dysfunction
 - c. 11% have Parkinsonism and autonomic dysfunction
 - d. 10% have MSA-P
 - e. Autonomic dysregulation develops to a significant degree in >90% of patients and is manifested by:
 - i. Impotence
 - ii. Urinary incontinence in females
 - iii. Orthostatic hypotension may be the most disabling manifestation:
 1. Upright hypotension
 2. Supine hypertension
 3. Syncope precipitated by heat, exercise and large meals

4. "Coat hanger headache" just prior to syncope
5. (posterior occipital and trapezius ridge discomfort)
6. Clinical manifestations of MSA-P:
 - a. Severe akinetic-rigid syndrome
 - b. Levodopa unresponsive
 - c. Dystonia (particularly of the upper extremity)
 - d. The arm levitates and the posture is maintained
 - e. The patients have greater cognitive impairment than is generally seen in idiopathic Parkinson's disease

Shy-Drager Syndrome

General Characteristics

1. Autonomic dysfunction is the seminal feature

Clinical Manifestations

1. The onset is between 40–69 years of age
2. The most prominent symptom is postural hypotension which may precede Parkinsonism
3. Forward-flexed rigid stance
4. Patients lose consciousness and fall due to severe hypotension
5. Iris atrophy (holes in the iris; deep anterior chamber of the eye)
6. Dementia
7. Ataxia
8. Bowel, bladder and sexual dysfunction early in the course of the illness
9. Cold mottled hands (livedo reticularis) at clinical presentation
10. Progression is more rapid than idiopathic Parkinson's disease

Neuropathology

1. Severe loss of cells in the intermediolateral column of the spinal cord
2. Loss of dopaminergic neurons of the SNpc

Laboratory Evaluation

1. Dopaminergic dysfunction in the basal ganglia by PET (fluorodopa) and SPECT

Progressive Supranuclear Palsy (PSP)

General Characteristics

1. Mutations in the MAPT gene that maps to chromosome 17q21.31 that also causes a form of frontotemporal dementia, have been described in both sporadic and familial PSP
2. The H1 haplotype of MAPT is a risk haplotype for PSP
3. Within the H1 haplotype, a subhaplotype (H1c) is associated with PSP

Differential Points of PSP vs PD: Clinical Manifestations

1. Median age of onset is 64 years of age (range is 50–77 years) in PSP
2. Parkinsonian patients who respond poorly to levodopa; 1–8% may have PSP pathologically
3. Supranuclear ophthalmoplegia is seminal in PSP:
 - a. Poor vertical saccades are an early feature
 - b. Downward saccades are affected first
 - c. Hypometria of saccades vertical > horizontal
 - d. Blepharospasm
 - e. Apraxia of eyelid opening
 - f. Ptosis; marked lid retraction
 - g. Decreased blinking
 - h. Pseudointernuclear ophthalmoplegia
 - i. Nystagmus
 - j. “Square wave jerks” (ocular recording)
 - k. Pathologic lid retraction
 - l. Poor convergence
 - m. Vertical saccades are accomplished by moving the eyes in a lateral arc
 - n. Complete ophthalmoplegia may occur late in the disease course
4. Personality change with frontal lobe dyscontrol
5. Falling, imbalance, gait disorder, occurs much earlier than with idiopathic Parkinson’s disease
6. Axial rigidity > appendicular
7. Dysphagia and dysarthria
8. Falling backwards
9. Rigid hyperextension of the neck (Doll’s eye maneuver to move the eyes downward); PD has a flexed neck
10. Gait abnormalities:
 - a. Stiff and broad based
 - b. Knees and trunk are extended (PD stooped with knees flexed); PSP the gait is narrow based
 - c. The arms are slightly adducted; in PD there is an increased flexion carrying angle of the arms
 - d. Patients pivot rather than turning “en bloc” as is the case with PD
11. There is no tremor in PSP
12. Characteristic faces:
 - a. Deep nasolabial folds (PSP)
 - b. Staring wide eyed expression (PSP)
13. Early in the course of illness there is prominent akinetic gait ignition failure and freezing
14. Rare manifestations of PSP:
 - a. Limb rigidity > axial
 - b. Mild tremor at rest
 - c. Upper limb apraxia, myoclonus and chorea
 - d. Respiratory dysfunction
15. Arm levitation (more commonly seen than the posterior “alien” hand that is seen with corticobasal ganglia degeneration)
16. Patients have a higher blood pressure than is seen with other neurodegenerative disorders
17. Clinical research criteria for PSP:

- a. Possible PSP:
 - i. Gradually progressive disorder
 - ii. Onset at age 40 or later
 - iii. Vertical supranuclear gaze palsy or slowing of vertical saccades
 - iv. Postural instability with falls within the first year of onset
- b. Probable PSP:
 - i. Vertical supranuclear gaze palsy
 - ii. Postural instability
 - iii. Falls within the first year of onset
 - iv. Other features of possible PSP
- c. Definite PSP:
 - i. A history of possible or probable PSP
 - ii. Histological verification of PSP

Neuropathology

1. Bilateral loss of neurons and gliosis in the periaqueductal gray, superior colliculus, subthalamic nucleus, red nucleus, the pallidum, dentate nucleus, pretectal and vestibular nuclei
2. Neurofibrillary degeneration of remaining neurons; tau deposition

Laboratory Evaluation

1. MRI:
 - a. Atrophy of the dorsal mesencephalon (superior colliculus and red nucleus)
2. PET:
 - a. Decreased CBF most marked in the frontal lobes

Differential Diagnosis of PSP

1. Progranulin (PRG) frontotemporal dementia, C9ORF72, CHMP2B and FUS
2. Kufor-Rakeb disease
 - a. Mutation in ATP13A2
3. Niemann-Pick type C (NPC1)
4. Perry syndrome (mutation in DCTN1)
5. Gaucher’s disease (mutation in GBA)
6. Mitochondrial disorders
7. Familial Creutzfeldt-Jakob disease (mutations in PRNP)

Corticobasal Degeneration (CBD)*General Characteristics*

1. The Armstrong criteria proposed 2013 include 4 CBD phenotypes:
 - a. Corticobasal syndrome (CBS)
 - b. Frontal behavioral/spatial syndrome (FBS)
 - c. Non-fluent/agrammatic variant of primary progressive aphasia (naPPA)
 - d. PSP
2. These phenotypic variants are comprised of sets of criteria:
 - a. Clinical research criteria for probable CBD (cr-CBD)

- b. Possible CBD (pCBD) that are more inclusive
- c. Two studies have failed to validate the criteria and it has been suggested that criteria need to be biomarker driven

Clinical Manifestations

1. CBD is clinopathologically heterogeneous thus its manifestations may best be considered syndromic (CBS)
2. Corticobasal ganglion degeneration (CBD) is now used for patients with histopathologic verification
3. Equal sex incidence
4. Average age of onset is 60 years of age
5. Usually a six to ten year duration of disease
6. There is symmetric presentation of extremity:
 - a. Rigidity
 - b. Clumsiness
 - c. Stiffness
 - d. Jerking of an arm or leg
 - e. Limb ideomotor apraxia
 - f. Postural instability
7. After 2–3 years:
 - a. Dystonic rigidity and akinesia of the limb
 - b. Hemimyoclonus
8. Posterior parietal alien hand or limb:
 - a. The limb moves without voluntary control
 - b. The patient may feel that the limb does not belong to him
 - c. The affected limb may assume an abnormal posture or levitate
9. Parietal S1 type sensory loss
10. Progression of the illness to:
 - a. Dysarthria
 - b. Dysphagia
 - c. Supranuclear gaze palsy
 - d. Rare cerebellar signs
11. Frontotemporal neurobehavioral disorder may develop
12. Non-fluent/agrammatic variant of primary progressive aphasia (naPPA)

Neuropathology

1. Abnormal accumulation of microtubule-associated tau protein in both neurons and glia, and filamentous threads
2. SNpc and STN are prominently involved
3. Affected cortical areas of involvement include:
 - a. Rolandic areas
 - b. The posterior frontal and parietal cortex
 - c. Late disease:
 - i. Insular cortex
 - ii. Tip of the temporal lobe

Laboratory Evaluation

1. MRI:
 - a. Asymmetrical cortical atrophy
 - i. Frontal and parietal lobes
 - b. Focal symmetric frontotemporal atrophy (some patients)

- c. Generalized atrophy
- d. Diffusion tensor imaging:
 - i. Cortical reduction of fractional anisotropy (FA) and coexistent increase in mean diffusivity (MD)

Post-Encephalitic Parkinsonism (1915–1927)

General Characteristics

1. Primarily categorized as a sequel of von Economo's or epidemic encephalitis; also known as encephalitis lethargica
2. At present very rare as most patients have died

Clinical Manifestations

1. Parkinsonism occurred weeks to years after the termination of the encephalitis
2. Tremor was as prominent as that seen in idiopathic PD
3. Oculogyric crises was prominent (usually spasm of the superior rectus and inferior oblique muscles; any ocular muscles were affected)
4. Personality and behavioral changes
5. Autonomic crisis:
 - a. Severe hypertension
 - b. Hyperhidrosis
6. Bulbar palsies
7. Ophthalmoplegia
8. Sleep wake cycle disturbance

Neuropathology

1. NFT (neurofibrillary tangles) and neuronal loss in SNpc
2. TDP-43 pathology is distributed widely

Drug-Induced Parkinsonism

MPTP (1-Methyl-4-2,3,6 Tetrahydropyridine)

General Characteristics

1. Designer drug produced from overheated demerol

Clinical Manifestations

1. An irreversible and progressive disease
2. Dramatically rapid onset of parkinsonism
3. The tremor is faster than the 4–6 Hz of PD
4. The disorder responds to L-dopa early in its course; side effects develop quickly and are dependent on the severity of dopaminergic denervation rather than the length of treatment
5. Reflexes are generally increased
6. Many other features are similar to PD

Neuropathology

1. MPTP is a lipophilic drug compound that easily crosses the blood-brain barrier
2. It is metabolized into the toxic (1-methyl-4-phenylpyridinium) MPP⁺ by the enzyme MAO-B that is located in glia
3. MPP⁺ interferes with complex I of the respiratory chain primarily in dopaminergic neurons of the SNpc

4. MPP+ has high affinity for the dopamine transporter of dopaminergic nerve terminals
5. There is severe loss of dopaminergic neurons and gliosis of the SNpc

Reversible Drug-Induced Parkinsonism

General Characteristics

1. Drug-induced parkinsonism is the second most common cause of parkinsonism after Parkinson's disease
2. Clinical differentiation may be difficult between drug-induced parkinsonism and the early stages of the primary disease

Clinical Manifestations

1. In drug-induced parkinsonism:
 - a. There is no hyposmia
 - b. No urinary urgency
 - c. Symmetry of symptoms and signs
 - d. Relative absence of resting tremor
 - e. Coexistence of oromandibular dyskinesia
 - f. The offending drug may unmask true Parkinson's disease
 - g. Signs and symptoms should clear within six months of drug withdrawal
 - h. Minimal if any response to levodopa
 - i. No REM behavior sleep disorder

Neuropathology

1. Primarily there is blockage of D2 receptors rather than destruction or degeneration of the SNpc dopaminergic system
2. Classes of drugs that cause drug-induced Parkinson's disease include:
 - a. Antipsychotic medication
 - b. Antiemetics
 - c. Cholinomimetics
 - d. Antidepressants
 - e. Anti-vertigo medications
 - f. Calcium channel blocking agents
 - g. Antiarrhythmics
 - h. Antiepileptics

Laboratory Evaluation

1. Dopamine transporter imaging (DaT-scan)
2. Cardiac MIBG uptake may be significantly reduced in patients with PD; in drug-induced parkinsonism it is normal >90% of patients

Differential Diagnosis of Toxic Causes of Parkinsonism

1. Manganese:
 - a. Manganese miners
 - b. Welders
 - c. Clinical manifestations:
 - i. Severe depression as an early symptom

- ii. Bradykinesia and akinesia are dominant signs at presentation
- iii. Severe loss of postural reflexes
- iv. Frequent falls
- v. Rare tremor

2. Post-hypoxic Parkinsonism:
 - a. Parkinsonism has a delayed onset from the sentinel event
 - b. Associated with myoclonus, choreoathetosis and cortical deficits
 - c. Bilateral GP destruction with carbon monoxide
3. Carbon Tetrachloride:
 - a. Utilized in the dry cleaning process
 - b. Akinetic rigid presentation
4. Methanol:
 - a. Suicide attempts; anti-freezes and may be an adulterant in "moonshine"
 - b. Akinetic-rigid presentation
 - c. Severe optic neuropathy with hemorrhagic optic neuritis
 - d. Increased signal in the striatum in T2-weighted MRI sequences
5. Carbon Monoxide:
 - a. Car mechanics, suicide attempts, poor inside heaters
 - b. Cherry red lips and extremities
 - c. Cortical basal ganglia and cerebellar signs and symptoms
 - d. Particular globus pallidus involvement
6. Mercury:
 - a. Industrial exposure
 - b. Akinetic-rigid presentation but some patients demonstrate severe choreoathetosis
 - c. Peripheral neuropathy
 - d. The Minamata Bay Japanese toxic exposure demonstrated the above features in various combinations

The Differential Diagnosis of Multiple System Atrophy from Parkinson's Disease

1. MSA is predominantly a preganglionic disorder; in PD the pathology is primarily post-ganglionic
2. Autonomic dysfunction in general is more severe in MSA than PD
3. Autonomic abnormalities have a more rapid progression in MSA than PD
4. Diffuse anhidrosis is more widespread in MSA than PD
 - a. Involvement of hypothalamic thermoregulatory centers in MSA

Differential Diagnosis by MRI of Familial Parkinsonism

1. The MRI may be normal
2. Pantothenate kinase 2 (PANK 2 gene)
 - a. Low signal in the internal segment of the globus pallidus
 - b. Axonal vacuolization (spheroids)

3. Fahr's disease:
 - a. Bilateral calcification of the basal ganglia
 - b. Calcification of subcortical white matter and the dentate nucleus
4. Niemann-Pick type C:
 - a. Diffuse cerebellar atrophy
 - b. Mild cerebral atrophy
5. Huntington's disease:
 - a. Severe atrophy of the caudate nucleus ("box car" atrophy)
 - b. Frontal lobe atrophy
6. Wilson's disease:
 - a. Putamen > caudate lesions on T2-weighted sequences
 - b. Midbrain and occasional thalamic lesions
7. Neuroferritinopathies
 - a. T2-weighted lesions (low intensity) of the basal ganglia
8. FTD (frontotemporal dementia) chromosome 17
 - a. Mesial temporal lobe atrophy
 - b. More severe white matter abnormalities occur with LBD
5. MSA-P and PSP:
 - a. Low FA in the primary motor cortex in MSA-P
6. In PSP:
 - a. A high ADC (high apparent diffusion coefficient) and low FA in the supplementary motor cortex
7. Anatomical connectivity studies demonstrate:
 - a. Lower number of corticospinal tract fibers in MSA and PSP relative to PD
 - b. In patients with PSP and MSA (late stage) versus PD
 - i. Fewer cortical projection fibers in PSP and MSA

Differential Diagnosis of Diffusion Tensor Imaging in Parkinsonian Syndromes

1. Parkinson's disease:
 - a. Reduction of fractional anisotropy (FA) in the substantia nigra
 - b. Reduced FA in PD patients that demonstrated anosmia in anterior olfactory structures
 - c. Reductions in FA in the motor areas of the cerebral cortex
2. Multiple System Atrophy:
 - a. Reduced FA in the pons and the cerebellum in MSA-P
 - b. Comparing MSA versus PD
 - i. FA reductions in the cerebellum (MSA-P)
 - ii. Increases in mean diffusivity (MD) in the pons and cerebellum (MSA-P)
 - iii. Utilization of FA and ADC measurement in the pons:
 1. There was a 70% similar sensitivity
 2. 100% specificity in differentiating MSA-P from Parkinson's disease
 - iv. FA and radial diffusivity are different (less in the former and greater in the latter) for MS-P than PD
 - v. Summary:
 1. Decreased FA and elevation in MD in the cerebellum, pons, and cerebellar peduncles may distinguish MSA from PD
 2. Putamen demonstrates FA decreases and increased mean diffusivity in MS-P versus PD
 3. Parkinson's disease dementia versus Parkinson's disease
 - a. Bilateral posterior cingulate FA reduction in PDD
 4. PDD and Lewy body dementia (LBD):
 - a. Similar regions of reduced FA in both disorders

Movement Disorders Associated with Long-Term Levodopa Treatment of Parkinson's Disease

1. End of dose failure:
 - a. Return to baseline of bradykinesia or akinesia
 - b. Tremor returns
2. Peak dose dyskinesia:
 - a. Choreoathetosis at period of maximum absorbed concentration of levodopa
3. Early morning dystonia:
 - a. Awakening with dystonia of the lower extremity (most often plantar flexion with inversion of the foot) with PD
4. "Off periods"
 - a. Severe bradykinesia – akinesia
 - b. May have sudden onset
 - c. May last 30 minutes to hours
 - d. Associated with "freezing" (inability to change motor programs); go through doorways; change directions
 - e. "On periods":
 - i. Duration of maximum benefit from medications
 - f. "On-off" phenomena:
 - i. Periods of benefit from medication associated with sudden episodes of bradykinesia
 - g. "On-off" dystonia
 - h. Dyskinesia-improvement-dyskinesia

Differential Diagnostic Features of Parkinsonism

The immediate clue that one is dealing with a system degeneration rather than idiopathic Parkinson's disease is the lack of response to levodopa, the symmetry of signs and symptoms, a low blood pressure and cold hands.

Shy-Drager syndrome is dominated by autonomic failure. Small cues are iris atrophy (deep anterior chamber of the eye and an atrophic iris) as well as cognitive impairment. MS-P is predominantly an akinetic-rigid parkinsonian patient that has no tremor at rest, more rigidity than an IPD patient and does not respond to levodopa. Occasionally these patients have lev-

itation of an arm. A difficult diagnostic problem may occur with early progressive supranuclear palsy (PSP) and IPD. In PSP, the supranuclear gaze palsy often is associated with eyelid apraxia, falls, and deep nasolabial folds. The head is held in extension. The hallmark of diffuse Lewy body disease is dementia, visual hallucinations and clear fluctuation of cognitive and parkinsonian features. These patients may demonstrate levitation of an extremity. Corticobasal ganglionic degeneration is suspected when a patient presents with an asymmetric akinetic rigid state, a posterior alien hand, and primary sensory (SI) modality loss. Pick's disease is dominated by a slowly progressive expressive aphasia.

Olivopontocerebellar degeneration is now MSA-C and may demonstrate dorsal column dysfunction, retinal disease and cranial nerve abnormalities in addition to clear cerebellar ataxia.

Differential Diagnosis of Secondary Parkinsonism

Hemiatrophy Hemiparkinsonism

General Characteristics

1. The incidence and prevalence of the disorder are unknown; there does not seem to be a genetic cause

Clinical Manifestations

1. Most often a childhood onset; late onset has been reported
2. Asymmetric parkinsonism
3. Slowly progressive
4. Hemiatrophy on the parkinsonian side
5. In one series, 50% of patients had dystonia at onset; dystonia was documented in 70% of patients
6. A significant proportion of patients have scoliosis
7. Some patients have a good response to levodopa
8. Difficulty walking in childhood

Neuropathology

1. In approximately 1/3 of patients there is a documented history of birth difficulties or a severe febrile illness in the first few months of life

Laboratory Evaluation

1. MRI:
 - a. Asymmetric (smaller brain volume) on the side opposite the hemiatrophy
2. The D2 receptor binding capacity is symmetrical whereas in CBD it is not

Idiopathic Normal Pressure Hydrocephalus

General Characteristics

1. A communicating hydrocephalus of the elderly

Clinical Manifestations

1. The classic clinical triad of:
 - a. Dementia
 - b. Urinary incontinence (precipitate urination)

- c. Ataxia (primarily of gait)
2. Variable features:
 - a. Falling backwards
 - b. Foot grasp (feet sticking to the floor in gait ignition)
 - c. Hyperactive patellar reflexes
 - d. Limitation of upgaze with Collier's sign (pathologic lid retraction)

Neuropathology

1. NPH may follow stroke, subarachnoid hemorrhage, head trauma or other conditions that may interfere with CSF absorption
2. It may remain as an idiopathic communicating hydrocephalus after a complete evaluation

Laboratory Evaluation

1. MRI:
 - a. Frontal convexity narrowing
 - b. Parietal convexity narrowing
 - c. Upward bowing of the corpus callosum
 - d. Empty sella
 - e. Narrowing of the CSF space at the high convexity
 - f. Marked dilatation of the Sylvian fissure
 - g. Disproportion between narrowing of the CSF space at the high convexity and dilatation of the Sylvian fissure
2. Reduced default mode network (DMN) connectivity
3. Tap test: removal of 35cc of CSF with subsequent gait analysis; response to CSF drainage

Vascular Parkinsonism

General Characteristics

1. Lacunar infarction of the basal ganglia
2. The gait and balance are most affected
3. Lower half parkinsonism
 - a. Vascular disease of the periventricular descending corticospinal tracts that project to leg anterior horn cells

Other Differentials for Secondary Parkinson's

1. Severe depression (pseudoparkinsonism)
2. Wilson's disease
3. Huntington's disease:
 - a. Juvenile akinetic-rigid phenotype
 - b. Seizures
 - c. An end-stage phenomenon in the choreic form
4. Pantothenate Kinase 2
5. Binswanger's disease
 - a. Atherosclerotic ischemic demyelination
6. Alzheimer's disease
7. Striatal Neoplasms
8. Creutzfeldt-Jakob disease
9. Repeated Head trauma
 - a. Pugilistic parkinsonism
10. Hypoparathyroidism
11. Fahr's disease

Hyperkinetic Disorders

Overview

Primary General Categories of Hyperkinetic Disorders

1. Tremor
2. Myoclonus
3. Tardive dyskinesia
4. Ballism
5. Chorea
6. Athetosis
7. Dystonia
8. Paroxysmal dyskinesia
9. Akathisia movements
10. Tics

Tremor

General Characteristics

1. Definition:
 - a. A tremor is a rhythmic oscillation of a body part
 - b. The mechanisms of the oscillations include:
 - i. Mechanical oscillations
 - ii. Reflex oscillations
 - iii. Oscillations due to central neuronal pacemakers
 - iv. Oscillations due to abnormal feedforward or feedback loops

Clinical Manifestations

Tremors are involuntary movements that are rhythmic and oscillatory about a fixed point. They are due to alternating or synchronous contractions of agonist and antagonist muscles and may occur at rest, or with movement or on holding a static posture.

Physiologic Tremor

General Characteristics

1. Physiologic tremor (PT) is generated and mediated by peripheral and central mechanisms
 - a. Central mechanism:
 - i. The central component, “the central oscillator” causes a weak 8–12 Hz low amplitude movement
 - ii. The central oscillator is minimally affected by inertial loading
 - iii. Motor units are not entrained (they don’t discharge in groups) under usual circumstances
 - iv. Under conditions of stress due to drugs, cold or emotion they become entrained
 - b. The peripheral component of physiologic tremor includes:
 - i. Mechanical factors of the body part
 - ii. Short and long loop reflexes influence the peripheral component
 - iii. The peripheral component of the physiologic tremor is termed the “mechanical reflex”

- iv. Inertial loading decreases the mechanical reflex frequency but is complicated by spindle stretch responses, muscle properties, thixotropy (time dependent viscosity) and neural membrane firing characteristics
- v. When motor units fire in groups i.e. entrained physiologic tremor develops into exaggerated physiologic tremor (EPT) that induces greater participation of the stretch reflex and the central oscillator
- vi. EPT may become clinically symptomatic with posture or movement and phenomenologically is similar to essential tremor
- vii. Physiologic tremor is enhanced by:
 1. Fatigue
 2. Anxiety
 3. Thyrotoxicosis
 4. Narcotic withdrawal
 5. Hypoglycemia
 6. Pheochromocytoma
 7. Alcohol withdrawal
 8. Catecholamine excess
 9. Steroids
 10. Caffeine
 11. Theophylline
- viii. Absent at rest
- ix. Present with maintained posture
- x. Activated by severe muscle fatigue

Pathologic Tremors

Rest Tremor

General Characteristics

1. Most often seen in PD or with parkinsonism

Clinical Manifestations

1. The tremor starts unilaterally and distally
2. It is a 3–6 Hz “pill-rolling” sinusoidal oscillation
3. It becomes more proximal as it generalizes bilaterally
4. The tremor may start anywhere in the body; the jaw is a rare example
5. Early in the course of the disease the tremor fluctuates with physical exercise or mental effort
6. There are oscillations in wrist extension and flexion, pronation and supination or finger flexion against the thumb
7. PD tremor increases with stress and disappears with sleep
8. The frequencies are similar in each extremity in patients with bilateral tremor
9. Head tremor is rare:
 - a. Up and down when present
 - b. Lip and jaw tremor are more prominent in PD than in other movement disorders
10. Thumb and finger movements of a metacarpophalangeal flexed hand give it the “pill-rolling” character
11. The chin and tongue may be affected

12. Advanced patients may demonstrate postural kinetic and intention tremor; the postural kinetic component has a latent period when the hands and arms are outstretched; essential tremor does not
13. Walking may increase the amplitude of the hand tremor

Neuropathology

1. Tremor severity does not correlate with striatal dopamine levels
 - a. Some patients have increased tremor with levodopa
 - b. It is proposed that rest tremors are modulated centrally but there may be multiple generators within both corticobasal ganglia and corticocerebellar circuits
 - i. One central generator that has been proposed is the VIM nucleus of the motor thalamus where burst neurons have been recorded that fire at the same frequency as the tremor
 - ii. Proprioceptive feedback from displaced joints modulates the tremor

Other Tremors that may Occur at Rest

Essential Tremor (ET)

1. Severe ET may occur at rest but must be differentiated from coexistent PD or incomplete postural relaxation
2. ET is asymmetric and there may be different frequencies between sides

Rubral Tremor

1. Is most often caused by midbrain lesions that involve the cerebellar outflow pathways from the dentate nucleus to the ventrolateral thalamic nucleus (VL) or the nigrostriatal pathways
2. The tremor may be seen at rest, with postural maintenance or with movement
3. The rest component:
 - a. Has a large amplitude
 - b. Is irregular
 - c. Involves both proximal and distal musculature
 - d. Its frequency is 2–5 Hz
 - e. The primary cause is midbrain infarction although it is occasionally seen in demyelinating disease or with infection and trauma

Thalamic Tremor

1. Most often causes an action tremor but a rest tremor has been reported
2. The lesion causing the tremor affects the ventrolateral posterior nucleus of the thalamus

Drug-Induced and Dystonic Tremor

1. Most often are action tremors but can occur at rest

Action Tremor

Alzheimer Disease

1. Most often encountered later in the course of the illness although it may have a variable onset

2. There is delayed onset of the tremor when the arm is held outstretched
3. The frequency is 3–6 Hz
4. Higher frequency 5–8 Hz tremor with a lower amplitude action tremor have been reported with PD

Essential Tremor (ET)

General Characteristics

1. ET is the most prevalent adult tremor disorder
2. Greater than 50% of patients have a positive family history
3. The most frequent genes linked to the disorder are LING01, FUS and TENM4 and it is thought to be autosomal dominant

Clinical Manifestations

1. The most common risk factor is age, although it has been diagnosed in children
2. It is slowly progressive
3. Initially it is of low amplitude and has a frequency of 4–12 Hz that decreases with age
4. It affects the hands and arms most severely but other body parts can be affected
5. The amplitude of the kinetic component is greater than that seen with postural tremor
6. The tremor increases as the hand approaches the target
7. Head tremor is in the horizontal plane and can rarely occur in isolation
8. The tremor can affect the jaw in distinction to PD which may affect the lower lip
9. It is more irregular and bilaterally symmetric than PD
10. Cogwheel tone may occur secondary to the tremor
11. The tremor is decreased with alcohol
12. The tremor is usually abduction, adduction or flexion-extension of the hand; rarely pronation-supination
13. Most often monosymptomatic
14. May be associated with:
 - i. Poor fine hand movement
 - ii. Balance and gait disturbance
15. Handwriting:
 - i. Large letters
 - ii. Rounded letters
16. Rare associations:
 - i. Malignant hyperthermia
 - ii. Dystonia
 - iii. Migraine (possible)
17. Commonly associations:
 - i. PD
 - ii. Fragile X-premutation

Neuropathology

1. Evidence supports that the tremor is generated in olivary cerebellar circuits
2. Recent experimental studies utilizing functional magnetic resonance imaging has demonstrated:

- a. Tremor variation during a motor task has an excitatory effect on extrinsic connections from cerebellar lobule V to the thalamus and as well as intrinsic activity of cerebellar lobule V and the motor thalamus
- b. A disease of functional connectivity between cortical and cerebellar motor regions during a motor task which correlates with an increase in tremor severity
- c. Functional MRI studies support abnormalities in the cerebello-dentate-thalamic system and cerebellar cortical connectivity as a cause of ET

Orthostatic Tremor (OT)

General Characteristics

1. Orthostatic tremor is defined as a high frequency tremor (13–18 Hz) in the legs when standing
2. In approximately one-third of patients, the tremor is related to Parkinson's disease, cerebellar or brainstem pathology and restless leg syndrome
3. Orthostatic tremor of <13 Hz is termed slow OT. There is controversy as to whether this is a component of the spectrum of OT or is a different entity as there are some clinical differences between the two patient populations

Clinical Manifestations (>13 Hz Classic OT)

1. A rapid irregular and asynchronous tremor of the legs and trunk induced by standing
2. The tremor is 13–18 Hz in frequency and is associated with burst firing in antigravity muscles
3. The onset is usually in middle age or elderly patients
4. Unsteadiness in the legs with fear of falling
5. Loss of extensor tone in the legs
6. Difficulty in initiating gait
7. Pain in the legs when standing (some patients)
8. Patients have a wide-based stance but walk normally
9. Signs and symptoms are abolished with sitting
10. The tremor may occur in the trunk and cranial musculature
11. Isometric contracture of muscles may induce tremor (16 Hz) during the supine posture
12. Asymptomatic hypertrophy of the thigh and calf musculature may occur rarely
13. Slow orthostatic tremor (<13 Hz):
 - a. Possibly greater gait disturbance
 - b. The frequencies reported are between 4 Hz to 10–11 Hz
 - c. Most patients with “slow OT” have been reported in conjunction with:
 - i. Grave's disease
 - ii. Multiple sclerosis
 - iii. Cerebellar ataxia
 - iv. Paraneoplastic syndromes
 - v. PD
 - d. There is less postural arm tremor in slow orthostatic tremor

Neuropathology

1. A central nervous system location in brainstem-cerebellar

circuits is generally thought to be the generator of the tremor

2. EMG frequency supplemented by intermuscular coherence at present appears to be the best study to confirm “classic” orthostatic tremor
3. Transcranial magnetic stimulation can reset the tremor phase which supports the existence of a supraspinal central generator
4. Frequency spectra analysis demonstrates a high degree of coherence between limbs

Dystonic Tremor

General Characteristics

1. Dystonic tremor most commonly occurs in a body part affected by dystonia; rarely in a patient without dystonia; tremor may occur in a clinically non-dystonic body part

Clinical Manifestations

1. The tremor is typically postural or task related
2. The frequency ranges from 1–6 Hz during dystonic contractions
3. It is irregular or jerky but is rhythmic and can increase in frequency with voluntary movement
4. The tremor has a null point, which is a position that dramatically dampens it
5. It may initially start with a specific movement but progressively generalizes to any task
6. Patients frequently have a “geste antagoniste”, a proprioceptive or tactile maneuver that decreases the abnormal posture
7. The tremor quality is jerky
8. Dystonic head tremor may occur in isolation which is very rare with ET in which head tremor occurs with co-existent hand tremor
9. Approximately 20% of dystonia patients have tremor
10. In some series, patients who suffered tremor had focal cervical dystonia more often than blepharospasm
11. Dystonia may be more likely to spread in patients with tremor
12. Tremor prevalence may be higher in patients with adult onset dystonia and cervical dystonia; it is highest in patients in which the dystonia has spread

Neuropathology

1. Neurophysiologic evaluation reveals decreased reciprocal inhibition between agonist and antagonist muscles
2. The generator for the tremor is suggested to be in the basal ganglia motor loop
3. Deep brain stimulation (DBS) has been successful with targets in Vim, GPi and the zona incerta

Neuropathic Tremor

General Characteristics

1. May occur with all forms of neuropathic pain but is particularly common in chronic regional pain syndrome (CRPS)

Clinical Manifestations

1. Frequency is usually 3–6 Hz in the upper limbs
2. It is usually irregular and most severe in the distal musculature
3. It is asymmetric and can occur at rest, with maintenance of posture or during movement
4. It is associated with mechanical and thermal hyperalgesia and allodynia or with sensory loss

Neuropathology

1. Abnormal sensory processing that is maladaptive
2. The basic processes occur both peripherally with sensitization of peripheral nociceptive afferent fibers and centrally by the process of central sensitization of motor and nociceptive neurons in the pain network
3. The generator is thought to be central

Task-Specific tremor*General Characteristics*

1. The tremor occurs predominantly during the movements required to accomplish a specific task. It is not associated with an abnormal posture or muscle spasm
2. The movement in which the tremor is noted occur in musicians, athletes, dentists, surgeons that perform repetitive or entrained tasks
3. Primary writing tremor (PWT):
 - a. General characteristics:
 - i. The most common form of task specific tremor
 - ii. There is controversy as to whether this tremor is a variant of ET, dystonia or a specific entity
 - iii. There is AD inheritance in some instances
 - b. Clinical manifestations:
 - i. The PWT is divided into:
 1. Type A (task induced tremor)
 2. Type B (positionally sensitive tremor)
 - ii. The frequency is 5–7 Hz
 - iii. The type B form occurs both with writing and also when the hand assumes the writing position
 - iv. Most commonly there is alternating contraction of agonist and antagonist muscles although other contraction patterns occur
 - c. Neuropathology:
 - i. PET analysis demonstrates hyperactivity of the cerebellar hemispheres
 - ii. Reciprocal inhibition of the H-reflex and intracortical excitability are normal

Drug-Induced Tremor*General Characteristics*

1. Drug-induced tremor occurs with antidepressants, sympathomimetics, antiarrhythmics and antiepileptic agents
2. A multitude of mechanisms is causative

Clinical Manifestations

1. Non-progressive

2. Usually temporally related to the onset of medication use and increase with dose escalation
3. Drug-induced rest tremor can occur in isolation or as a component of Parkinsonism with the use of antipsychotics
4. All medications that can cause secondary Parkinsonism the most common of which are lithium carbonate, valproate, or serotonin specific reuptake inhibitors, can cause a rest tremor
5. Many drugs also cause an action tremor (lithium carbonate) as well as a rest tremor
6. Specific tremorogenic drugs:
 - a. Lithium:
 - i. Tremor may occur at non-toxic levels
 - ii. It may develop acutely or after months of treatment
 - b. Valproate:
 - i. May cause a 6–9 Hz tremor
 - ii. Rhythmic postural tremor that may mimic ET and is similar to tremors from tricyclic antidepressants
 - c. Alcohol, cocaine and amphetamines all induce tremor from intoxication, chronic use or withdrawal
 - d. Caffeine and β -adrenergic agonists
 - e. Drug-induced parkinsonism:
 - i. Metoclopramide
 - ii. Neuroleptics
 - iii. Phenothiazines

Neuropathology

1. Multiple mechanisms for drug-induced tremor depend on the specific pharmacology and physiology of each specific drug. The neuroleptics block D2 dopaminergic receptors in the striatum as well as affecting other aspects of basal ganglionic circuitry. The reticular formation and cerebellothalamic cortical circuitry is often prominently involved with drug-induced tremors

Psychogenic Tremor*General Characteristics*

1. Psychogenic tremors occur as a component of somatoform or factitious disorders as well as with malingering
2. Clinical manifestations:
 - a. Unusual phenomenology
 - b. Abrupt onset
 - c. Inconsistencies in tremor pattern
 - d. Spontaneous remissions
 - e. Distractibility
 - f. Response to placebo
 - g. Increase in tremor amplitude with inertial loading
 - h. Large fluctuations in frequency and amplitude
 - i. Coactivation of antagonist muscles at tremor onset
 - j. Absence of finger tremors
3. Neuropathology:
 - a. Psychogenic tremors depend on reflex mechanisms

- b. Electrophysiologic features of psychogenic tremors include:
 - i. Variability
 - ii. Constrainability
 - iii. Coactivation
 - iv. Distractibility
 - v. Increase in amplitude and frequency with inertial coaching
- c. Differential electrophysiological features:
 - i. Psychogenic myoclonus:
 - 1. Movement-related cortical potentials (Bereitschaftspotentials) are noted
 - ii. Triphasic contraction of muscles and absence of co-contraction
 - iii. Longer latency of C-reflex as compared to organic myoclonus

Palatal Tremor

General Characteristics

1. Palatal tremor (formerly palatal myoclonus) is associated with cerebellar dysfunction

Clinical Manifestations

1. Acquired onset of palatal tremor 1–2 Hz
2. Dysarthria
3. Ataxia
4. Slowly progressive cerebellar dysfunction

Neuropathology

1. MRI is normal at the presymptomatic phase but as the disorder progresses there is concomitant olivary hypertrophy
2. Brain [18 F]-fluorodeoxyglucose (FDG) positron emission tomography (PET) demonstrates hypermetabolism in the olivary nuclei

Variant Oculopalatal Tremor

General Characteristics

1. A delayed complication of a brainstem lesion

Clinical Characteristics

1. Average age of patients is 54 years
2. Male predominance
3. Vertical pendular nystagmus occurs in 90% with the palatal tremor
4. There may be dissociated unilateral nystagmus opposite the MRI identified olivary hypertrophy

Neuropathology

1. The usual lesion is vascular that disrupts the dentato-rubro-olivary circuit
2. A dual-mechanism model proposes that the oscillatory component is the inferior olive and the modulator is the cerebellum:
 - a. Electronic coupling and specific calcium channels drive the inferior olivary neurons

Cerebellar Kinetic or Action Tremor

General Characteristics

1. Oscillation increases perpendicularity to the line of movement as the target is approached

Clinical Manifestations

1. Specific cerebellar lesions cause specific patterns of the tremor:
 - a. Lateral cerebellar hemispheric lesions that affect the dentate nucleus and superior cerebellar peduncle cause extremity tremor
2. Tremor of the head and trunk are caused by vermal or fastigial nucleus lesions
3. Postural kinetic tremors:
 - a. Usually oscillate at 6–10 Hz frequency
 - b. Often involve the superior cerebellar peduncle near the red nucleus (has been termed a rubral tremor):
 - i. In some patients the tremor is more severe with lesions that are near the red nucleus
 - ii. The usual frequency is 2–3 Hz

Neuropathology (Rubral Tremor)

1. Sequelae of severe head trauma
2. Vascular lesions:
 - a. Occlusion of the interpeduncular artery (top of the basilar artery)
3. Thalamoperforate artery (PI) branch of the posterior cerebral artery
4. Medial posterior choroidal artery (branch of the PCA)
5. Involvement of the cerebellothalamic cortical networks are critical in cerebellar induced action tremors:
 - a. The combination of electromyography and functional magnetic imaging have demonstrated:
 - i. In essential tremor, there is decreased functional connectivity between cortical and cerebellar motor regions

Wilson's Disease

General Characteristics

1. Wilson's disease is caused by homozygous or compound heterozygous mutation of the ATP7B gene that maps to chromosome 13q14.3
2. Approximately 75% of patients present with liver signs and symptoms
3. Hepatitis and cirrhosis may present prior to CNS manifestations
4. Nephropathy occurs and is associated with aminoaciduria, phosphaturia, uricosuria and increased copper excretion

Clinical Manifestations

1. Kayser-Fleischer ring (copper deposition on Descemet's membrane; seen in the upper limbus of light-eyed patients with CNS manifestations)
2. Neurologic manifestations:

- a. "Wing beating" postural kinetic tremor
- b. Cerebellar intention tremor
- c. Dystonia
- d. Chorea
- e. Myoclonus
- f. Gait disturbance
- g. Dysarthria
- h. Seizures
- i. Parkinsonism
- j. Cerebellar signs

Neuropathology

- 1. The greatest degree of atrophy is in the putamen; there is moderate atrophy of the globus pallidus
- 2. Diffuse atrophy of the cerebral cortex and cerebellar cortex
- 3. Opalski cells are detected
- 4. Excessive copper accumulation results from the inability of the liver to excrete copper in the bile from dysfunction of the copper transporting P-type ATPase
- 5. Successful DBS for tremor has targeted:
 - a. Globus pallidus pars interna
 - b. Ventral intermedialis nucleus of the thalamus

Chorea

Overview

Choreic movements are sudden irregular unpredictable brief involuntary movements (not preceded by a Bereitschaftspotential) of the extremities, face or truncal musculature that may include cocontraction of agonist and antagonist muscles. Early cortical median nerve somatosensory evoked potentials have reduced amplitudes which correlate with reduced glucose utilization in the caudate nucleus. Long latency stretch reflexes evoked from intrinsic hand muscles are depressed that suggest dysfunction of thalamocortical relay of afferent sensory input. The specific muscles that are involved depend on the illness. In Huntington's disease there is more truncal muscular involvement than appendicular, while in Sydenham's disease there is more appendicular than truncal involvement. The movements may occur at rest or with intention (in this instance they may be masked as semi-purposeful parakinesia). The movements may be unilateral or bilateral, cease in sleep and are exacerbated by stress. There may be increased or decreased muscle tone.

Hereditary Causes of Chorea

Huntington's Disease

General Characteristics

- 1. HD is caused by an expanded trinucleotide repeat (CAG) that encodes glutamine in the Huntington gene HTT that maps to chromosome 4p16. It is autosomal dominant (AD)

- 2. Its prevalence is between 4–7/100,000 of the population in the USA
- 3. The CAG repeat range for disease is 37–86 repeats
- 4. There is an inverse correlation of CAG repeat length with:
 - a. Age of onset
 - b. Age at death
 - c. Rate of progression
 - d. Other clinical features
- 5. The correlation is stronger with early-onset disease than with late-onset disease
- 6. Sporadic HD:
 - a. There may be expansion from a large repeat in an unaffected male patient
 - b. Intermediate allele number of repeats
 - c. An unstable expansion
- 7. There is no variance of repeat length in different tissues:
 - a. The repeat size is altered in gametogenesis:
 - i. Highest in spermatogenesis
 - ii. In patients with juvenile onset with paternal transmission

Clinical Manifestations

- 1. Variable onset:
 - a. Juvenile onset (4–19 years of age)
 - b. Early onset (20–45 years of age)
 - c. Late onset (greater than 50 years of age)
 - d. 10% present as juvenile onset
 - e. 25% present as late onset
- 2. Anticipation:
 - a. A progressive increase in the length of the tandem repeat
 - b. The longest tandem repeats are associated with the earliest onset
 - c. Late onset disease has maternal transmission
- 3. Clinical patterns:
 - a. Hyperkinetic:
 - i. The most common form
 - ii. Chorea is the first clinical manifestation
 - iii. The usual form: middle or late onset disease
 - iv. Hyperreflexic
 - v. Hypotonic
 - vi. Lurching gait
 - vii. Choreatic eye movements
 - viii. Dementia:
 - 1. Frontal lobe features
 - 2. Choreatic movements may precede or follow the cognitive impairment
 - b. Juvenile or early-onset disease (Westphal variant):
 - i. Inheritance of the gene from an affected father
 - ii. Rapid clinical progression
 - iii. In some patients, the neuropsychological disturbance is greater than the movement disorder
 - iv. Bradykinesia and rigidity
 - v. Seizures

- vi. Movements persist during sleep
- vii. Differential diagnosis of akinetic-rigid HD
 - 1. Wilson's disease
 - 2. Juvenile Parkinsonism
 - 3. Neuroaxonal dystrophy
 - 4. Metabolic storage disorders
- c. Late-onset disease:
 - i. Patients are uncommunicative
 - ii. Orolingual chorea
 - iii. Cognitive impairment
 - iv. Rigidity
 - v. Dystonia
 - vi. Dysphagia (frequent aspiration pneumonia)
 - vii. Duration of the disease: shorter in patients with juvenile or early-onset disease

Neuropathology

1. Loss of large pyramidal cells in the neocortex, allocortex and hippocampus in the absence of astrocytosis; some neuronal loss in the hypothalamus and substantia nigra
2. Loss of Purkinje cells particularly in early-onset patients
3. Loss of neurons in the rostral interstitial nucleus of the medial longitudinal fasciculus
4. Severe atrophy of the caudate nucleus with moderate atrophy of the putamen and globus pallidus; atrophy of the caudate nucleus is associated with astrocytosis
5. The known genetic cause of the disease has led to new therapeutic approaches that are limited to the causative mutation and include:
 - a. RNA interference or antisense oligonucleotides to reduce expression of the mutant huntingtin protein
 - b. Zinc-finger transcriptional repression to decrease mHTT expression
 - c. Modulation of mHTT phosphorylation
 - d. Chaperone upregulation
 - e. Enhancement of autophagy
6. Critical striated circuits are primarily involved, but recent work has demonstrated that mutated HTT is widely expressed outside of the CNS, which may be manifested as weight loss and proinflammatory signalling

Laboratory Evaluation

1. MRI:
 - a. Severe caudate nucleus atrophy that leads to enlarged lateral ventricles ("boxcar ventricles")
 - b. Flattening or absence of the caudate nucleus
2. PET evaluation: hypometabolism of the caudate and putamen
3. PDE10A is decreased in the striatum and pallidum and increased in motor thalamic nuclei in early Huntington's disease
4. Increased activation of central microglia as demonstrated with [¹¹C] PK11195 PET that correlate with plasma IL-1 β levels in premanifest HD gene carriers

Neuroacanthocytosis Syndrome

Overview

Neuroacanthocytosis refers to disorders with neurological signs and symptoms that are associated with acanthocytes. The term encompasses diseases of the basal ganglia and those with inherited abnormalities of serum lipoproteins that cause vitamin E malabsorption with consequent spinal cord and peripheral nerve deficits.

There are four core neuroacanthocytosis syndromes that include:

1. Chorea-acanthocytosis (ChAc)
2. McLeod syndrome
3. Pantothenate kinase associated neurodegeneration (PKAN) with brain iron accumulation (NBIA)
4. Huntington's disease-like 2 (HDL2)

Acanthocytes are seen in approximately 10% of patients with PKAN and HDL2, and rarely in mitochondrial disorders, anorexia nervosa and hypothyroidism.

Chorea-Acanthocytosis (ChAc)

General Characteristics

1. ChAc is caused by mutation in the VPS13A gene that maps to chromosome 9q21. Inheritance is autosomal recessive
2. The gene encodes the protein "chorein"
3. The affected protein functions in the polymerization of actin that is dysfunctional and causes membrane disruption and the abnormal red blood cell shape. Abnormalities of protein phosphorylation have also been described
4. Two splice variants are found; the longer variant is associated with chorea
5. The encoded VPS13B protein may also be involved in intracellular trafficking and vesicle physiology

Clinical Manifestations

1. The disorder presents in early adulthood with chorea and orolingual dystonia
2. Tongue protrusion dystonia with eating is a prominent feature; this may also be seen with tardive dyskinesia, McLeod syndrome, and PKAN
3. Self-mutilation from tongue and lip biting
4. Patients may use an object in the mouth to decrease tongue biting and tooth grinding
5. Sialorrhea
6. Patients may extend their head to push food into the back of their mouth and throat to avoid the tongue protrusion
7. "Head drops" (neck flexion) and truncal flexion
8. An abnormal gait with anterior flexion of the trunk at the hips and leg dystonia
9. Parkinsonism may be a presenting sign, but is most often seen in the later course of the illness

10. Psychiatric symptoms include depression and obsessive-compulsive behavior
11. Tics
12. Seizures:
 - a. Patients may present with seizures which most commonly are partial complex
 - b. Occur in approximately 40% of patients
13. Peripheral neuropathy (sensorimotor)
14. Autonomic nervous system involvement; cardiac abnormalities have been reported but cardiomyopathy is not typical (more common with McLeod syndrome)
15. Extraocular movements:
 - a. Squarewave jerks (similar to HD)
 - b. Impaired saccades
 - c. Limited upgaze
16. Severe swallowing and speech impairment; in the later stages of the illness, patients may become mute
17. Muscle atrophy
18. Hepatomegaly

Neuropathology

1. The primary area of involvement is the basal ganglia
 - a. The caudate nucleus demonstrates the greatest neuronal loss and gliosis. There is lesser involvement of the putamen, globus pallidus and substantia nigra. Some patients with parkinsonism have demonstrated a normal substantia nigra
 - b. Two patients with parkinsonism demonstrated selective loss of striatal substance P-containing neurons and of parvalbumin-containing interneurons (rapidly firing inhibitory interneurons) in both the striatum and cerebral cortex
 - c. Atrophy of the pyramidal tract has been described
 - d. Muscle biopsy: neurogenic atrophy

Laboratory Evaluation

1. Elevated serum creatine kinase
2. Acanthocytosis in the peripheral bloodstream is inconsistent
3. Elevated liver enzymes (in patients with hepatomegaly)

Neuroimaging

1. MRI:
 - a. Atrophy of the head of the caudate nucleus, similar to what is seen in HD
 - b. Variable features:
 - i. Iron deposition in the striatum and globus pallidus
 - ii. Cerebellar atrophy
2. PET and metabolic evaluation:
 - a. Decreased metabolism in the caudate and putamen
 - b. Dopamine and serotonin transporter binding is normal
3. MRS:
 - a. Neuronal loss and glial activation
4. EMG:
 - a. Sensorimotor neuropathy

McLeod Syndrome

General Characteristics

1. McLeod syndrome is caused by mutation of the XK gene that maps to the X chromosome
 - a. The encoded protein is XK which is localized in the surface of the erythrocytic membrane
 - b. The XK protein is linked to the Kell protein by a disulfide bond
 - c. Abnormal XK causes reduced expression of antigens that are expressed by Kell
 - d. XK is a membrane transport protein that affects the movement of divalent cations
 - e. Missense mutations may only affect the position of the protein in the erythrocyte membrane, with minimal clinical effects

Clinical Manifestations

1. There may be symptomatic female carriers (X-chromosome inactivation)
2. Clinical features overlap with those of chorea-acanthocytosis
3. There is greater phenotypic variability and severity in McLeod syndrome than ChAc (chorea-acanthocytosis)
4. Neurologic and psychiatric symptoms and signs develop in men during midlife
5. Initial presentation may be with cognitive impairment or psychiatric difficulties
6. Movement disorders include chorea, dystonia and parkinsonism
7. Variable features:
 - a. "Head drops"
 - b. Orolingual dystonia
8. Patients with chorea may progress to parkinsonism
9. No self-mutilating lip biting
10. Peripheral sensorimotor neuropathy may be an early manifestation
11. Approximately 50% of patients develop seizures that are medication-responsive
12. Hepatomegaly and splenomegaly may occur
13. A distinctive feature is cardiomyopathy, which occurs in approximately 2/3 of patients
14. Myopathy and rhabdomyolysis have been reported

Neuropathology

1. Neuronal loss and gliosis in the caudate, putamen, and globus pallidus

Laboratory Evaluation

1. McLeod phenotype on blood typing from a panel of anti-KX and anti-Kell antibodies
2. Elevated liver enzymes (in those patients with hepatic dysfunction)
3. Echocardiography is positive in those with cardiomyopathy

4. Elevated CK
5. Neuroimaging:
 - a. MRI:
 - i. Atrophy of the caudate nucleus and putamen
 - ii. Scattered white matter changes
 - b. PET evaluation:
 - i. Decreased striatal glucose metabolism
 - c. MRS: mixed results
6. EMG:
 - a. Sensorimotor neuropathy

Huntington's Disease-Like 2 (HDL-2)

General Characteristics

1. HDL2 is caused by a CTG/CAG repeat expansion within the junctophilin-3 gene (JPH3) that maps to chromosome 16q24.3
 - a. Expansion greater than 41 repeats causes disease (normal repeat size is 16–27)
 - b. Possibly a rare African ancestral mutation
 - c. The encoded junctophilin-3 protein:
 - i. Is involved in calcium regulation
 - ii. Junctional membrane structures

Clinical Manifestations

1. Onset is the 3rd to 4th decade
2. Cognitive impairment
3. Chorea, dystonia, myoclonus, or parkinsonism
4. Parkinsonism and dystonia are more severe than in HD
5. The early manifestations may be psychiatric or behavioral
6. Acanthocytosis is seen in 10% of patients
7. Eye movements are normal or demonstrate hypometric saccades; choreatic eye movements are prominent in HD

Neuropathology

1. Neuropathology is similar to HD
2. There is a gradient of neuronal loss from ventral to dorsal in the caudate nucleus and the putamen
3. Ubiquitin and expanded polyglutamine repeats are found throughout the cortex
4. HDL2 pathogenesis may be related to:
 - a. Formation of toxic mRNA inclusions in the cytoplasm
 - b. Loss of the mutant protein

Laboratory Evaluation

1. Acanthocytosis occurs in approximately 10% of patients
2. Neuroimaging:
 - a. MRI: Similar to that seen with HD
 - b. Cortical atrophy
 - c. 3 patients have demonstrated hyperintensity of the rim of the putamen

Pantothenate Kinase-Associated Neurodegeneration (PKAN)

General Characteristics

1. PKAN is the most common NBIA

2. PKAN is caused by mutation in the PKAN2 gene that maps to chromosome 20p13; AR disorder
3. The encoded protein is pantothenate kinase 2, which is critical for the synthesis of coenzyme A. The enzyme is prominent in the infantile basal ganglia and the retina
4. The enzyme deficit may cause mitochondrial dysfunction
5. It is not known if iron deposition is pathogenic or an epiphenomenon

Clinical Manifestations

1. Onset is in childhood
2. Progressive dystonia and parkinsonism
3. Retinitis pigmentosa (but late-onset patients (atypical) tend not to have retinitis pigmentosa)
4. Cognitive impairment
5. Dystonia affects the lower face with grimacing and tongue protrusion
6. Rare chorea
7. Acanthocytosis is seen in a small percentage of patients

Neuropathology

1. It is the major neurodegeneration with brain iron accumulation
2. The PKAN2 gene encodes a mitochondrial enzyme involved in the first regulatory step of coenzyme A (CoA), which is synthesized from pantothenate (vitamin B5). CoA is essential for fatty acid metabolism and amino acid synthesis. Pantothenate is phosphorylated by pantothenate kinase. There are four isoforms of pantothenate kinase. PKAN2 is located in the mitochondrial intermembrane space
3. Alteration in cholesterol and lipid metabolism has been demonstrated in some PKAN2 patients
4. Neuronal loss and gliosis of the globus pallidus, and to a lesser extent the putamen, with concomitant iron accumulation

Laboratory Evaluation

1. MRI:
 - a. "Eye-of-the-tiger" sign in the globus pallidus, consisting of central edema surrounded by iron deposition. It may not be demonstrated in all patients. In late-onset patients, the sign may appear after the onset of neurologic disability

The HARP Syndrome

General Characteristics

1. Caused by the identical mutation which causes PKAN

Clinical Manifestations

1. Hypoprebetalipoproteinemia
2. Acanthocytosis
3. Retinitis pigmentosa
4. Pallidal degeneration

Laboratory Evaluation

1. High resolution lipoprotein electrophoresis:
 - a. Absence of the pre-beta fraction and normal cholesterol, triglycerides, high- and low-density lipoprotein cholesterol and apolipoproteins A, B, and E

Differential Diagnostic Features of the Neuroacanthocytoses

1. ChAc (chorea-acanthocytosis)
 - a. Self-mutilating lip and tongue biting
 - b. Seizures
 - c. Peripheral neuropathy
 - d. Liver enzymes and CK are elevated
2. McLeod syndrome
 - a. A wider range of phenotypic variability and severity than with ChAc
 - b. Cardiomyopathy
 - c. Age of onset and gender
 - d. Elevated liver and creatine kinase enzyme levels
3. Huntington's disease-like 2 (HDL2)
 - a. Parkinsonism and dystonia more severe than in HD
 - b. Ethnic background and inheritance pattern
4. PKAN (Pantothenate Kinase Associated Neurodegeneration)
 - a. The "eye of the tiger" on MRI in the globus pallidus
 - b. Onset in childhood
 - c. Retinitis pigmentosa
 - d. Cognitive impairment
 - e. Dystonia affects the lower face with grimacing and tongue protrusion

Familial Hypobetalipoproteinemia (FHBL)*General Characteristics*

1. Genetically heterogeneous, with linkage to truncating-specifying mutations of the APOB gene that maps to chromosome 2, in a minority of patients, or to chromosome 3p21 in other families
2. Inheritance is AD
3. A percentage of familial hypobetalipoproteinemia patients have no known gene defect

Clinical Manifestations

1. Neurologic disease is secondary to vitamin E deficiency
2. Retinitis pigmentosa
3. Primarily dorsal column modality sensory loss
4. Proximal myopathy

Neuropathology

1. Impaired packaging and secretion of apolipoprotein (apo) B-containing lipoprotein particles due to mutations in both alleles of the MTP gene that encodes microsomal triglyceride transfer protein (MTP) or both alleles of the APOB gene
2. Dorsal column degeneration

Laboratory Evaluation

1. Acanthocytosis in peripheral blood smear
2. Severely decreased apo B-containing lipoproteins that include:
 - a. Chylomicrons
 - b. Very low density lipoprotein (VLDL)
 - c. Low density lipoprotein (LDL)
3. Hypocholesterolemia
4. Malabsorption of lipid-soluble vitamins
5. Heterozygous parents of homozygous hypobetalipoproteinemia (HHBL) patients have half-normal levels of apo B-containing lipoproteins, which supports autosomal co-dominant inheritance

Abetalipoproteinemia (Bassen-Kornzweig Syndrome; ABL)*General Characteristics*

1. Abetalipoproteinemia is caused by homozygous or compound heterozygous mutation in the MTP gene that maps to chromosome 4q23
2. Obligate heterozygous parents of abetalipoproteinemia patients usually have normal lipids consistent with an autosomal recessive inheritance pattern

Clinical Manifestations

1. Celiac syndrome
2. Progressive large fiber neuropathy
3. Proximal myopathy
4. Pigmentary degeneration of the retina
5. Ataxia
6. Dorsal column dysfunction; loss of proprioception, vibration sensibility and deep tendon reflexes
7. Decreased cognition in approximately 1/3 of patients

Neuropathology

1. Extensive peripheral nerve and central demyelination
2. Pathology of vitamin E deficiency
3. Impaired packaging and secretion of apolipoprotein apo B-containing lipoprotein
 - a. Lipoprotein particles
4. Steatosis occurs in some patients

Laboratory Evaluation

1. Acanthocytosis on peripheral blood smear
 - a. Decreased fluidity of the red blood cell membrane
2. Deficiency of fat soluble vitamins A and E
3. Hypocholesterolemia
4. Absence of low density lipoproteins
5. Chylomicron fragments in the plasma

Neuroferritinopathy (NBIA2)*General Characteristics*

1. Alternate name is neurodegeneration with brain iron accumulation type 2 (NBIA2)
2. AD; NBIA2 is caused by mutation in the FTL gene that maps to chromosome 19q13.33

3. It is the only AD disorder of the neurodegenerations with brain iron accumulation
4. Severe pathogenic mutations in the FTL1 gene have been described to date, six of which are frame-shift that alter the reading frame
5. Pantothenate kinase associated neurodegeneration and PLA2G6-associated neurodegeneration are present in infancy and childhood and are often classified as inborn errors of metabolism

Clinical Manifestations

1. Presentation is in mid-adult life but longitudinal studies have demonstrated that iron deposition begins in early childhood
2. The most frequent presentation is chorea (50%) of patients
3. Dystonia occurs in 42.5% of patients
4. Parkinsonism is seen in 7.5% of patients (akinetic-rigid syndrome)
5. Variable features include:
 - a. There are seven different mutations that cause clinical features
 - b. Minimal cognitive impairment (some patients)
 - c. Minimal cerebellar involvement (some patients)
 - d. Some patients with known genetic mutations and clinical features of NBIA have been reported with no iron deposition by neuroimaging

Neuropathology

1. Iron deposition in the basal ganglia with cavitation
2. Neuronal loss in the cerebral cortex, cerebellum and basal ganglia
3. Ferritin inclusion bodies have been demonstrated within neurons and glia
4. Patient derived fibroblasts and HeLa cells that express mutations in ferritin accumulate iron and demonstrate oxidative stress. The link between iron dysregulation and oxidation stress with concomitant neuronal damage is supported by the pathogenesis of Friedreich's ataxia, where the loss of frataxin impairs iron handling in mitochondria with subsequent oxidative damage

Laboratory Evaluation

1. MRI
 - a. 3D-T1 and quantitative T2 MRI demonstrate;
 - i. Iron deposition in the head of the caudate
2. Cavitation in the lateral globus pallidus
3. Voxel-based morphometry:
 - a. Neuronal loss in the substantia nigra, midbrain and dentate nucleus
 - b. Cerebellar atrophy

NBIA2B

General Characteristics

1. NBIA2B is caused by mutation in the PLA2G6 gene that maps to chromosome 22q13
2. Is allelic to infantile neuroaxonal dystrophy

Clinical Manifestations

1. Widely varying phenotypes
2. Childhood onset
3. Ataxia and gait instability
4. Optic atrophy (some patients)
5. Variable features:
 - a. Truncal hypotonia
 - b. Behavioral disturbance
6. No chorea described

Neuropathology

1. Study from 1 patient:
 - a. Generalized brain atrophy with neuronal loss and gliosis
 - b. Axonal swellings in the cortex, striatum, cerebellum brainstem and spinal cord
 - c. Lewy bodies and neurofibrillary tangles were demonstrated

Laboratory Evaluation

1. MRI:
 - a. Iron accumulation in the globus pallidus; distinct from the "eye of the tiger" sign that is seen in NBIA1 and Karak syndrome

Karak Syndrome

General Characteristics

1. Probable autosomal recessive inheritance. The disorder was described in 2 sons of consanguine patients
2. The disorder is caused by homozygous missense mutation in the PLA2G6 gene that maps to chromosome 22q13.1

Clinical Manifestations

1. Childhood onset
2. Slowly progressive ataxic gait
3. Cognitive impairment
4. Adults:
 - a. Dystonia, rigidity, spasticity
 - b. Choreiform movements

Neuropathology

1. Autopsy results have not been reported
2. By MRI the globus pallidus and the substantia nigra show excess iron accumulation

Laboratory Evaluation

1. MRI:
 - a. The "eye of the tiger" sign is demonstrated in the globus pallidus

Aceruloplasminemia

General Characteristics

1. Aceruloplasminemia is autosomal recessive and is caused by mutation in the gene that encodes ceruloplasmin that maps to chromosome 3q24-q25

2. Ceruloplasmin:
 - a. Is a multi-copper oxidase with ferroxidase activity that functions to oxidize ferrous iron after its transfer to extracellular transferrin
3. In the CNS, the major isoform is a glycosylphosphatidylinositol-linked ceruloplasmin that is bound to the cell membrane
4. Ceruloplasmin contains 95% of the copper in serum and is essential for iron efflux from brain cells due to its ferroxidase activity
5. The ferroxidase oxidizes ferrous iron subsequent to its transfer to the cell surface via ferroportin, the iron transporter
6. The transporter delivers ferric iron to cellular transferrin

Clinical Manifestations

1. Onset is middle age
2. Cognitive impairment
3. Cerebellar ataxia
4. Chorea
5. Retinal degeneration
6. Extrapyrmidal signs
7. Diabetes mellitus

Neuropathology

1. Autopsy of one patient:
 - a. Iron deposition in the basal ganglia and dentate nucleus
 - b. Iron deposition in both neurons and glial cells
 - c. Cerebral cortex showed some iron deposition in glial cells but none in neurons
 - d. Redox-active iron accumulation is more prominent in astrocytes than in neurons, characteristic findings are deformed astrocytes
 - e. Iron-mediated oxidative damage to neurons in later disease stages

Laboratory Evaluation

1. Mild anemia (microcytic), low serum iron and elevated serum ferritin
2. Absent serum ceruloplasmin
3. MRI:
 - a. T1- and T2-weighted sequences revealed low signal in the dentate nucleus, thalamus, putamen and caudate nucleus
4. Electron microscopy:
 - a. Iron deposition in hepatocytes, neuronal and glial cells

Mitochondrial Membrane Protein-Associated Neurodegeneration (MPAN)

General Characteristics

1. In patients from Western Europe a founder mutation in the gene C19orf12 that maps to chromosome 19q12 is common
2. It is estimated to account for 5% of NBIA patients worldwide

Clinical Manifestations

1. There are both early childhood and adult onset patients
2. Gait impairment
3. Spasticity of both upper and lower extremities
4. Dystonia may begin in the feet and then spread to the hands or is generalized
5. Parkinsonism occurs predominantly in late onset patients. It includes bradykinesia, resting tremor and postural instability
6. Optic atrophy (similar to PLA2G6)
7. Neuropsychiatric features
8. Dementia
9. A subset of patients have a motor axonal neuropathy; loss of proprioception has also been described
10. Incontinence
11. Dysarthria and dysphagia
12. A milder course than PKAN
13. Rarely there is rapid deterioration
14. An upper and lower motor neuron phenotype similar to juvenile ALS has been described
15. A mutation in C19orf12 has been described in spastic paraplegia 43

Neuropathology

1. Swollen and dystrophic axons and degenerating neurons ("neuroaxonal spheroids") are a hallmark. Only PLA2G6 has a similar pathology in peripheral tissue
2. Prominent alpha-synuclein positive Lewy bodies and Lewy neurites are seen
3. Tau containing inclusions have been described
4. Iron deposits occur in the globus pallidus and substantia nigra
5. Demyelination in the optic nerves and pyramidal tracts
6. Neuroaxonal spheroids are seen in the brain
7. C19orf12:
 - a. A transmembrane protein that localizes to the mitochondria
8. Putative role is in lipid metabolism

Beta Propeller Protein-Associated Neurodegeneration (BPAN)

General Characteristics

1. Mutation in WDR45 (a Beta propeller domain-containing protein) is caused by de novo heterozygous or hemizygous mutation in the WDR45 gene that maps to chromosome Xp11.23
2. BPAN is estimated to be 1–2% of NBIA patients. It is the only NBIA that has an X-linked dominant inheritance pattern
3. Most mutations are de novo

Clinical Manifestations

1. A static encephalopathy in childhood with cognitive impairment and spastic paraplegia or quadriplegia
2. Some patients have seizures

3. After childhood the disorder may not progress for decades
4. During early adulthood patients develop extrapyramidal signs and symptoms. The onset of this new symptomatology may be abrupt
5. In adulthood:
 - a. Falls
 - b. Dystonia
6. Parkinsonism
7. Intellectual impairment
8. Akinetic mutism

Neuropathology

1. Autopsy (3 suspected patients):
 - a. Cortical atrophy
 - b. Iron deposition in the globus pallidus and substantia nigra; both nuclei demonstrated axonal spheroids but were widespread
2. Neurofibrillary tangles were seen throughout the cortex, deep gray nuclei, hippocampus and brainstem
 - a. The function of WDR45 is within cellular autophagic processes. The protein family (WD-40) is characterized by a seven bladed Beta-propeller structure that provides a scaffold for protein-protein interactions which regulate the formation of multimeric protein complexes
 - b. Experimental studies suggest that abnormal autophagosomes accumulate with deficient WDR45

Laboratory Evaluation

1. MRI:
 - a. T1 hyperintensity of the cerebral peduncles and substantia nigra that may extend into the globus pallidus (pathognomonic of this form of NBIA)
 - b. T2-weighted sequences demonstrate hypointensity of the globus pallidus and substantia nigra
 - c. T1-weighted sequences show a region of hyperintensity in the substantia nigra
 - d. In BPAN, T2-weighted sequences has greater hypointensity of the substantia nigra than the globus pallidus

Lesch-Nyhan Syndrome (LNS)

General Characteristics

1. LNS is caused by mutation in the HPRT gene that maps to chromosome Xq26.2-q26.3
2. The encoded protein is the enzyme hypoxanthine guanine phosphoribosyl transferase
3. A deficiency of HGPRT in males causes a spectrum of disease that is dependent upon the extent of the deficiency
4. A complete deficiency is associated with the Lesch-Nyhan syndrome whose incidence is 1 in 100,000 of the population; less than 1.5% of enzyme activity is seen in classic patients
5. Partial deficiency is associated with gout (approximately 1 in 200 male patients with gout); approximately 8% of enzyme activity
6. The mutations (400 described) are of substitution, frame shift, micro- and macrodeletion and splicing errors

Clinical Manifestations

1. Neurologic manifestations occur in patients with 1.5–8% of HPRT activity
2. There is wide phenotypic variation
3. Severe enzyme deficiency:
 - a. Self-mutilation from biting of the fingers and lips
 - b. Cognitive impairment
 - c. Delayed development
 - d. Dystonia
 - e. Spasticity
 - f. Choreaathetosis
4. Kelly-Seegmiller syndrome:
 - a. Associated only with the consequences of increased purine production:
 - i. Renal stones
 - ii. Uric acid nephropathy
5. After puberty the hyperuricemia causes gout
6. One described family had short stature, cognitive impairment, spasticity, proximally placed thumbs and fifth finger clinodactyly

Neuropathology

1. Autopsy of 3 LNS patients
 - a. A marked reduction in the dopamine content and in the activity of DNA-synthesizing enzymes in the caudate and putamen
 - b. There is a 50–63% reduction of binding to dopamine transporters in the caudate and up to 75% in the putamen

Laboratory Evaluation

1. MRI:
 - a. Volumetric determined loss of volume in the caudate of 30%
2. It is proposed and supported by fluorodopa-F18 tracers with PET that there is an abnormality in all dopaminergic pathways that is developmental in origin
3. Patients with classic Lesch-Nyhan disease have the lowest HPRT enzyme activity (less than 1.5% normal) in intact cultured fibroblasts
4. Serum hyperuricemia
5. Megaloblastic anemia (some patients)

Dentatorubral-Pallidoluysian Atrophy (DRPLA)

General Characteristics

1. DRPLA is caused by an expanded trinucleotide repeat in the ATN1 gene that maps to chromosome 12p13.31
2. CAG repeat length in affected individuals ranges from 48 to 93 repeats
3. Inheritance is AD

Clinical Manifestations

1. Patients under age 20 have:
 - a. Ataxia
 - b. Myoclonus

- c. Seizures
- d. Progressive cognitive impairment
- 2. Patients over age 20 have:
 - a. Ataxia
 - b. Choreoathetosis
 - c. Dementia
 - d. Psychiatric disorders
- 3. The onset of DRPLA ranges from childhood to late adulthood (1–62 years; mean age of 30)
- 4. Ataxia and dementia are cardinal features irrespective of age of onset
- 5. Myoclonic epilepsy and absence or atonic seizures may occur in patients with onset prior to age 20; seizures are rare in patients with onset after age 40
- 6. Anticipation occurs

Neuropathology

- 1. Degeneration of the dentatorubral and pallidoluysian systems of the CNS
- 2. Accumulation of the protein atrophin-1 occurs in neuronal nuclei that is demonstrated as diffuse nuclear staining by antibody that detects expanded polyglutamine stretches
- 3. White matter lesions that demonstrate diffuse myelin pallor, axonal preservation, and reactive gliosis are seen in the cerebral cortex

Laboratory Evaluation

- 1. MRI:
 - a. FLAIR sequences:
 - i. Cerebral cortical atrophy
 - ii. Cerebellar and pontomesencephalic tegmental atrophy
 - iii. Cerebral white matter and a component of white matter pathways within the brainstem demonstrate high signal intensities on FLAIR sequences
 - iv. High intensity signals in the globus pallidus on proton and T2-weighted sequences

Haw River Syndrome

General Characteristics

- 1. Described from the Haw River area of North Carolina in a 5 generation kindred
- 2. Autosomal dominant inheritance; the same CTG-B37 repeat as DRPLA

Clinical Manifestations

- 1. Onset is between 15–30 years of age
- 2. Ataxia
- 3. Seizures
- 4. Choreiform movements
- 5. Progressive
- 6. Death after 15–25 years of illness

Neuropathology

- 1. Neuronal loss in the dentate nucleus

- 2. Microcalcification of the globus pallidus
- 3. Neuroaxonal dystrophy of the nucleus gracilis
- 4. Demyelination of the centrum semiovale

Laboratory Evaluation

- 1. MRI:
 - a. Not defined

Differential Diagnosis of DRPLA

- 1. Huntington's disease
 - a. Ataxia in DRPLA is a differentiating point
 - b. Atrophy of the cerebellum and the brainstem (pontine tegmentum) rather than the caudate head in DRPLA
- 2. Patients with DRPLA with minimally expanded repeats in early stages may manifest only cerebellar symptoms and signs without cognitive impairment, and choreoathetosis that resembles autosomal dominant spinocerebellar ataxias
- 3. The differential diagnosis of DRPLA patients with onset prior to age 20 that manifest cognitive impairment, myoclonus and seizures includes:
 - a. Lafora-type progressive myoclonic epilepsy
 - b. Unverricht-Lundborg disease
 - c. Neuronal ceroid lipofuscinosis
 - d. Neuroferritinopathy (globus pallidus)
 - e. MERRF (hearing loss, short stature)
 - f. Sialidosis (cherry red spots in the retina)
 - g. Galactosialidosis
 - h. Gaucher's disease
 - i. Infantile neuroaxonal dystrophy
 - j. Pantothenate kinase 2 ("eye of the tiger")
 - k. Benign adult familial myoclonus epilepsy (BAFME)

Benign Hereditary Chorea (BHC)

General Characteristics

- 1. BHC may be caused by mutation of the NKX2-1 gene that maps to chromosome 14q13.3 and mutation of ADCY5 that maps to chromosome 3q21.1
- 2. NKX2-1 gene
 - a. Encodes thyroid transcription factor T1TF1
- 3. Prevalence of 2/10,000,000 of the population
- 4. Penetrance is 100% in men and 75% in women

Clinical Manifestations

- 1. Age at onset is usually before 5 but varies from infancy to late childhood and adolescence
- 2. Late walking, incoordination and frequent falls
- 3. Speech and cognitive function are usually unaffected, a differential point from Huntington's disease
- 4. Rare progression during adulthood (some patients have improved)
- 5. Atypical manifestations include:
 - a. Dysarthria
 - b. Gait abnormalities

- c. Axial dystonia
- d. Cognitive impairment
- e. Progression in adulthood
- 6. Pulmonary disease and/or congenital hypothyroidism may be seen

Neuropathology

1. Seventy-seven mutations in the T1TF1 gene have been identified in BHC patients (large and small deletions, missense and nonsense mutations)
2. The encoded protein thyroid-specific transcription factor-1 (TTF-1) is a thyroid-specific enhancer-binding protein that regulates the expression of thyroid-specific genes that are involved in transcription of:
 - a. Thyroglobulin
 - b. Thyroid peroxidase
 - c. Thyrotropin receptor
 - d. Surfactant protein
 - e. Secretory protein in the lungs
 - f. Organogenesis of:
 - i. Thyroid
 - ii. Lung
 - iii. Brain (ventral fore brain, posterior pituitary and the hypothalamus)
3. Autopsy (1 patient)
 - a. Mild frontal-parietal-temporal atrophy
 - b. Normal striatum and pigmented striatum
 - c. Non-specific astrocytosis without neuronal loss of the globus pallidus, thalamus, hippocampus and periaqueductal gray
 - d. Reduced density of striatal met-enkephalin and substance P immunoreactive nerve fibers
4. Cystic pituitary and sella turcica abnormalities have been seen in a few patients (6.4%). They have been associated with missense, nonsense and large deletions

Laboratory Evaluation

1. MRI:
 - a. Some patients have cystic posterior pituitary mass lesions and abnormalities of the sella turcica
2. Congenital hypothyroidism
3. Pulmonary disease

ADCY5 Mutation and Benign Hereditary Chorea

General Characteristics

1. Adenylate cyclase 5 mutations that map to chromosome 3q21 is another cause of BHC
2. Other mutations also cause autosomal dominant familial dyskinesia and facial myokymia

Clinical Manifestations

1. Early childhood onset
2. Brief choreic movements at rest that affect the face and all extremities

3. The disorder is progressive
4. Painful spasms upon awakening
5. Dysarthric speech
6. Generalized chorea with facial grimacing and dystonia
7. Chorea and dystonia are present at rest; increased by stress and emotion
8. Gaze impersistence; head thrust utilized to initiate saccades
9. Normal cerebellar function
10. Choreic and dystonic elements in gait abnormality
11. No facial myokymia
12. No other major neurology abnormalities are detected
13. Normal cognitive function
14. Late in the course, 3 patients have been described with ballistic movements and severe spasms

Neuropathology

1. Expression profiling of ADCY5 and mRNA by microarray analysis:
 - a. Higher expression ADCY5 and NKX2-1 in the putamen than in other brain regions
 - b. ADCY5 has higher expression in the adult striatum than NKX2-1
 - c. Longitudinal studies of brain tissue during development demonstrate an increase of ADCY5 and decrease of NKX2-1 from 50–500 days after conception

Laboratory Evaluation

1. Molecular genetic testing (WES) to define the mutation
2. EMG:
 - a. No facial myokymia

Differential Diagnosis

1. ADCY5 mutation carriers from those patients with NKX2-1 mutations:
 - a. NKX2-1 may have pulmonary or endocrine defects
 - b. Some patients with familial dyskinesia and facial myokymia (mutations of the same gene as ADCY5) have congestive heart failure
 - c. Progression of the disorder:
 - i. NKX2-1 patients remain mildly affected and may improve after childhood while ADCY5 progresses
 - d. Dystonic posturing is more severe in the ADCY5 patients than those with NKX2-1 mutations
 - e. ADCY5 related dyskinesia are worsened by action, excitement or stress
 - f. Need to rule out the disorders with mutations in the genes most commonly associated with chorea that include:
 - i. Huntington's disease
 - ii. SCA17
 - iii. DRPLA

Acquired Causes of Chorea Vascular Hemichorea

General Characteristics

1. Vascular lesions primarily interrupt striatal cortical motor

- loops and are found in the contralateral subthalamic nucleus, thalamus or caudate nucleus in hemichorea
- 2. Middle cerebral artery and PCA occlusion have been described as causative

Clinical Manifestations

1. Hemichorea may occur in acute stroke (often the thalamoperforate artery whose origin is P1) or from hypoperfusion of the middle cerebral artery territory
2. It occasionally is delayed or progressive
3. Cerebrovascular disease is the most common cause of sporadic chorea

Neuropathology

1. Lesions are most often found in the thalamus (thalamoperforate and thalamogeniculate arteries) and less frequently in the subthalamic nucleus (most often the interpeduncular artery from P1)

Laboratory Evaluation

1. MRI:
 - a. Diffusion weighted (for acute stroke) or T1 and T2-weighted sequences demonstrate lesions in the affected territories
 - b. Extremely rarely, a vascular malformation with hemorrhage may be demonstrated
 - c. In diabetic patients the thalamoperforate artery may be involved by stenosis of P1 or thrombotic or embolic occlusion

Diabetic Hemichorea

General Characteristics

1. Often seen in the setting of hyperglycemia and non-ketotic diabetic acidosis

Clinical Manifestations

1. Acute or subacute onset of hemichorea that most often spares the face
2. After normoglycemia has been restored the movement disorder may persist for 24–48 hours
3. Most often associated with hyperglycemia and non-ketotic diabetic acidosis

Neuropathology

1. Open biopsy (1 patient):
 - a. Gemistocytic astrocytes with zinc-laden metallothionein protein
 - b. No petechial hemorrhages

Laboratory Evaluation

1. MRI:
 - a. Contralateral T1 MRI sequence hyperintensities of the putamen are almost always detected
 - b. The caudate and globus pallidus may occasionally be involved

- c. The lesion is well circumscribed and is not in a vascular distribution
- d. DWI and ADC demonstrate restricted diffusion in the affected putamen. Increased susceptibility is also seen in a similar distribution with susceptibility-weighted imaging (SWI)
- e. PET:
 - i. Relative hypometabolism in the involved areas has been demonstrated
- f. Rarely similar changes on MRI imaging sequences have been seen ipsilaterally
- g. Non-ketotic diabetic acidosis

Differential Diagnosis of Hemichorea-Hemiballism Syndrome

1. Ischemia
2. Hyperglycemia with non-ketotic diabetic acidosis
3. Neoplasm
4. Systemic lupus erythematosus
5. Wilson's disease
6. Thyrotoxicosis
7. Hyperglycemic hyperosmolar non-ketotic coma

Sydenham's Chorea (SC)

General Characteristics

1. Sydenham's chorea is the neurological component of rheumatic fever
2. It is associated with antibodies against group A beta-hemolytic streptococci that cross-react with either:
 - a. Extracellular cell surface epitopes
 - b. Intracellular cytoplasmic or cytoskeletal antigens
3. PANDAS (pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection) occurs in children that develop:
 - a. Fulminant onset
 - b. Movement and behavioral disorder that include tics and OCD

Clinical Manifestations

1. Following infection by group A beta-hemolytic streptococcal infection with rheumatic fever and heart valve involvement; mitral > aortic
2. Familial tendency
3. The neurologic manifestations rarely occur without heart involvement
4. Adult recrudescence:
 - a. Associated with increased anti-streptolysin titer (ASO titer)
 - b. Jaccoud's arthritis (adults)
 - c. Generalized chorea
5. Behavioral abnormalities (hyperactivity in children and adolescents)
6. "Milk maids" hands; inability to sustain a movement
7. Incoordination and hypotonia

8. Usually the chorea has an abrupt onset that worsens over the ensuing 2–4 weeks
9. Quick semi-purposeful movements:
 - a. Jerking movements of the arms and legs
 - b. Decreased ability to walk
 - c. Involuntary movements of facial musculature with dysarthria
10. Hand posture:
 - a. Flexed wrist with extended fingers
11. Chorea may recur:
 - a. First recurrence may be during pregnancy (chorea gravidarum)
 - b. While taking oral contraceptives
12. The distal extremities are primarily involved
13. Choreiform tongue movements are common

Neuropathology

1. Elevated dopamine-2 receptor immunoglobulin G has been detected in approximately 1/3 of patients with Sydenham's chorea
2. It has been proposed that dopamine D1 and D2 receptors are the primary antibody target in SC although antibodies that bind to CNS lysoganglioside-GM and the cytoskeleton protein tubulin have also been demonstrated
3. The putative cause of the neurological symptomatology is an alteration of neuronal cell signaling transduction by calcium calmodulin-dependent protein kinase II (Camk11)
4. In acute rheumatic fever antibodies are raised against N-acetyl-beta-D-glucosamine (NABG) or GLcNAc
5. Different subsets of NABG antibodies are correlated with specific clinical manifestations of acute rheumatic fever (ARF)
6. Tubulin antibodies are not found in patients with ARF without SC

Laboratory Evaluation

1. MRI:
 - a. Non-specific signal intensities occur in the white matter, brainstem and caudate nucleus in approximately 50% of patients
 - b. PET evaluation (1 patient):
 - i. Increased glucose metabolism in the contralateral caudate and putamen that was noted to be reversible in three months
2. Increased ASO titer occurs with recrudescence of rheumatic fever and chorea

Antiphospholipid Antibodies

General Characteristics

1. Low titers of antiphospholipid (aPL) may be seen in 2–9% of the normal population
2. Titers may increase with mycoplasma, chlamydia, HIV, Lyme's disease and Hepatitis C
3. Chorea may occur in patients with high titers of aPL antibodies in the absence of concurrent autoimmune disease or clinical antiphospholipid syndrome

Clinical Manifestations (Chorea Associated with a High Titer of aPL Without APS Syndrome)

1. Age from 5–21 years
2. Increased titer of anticardiolipin aPL and absent lupus anticoagulant (LAC) in all reported patients
3. Chorea
4. Variable manifestations include:
 - a. Seizures
 - b. Cognitive impairment
 - c. Dystonia

Neuropathology

1. Putative mechanisms:
 - a. aPL antibody damage to nigrostriatal pathways due to high binding affinity of the antibodies for phospholipids of neurons in dopaminergic pathways that causes depolarization of striatal neurons
 - b. aPL-induced damage of vascular endothelium of the striatum
2. "Pre"-APS syndrome:
 - a. The detection of aPL antibodies but the condition does not meet criteria for APS but may manifest:
 - i. Livedo reticularis
 - ii. Chorea
 - iii. Thrombocytopenia
 - iv. Valvular heart disease
 - v. Nephropathy (not included in the criteria for APS)

Laboratory Evaluation

1. Pre-APS patients:
 - a. An increase of aCL antibodies (anticardiolipin) with normal lupus anticoagulant (LAC); in APS secondary to SLE there is thrombosis associated with elevated LAC antibody titers
2. High titers of IgM aCL develop in pre-APS patients that are thought to damage the striatum with consequent chorea whereas in APS there is vessel occlusion. In pre-APS the MRI is normal and in APS it may demonstrate abnormalities
3. PET (deoxyglucose) in pre-APS:
 - a. Demonstrates an increased metabolic rate for glucose utilization in the basal ganglia

Chorea in Systemic Lupus Erythematosus

General Characteristics

1. The incidence of chorea in SLE varies from 1–8% in various reports
2. It is strongly associated with aPL antibodies; most prominent are anticardiolipin and lupus anticoagulant (LAC) antibodies

Clinical Manifestations

1. Chorea usually occurs during the course of the illness but rarely may be the initial manifestation and may precede other signs and symptoms for years

2. The chorea may last days to years
3. May occur in children
4. May be episodic

Neuropathology

1. Immune-mediated mechanism is secondary to aPL antibodies primarily anticardiolipin IgG attack on the striatum
2. Ischemia of the basal ganglia, thalamus and cerebral cortex

Laboratory Evaluation

1. Positive titers of aPL antibodies, lupus anticoagulant (LAC), anticardiolipin (aCL) IgG, single or double stranded anti-DNA antibodies and positive sed rate
2. MRI:
 - a. In neuropsychiatric SLE there is periventricular white matter hyperintensities on T2 and FLAIR sequences
 - b. Scattered evidence of small vessel infarction
3. SPECT:
 - a. Scattered areas of hypoperfusion

Chorea Gravidarum

General Characteristics

1. The most common movement disorders of pregnancy are restless leg syndrome and chorea gravidarum
2. The incidence has dramatically decreased in Western countries putatively due to the decrease of rheumatic fever

Clinical Manifestations

1. It is a disorder of young patients the average age being 22
2. 80% of attacks occur during the first pregnancy; approximately 50% start during the second trimester
3. Recurrences may occur during subsequent pregnancies especially if antiphospholipid syndrome is causative
4. Some patients have a family history of transient chorea
5. Emotional stress aggravates the chorea; the movements are absent during sleep
6. The patients may be restless and fidgety and unaware of the movements
7. The extremities are primarily affected
8. The chorea may be unilateral hemichorea
9. The affected limb is hypotonic, the joints are lax and the wrist and fingers shape the hand into a spoon configuration (an imbalance of flexor and extensor musculature)
10. There may be uncontrollable tongue movements (darting in and out of the mouth)
11. The choreic movements are rapid, purposeless, and irregular. They randomly flow from one part of the body to another
12. Rheumatic encephalopathy:
 - a. May occur in patients with clinical manifestations of chorea
 - b. EEG demonstrates slow waves of 3–6 Hz which occur continually or in intermittent rhythmic paroxysms

- c. The EEG changes may be generalized or are seen predominantly over the frontal and central regions
- d. Changes are usually unilateral in hemichorea
- e. EEG improvement parallels recovery from rheumatic carditis and chorea usually within 6 months

Neuropathology

1. Putative autoimmune-mediated mechanism affecting the basal ganglia

Laboratory Evaluation

1. Dependent upon the underlying etiology
2. Approximately 50% of patients have no determined cause; most common etiologies include: 1. SLE; 2. Huntington's disease; 3. rheumatic fever; 4. APS; 5. syphilis (rare)

Post-Pump Chorea

General Characteristics

1. Definition:
 - a. Post-pump chorea is choreoathetoid movements that develop within two weeks of cardiopulmonary bypass surgery. There is often an initial asymptomatic period
2. The syndrome occurs in 1–3% of patients from infants to mid-childhood

Clinical Manifestations

1. Generalized chorea
2. Orofacial dyskinesia
3. Hypotonia
4. Ballismus
5. Supranuclear gaze palsy
6. Change in affect
7. Pseudobulbar signs
8. 10 years follow up of chorea in 8 children from a cohort of 668 who had open cardiac surgery
 - a. Clinical manifestations:
 - i. None of the children were developmentally normal 22 to 130 months after surgery
 - b. Mild learning disability
 - c. Progressive hypotonia
 - d. 3/8th patients had transient chorea while in 5 patients it was persistent
 - e. 1/8th children expired

Neuropathology

1. Strong association with deep hypothermia and circulatory arrest
2. Lack of macroscopic changes
3. Putative biochemical or microembolic etiology in some patients

Laboratory Evaluation

1. MRI:
 - a. Generalized brain atrophy but no focal changes
2. PET evaluation [¹⁸F] fluorodeoxy-glucose
 - a. Patchy areas of decreased glucose utilization

Chorea from Contraceptives*General Characteristics*

1. Use of oral contraceptives is a well-documented but rare cause of acquired chorea
2. Many patients with chorea induced by OCPs had prior or coexisting antiphospholipid syndrome, SLE or prior rheumatic fever

Clinical Manifestations

1. Insidious onset of hemichorea
2. Insidious onset of bilateral chorea

Neuropathology

1. It has been suggested that oral contraceptives cause a recrudescence of Sydenham's chorea
2. Estrogen increases the sensitivity of dopaminergic neurons
3. Anti-basal ganglia antibodies have been detected by Western immune-blot; the antigens were of 40–45 kDa in size (one patient)

Laboratory Evaluation

1. MRI:
 - a. Most often normal in all sequences
2. PET with FDG (one patient):
 - a. Increased glucose utilization in the contralateral caudate nucleus in a patient with hemichorea

Acute Carbon Monoxide Poisoning*General Characteristics*

1. Acute brain injury in CO-exposed patients are primarily caused by hypoxia
2. The affinity of CO for heme protein is 250 times that of oxygen
3. The formation of carboxyhemoglobin reduces the oxygen carrying capacity of blood that leads to varying areas of cerebral tissue hypoxia

Clinical Manifestations

1. Acute poisoning:
 - a. Diffuse hypoxic-ischemic encephalopathy that predominately involves the gray matter
2. Delayed encephalopathy after carbon monoxide poisoning is uncommon:
 - a. It may occur 14–45 days after recovery from acute poisoning and is characterized by:
 - i. Cognitive impairment
 - ii. Dementia or psychosis
 - iii. Parkinsonism
 - iv. Urinary incontinence
 - v. Generalized or mono limb chorea
 - vi. Dystonia

Neuropathology

1. Putative mechanisms include:

- a. Hypoactivity in the indirect pathway of the basal ganglia-thalamocortical motor circuit
 - b. White matter lesions that destroy subcortical inhibitory motor circuitry
2. Necrosis and apoptotic neuronal death
 3. CO inhibits the mitochondrial electron transport chain and activates polymorphonuclear leukocytes which diapede into the brain and cause brain lipid peroxidation

Laboratory Evaluation

1. MRI:
 - a. Diffuse hypoxic-ischemic and focal cortical lesions with predilection for the temporal lobe and the hippocampus
 - b. Necrosis of the globus pallidus:
 - i. The most common CNS structure involved in CO poisoning
 - ii. The medial globus pallidus demonstrates low signal intensity on T1-weighted sequences and high signal intensity on T2-weighted and FLAIR images
 - iii. DWI MRI and apparent diffusion coefficient maps demonstrate restriction of water diffusivity
 - c. The caudate, putamen and thalamus are occasionally involved
 - d. There are rare brainstem and cerebellar lesions
 - e. Diffuse brain atrophy
 - f. Cerebral white matter demyelination:
 - i. Not seen in the acute stage of CO poisoning
 - ii. The periventricular white matter and the centrum semiovale are primarily involved
 - iii. In severe poisoning, there is demyelination in the subcortical white matter, corpus callosum, external and internal capsules

Differential Diagnosis of Acquired Chorea*Stroke*

1. The most common movement disorder to occur following stroke
2. Stroke-induced chorea occurs in older stroke patients
3. It is usually hemichorea and occurs contralateral to the lesion
4. Thalamic lesions are the most common localization
5. The majority of patients show some improvement by 1 year

Post-Pump Chorea

1. Occurs in children
2. Risk factors are prolonged pump time, older aged children, preoperative cyanosis and deep anesthesia

Polycythemia Vera

1. Chorea may be acute or subacute
2. May precede the hematologic changes
3. Occurs in 1–5% of patients and is most common in elderly females
4. It improves with phlebotomy

Autoimmune Causes of Chorea*Sydenham's Chorea*

1. Occurs in approximately 25% of acute rheumatic fever patients
2. It develops weeks to months after infection with group A-B-hemolytic streptococcus
3. The average age of onset is 9 years
4. Anti-basal ganglia antibodies have been identified. The putative mechanism is "molecular mimicry"

Systemic Lupus Erythematosus

1. Chorea occurs in approximately 1% of patients with SLE
2. Often associated with the antiphospholipid antibody

Sjögren's Disease

1. Oral contraceptives:
2. Estrogen enhances central dopaminergic sensitivity

Chorea Gravidarum

1. Usually begins in the first trimester and improves in later pregnancy and after delivery

Paraneoplastic Causes of Chorea

1. Paraneoplastic chorea most often occurs with anti-CRMP-5 antibodies that are associated with small cell lung cancer
2. Paraneoplastic chorea occurs with other malignancies

Metabolic Causes of Chorea

1. Glucose metabolism:
 - a. Non-ketotic hyperglycemia induced chorea:
 - i. Most common in women and occurs with very high glucose levels (~500 mg is average)
 - ii. MRI high signal intensities occur in the putamen (T1-weighted sequences)
 - iii. Most often a reversible hemichorea
2. Thyroid disease:
 - a. Chorea rarely occurs with hyperthyroidism
 - b. Can occur with thyroid replacement therapy
 - c. May be associated with Hashimoto's encephalopathy
 - d. Putative mechanism is enhancement of catecholamine effects on striatal neurons
 - e. It may persist after patients are euthyroid
 - f. Hypothyroidism may cause chorea
3. Renal failure:
 - a. Uremia has been associated with the sudden onset of chorea
 - b. Diabetic end-stage renal disease patients may develop MRI changes in the basal ganglia consistent with vasogenic edema
4. Calcium metabolism:
 - a. Hypoparathyroidism with hypocalcemia is associated with chorea that improves when the calcium is normalized
5. Chorea may occur with other movement disorders in association with several inborn errors of metabolism

Drugs That Cause Chorea

1. Dopamine receptor antagonists:
 - a. These drugs most often cause tardive dyskinesia but may be associated with limb chorea
- b. Other drugs that may cause chorea:
 - i. Levodopa
 - ii. Phenothiazine
 - iii. Lithium
 - iv. Cimetidine
 - v. Isoniazid
 - vi. Verapamil
 - vii. Theophylline
 - viii. Baclofen
 - ix. Tricyclic antidepressants
 - x. Steroids
 - xi. Antiepileptics (Phenytoin)
- c. Drugs of abuse that cause chorea:
 - i. Cocaine ("crack dancing")
 - ii. Amphetamines

Infectious Causes of Chorea

1. Neurosyphilis
2. Lyme's disease
3. Subacute sclerosing panencephalitis (measles)

Toxins That Cause Chorea

1. Carbon monoxide
2. Mercury

Senile Chorea*General Characteristics*

1. Many known etiologies of chorea present in late adulthood, examples of which are PKAN, Huntington's disease, antiphospholipid antibody syndrome
2. Rare causes of late sporadic senile chorea are in association with tardive dyskinesia, hypocalcemia and basal ganglia calcification
3. There remains a group of late onset sporadic chorea that to date has no known cause

Clinical Manifestations

1. Insidious onset
2. Mild involvement of the limbs
3. Rare lingual facial movements
4. Slow progression

Neuropathology

1. Not defined if there is no underlying cause

Laboratory Evaluation

1. Dependent upon the underlying cause

Differential Diagnosis of Hereditary Causes of Chorea

1. Huntington's disease

2. Neuroacanthocytosis
3. McLeod disease
4. HDL-2
5. PKAN
6. Abetalipoproteinemia
7. Hypobetalipoproteinemia
8. Wilson's disease
9. Spinocerebellar ataxia 17
10. Glucose transporter (GLUT-1)
11. Fahr's disease
12. Lesch-Nyhan syndrome
13. DRPLA
14. Karak syndrome
15. ADCY5 mutations
16. NKX-2 mutations
17. Benign hereditary chorea
18. Neuroferritinopathy
19. Aceruloplasminemia

Dyskinesia

Overview

Plasticity is the ability of the nervous system to change the effectiveness of synaptic transmission in neural circuits. It occurs at neuronal, synaptic, protein or genomic structures which modulate the structure and function of neural networks. Maladaptive plasticity is the development of dyskinesia associated with dysfunctional neural plasticity from increased transmitter release, receptor regulation and synaptic changes of long term potentiation (LTP) or long term depression (LTD). It may also occur from anatomical remodeling, axonal regeneration, synaptogenesis and neurogenesis. It has been proposed that these alter cortical-thalamic and striatal circuits (the indirect pathway) that disinhibits GABA-ergic regulation of the ventrolateral thalamic (VL) neurons that project to the motor and supplementary motor cortices.

Paroxysmal Kinesigenic Dyskinesia (Paroxysmal Kinesigenic Choreoathetosis)

General Characteristics

1. Paroxysmal kinesigenic dyskinesia (PKD) may be caused by heterozygous mutation in the PRRT2 gene that maps to chromosome 16p11
2. Allelic disorders are:
 - a. Familial infantile convulsions (BF1C2)
 - b. Infantile convulsions and paroxysmal choreoathetosis (ICCA)
 - c. Inheritance for PKC is AD

Clinical Manifestations

1. Attacks are initiated by sudden movement or startle
2. Last seconds to minutes
3. Hyperventilation may induce attacks

4. Movements may be preceded by paresthesias, crawling sensations or anxiety
5. Movements consist of dystonic posture, ballism, chorea, athetosis, or various combinations of the above
6. Movements may affect speech and cause falls
7. The movements habituate
8. Incomplete atonic attacks may be more frequent in Japanese patients
9. Consciousness is maintained
10. Generalized and partial seizures have been documented in some kindreds
11. A large percentage of patients are responsive to antiepileptics
12. PRRT2 mutations are associated with an earlier age at onset, longer duration of attacks and combined phenotypes of dystonia and chorea

Neuropathology

1. Epileptic mechanisms, channelopathy and abnormalities in basal ganglionic circuitry have been suggested as etiologic

Laboratory Evaluation

1. Ictal and interictal single photon emission computed tomography (SPECT)
 - a. Perfusion changes in the left frontal/temporal cortices
2. Increased ictal perfusion of the thalamus:
 - a. One 6 year old patient demonstrated increased CBF by SPECT in the posterolateral thalamus on the contralateral side to the unilateral PKC

Acquired Etiologies

1. Head trauma
2. Demyelinating disease
3. Putaminal and thalamic infarction
4. Hypoparathyroidism with basal ganglia calcification
5. Hyperglycemia
6. Vascular malformations

Paroxysmal Non-Kinesigenic Dyskinesia (PNKD)

General Characteristics

1. PNKD is caused by heterozygous mutation in the myofibrillogenesis regulator-1 gene (MRI) that maps to chromosome 2q35
2. Inheritance is AD

Clinical Manifestations

1. Patients with MRI mutations have a more homogenous phenotype than those without the mutation; they also have an earlier age at onset of 3 months to 12 years
2. Attacks last minutes to hours
3. They may occur spontaneously at rest
4. Dystonia, chorea, athetosis and ballism occur in various combinations

5. Speech and swallowing may be involved
6. Attacks may be preceded by feelings of stiffness and occasionally by formications in the affected extremities
7. Attacks are triggered by stress, fatigue, caffeine and alcohol
8. Fewer attacks during pregnancy
9. Usually at least one attack per week
10. Good response to benzodiazepines
11. Migraine headaches occur in approximately 50% of patients
12. Patients with PNKD without the MRI mutation:
 - a. Exercise is a precipitating factor (68%)
 - b. Alcohol is not a precipitating factor
 - c. More variable age at onset
 - d. Ballism in 10% of patients
 - e. Seizure in 23% of patients

Neuropathology

1. The pathophysiology of PNKD has not been elucidated
2. 60% of patients have mutations in the PNKD gene (formerly MRI) that maps to 2q35; another locus on 2q31 (PNKD2) has been found in a Canadian kindred

Laboratory Evaluation

1. The diagnosis is purely clinical

Differential Diagnosis of PNKD

1. Wilson's disease
2. Paroxysmal kinesigenic dyskinesia
3. Infantile convulsions and choreoathetosis (ICCA syndrome)
4. Paroxysmal exertion-induced dyskinesia (PED)
5. Autosomal dominant nocturnal frontal lobe epilepsy
6. Paroxysmal dystonic choreoathetosis with episodic ataxia and spasticity
7. Huntington's disease
8. Acquired

Differential Diagnosis of Acquired PNKD

1. Demyelinating disease
2. Vascular thalamic lesions
3. Hypoparathyroidism
4. Thyrotoxicosis
5. Basal ganglia calcification
6. Brain tumor
7. Head trauma

Paroxysmal Exercise-Induced Dyskinesia (PED)

General Characteristics

1. PED is caused by heterozygous mutation in the SLC2A1 gene that maps to chromosome 1p34.2
2. It encodes the GLUT1 transporter and is autosomal dominant
3. Allelic disorders with overlapping features include:
 - a. GLUT1 deficiency syndrome-1
 - b. Dystonia-9
 - c. Idiopathic generalized epilepsy-12

Clinical Manifestations

1. Age of onset is usually in childhood but may range from 1–30 years
2. Dyskinesias are induced by exercise of 15–60 minutes duration
3. Attacks last between 5 minutes to 2 hours and are most often in the exercised extremities
4. Dystonic movements are bilateral and are exacerbated by cold, stress, fatigue and sleep deprivation
5. The frequency of attacks vary from one per day to one per month
6. Variable features include:
 - a. Increased deep tendon reflexes
 - b. Developmental delay
 - c. Cognitive impairment
 - d. Seizures and migraine can occur concomitantly in some familial forms
7. PED may be associated with:
 - a. Paroxysmal dystonic choreoathetosis with episodic ataxia and spasticity
 - b. Benign familial infantile seizures (BFIE)
 - c. Infantile convulsions and choreoathetosis (ICCA syndrome)
 - d. Rolandic epilepsy, paroxysmal exercise-induced dystonia and writer's cramp

Neuropathology

1. PED is associated with mutations in the SLC2A1 gene that encodes the glucose transporter GLUT1
2. All mutations affect the ability of GLUT1 to transport glucose into the CNS which causes bioenergetic failure with exertion

Laboratory Evaluation

1. There is hypoglycorrhachia in the CNS (CSF) and serum hypoglycemia
2. EEG and neuroimaging are normal
3. The diagnosis is confirmed with molecular genetic screening of the SLC2A1 gene

Differential Diagnosis of PED

1. PKD
2. Young adult onset Parkinsonism
3. GLUT1 deficiency
4. Pyruvate dehydrogenase deficiency:
 - a. MRI demonstrates bilateral globus pallidus involvement
 - b. Dystonia responds to thiamine

Paroxysmal Hypnogenic Dyskinesia (PHD)

General Characteristics

1. PHD in the overwhelming majority of patients is a form of mesial frontal lobe epilepsy. In familial patients it is referred to as autosomal dominant nocturnal frontal lobe epilepsy

2. Autosomal dominant nocturnal frontal lobe epilepsy is caused by heterozygous mutation in the CHRNA4 gene that maps to chromosome 20q13.33
3. It is a genetically heterogeneous condition with mutations in genes located on chromosomes 15q24, 1q21, 8p21 and 7q34

Clinical Manifestations

1. Intermittent dystonia and choreoathetoid movements that are exclusively seen during sleep
2. They often occur every night
3. Consciousness is preserved during an attack when the patient is wakened
4. Most often misdiagnosed as parasomnia

Neuropathology

1. Support for a subcortical focus includes:
 - a. The absence of EEG abnormalities
 - b. Absence of a generalized or local convulsion
 - c. No loss of consciousness or amnesia from the event
 - d. The clinical characteristics of the involuntary movements are most suggestive of a basal ganglia origin
 - e. PET scan evaluation in 12 patients with ADNFLE with the CHRNA4 gene mutation revealed:
 - i. Decreased striatal D1 receptor binding predominantly in the right putamen
 - ii. It was postulated that a gain of function in mutation of the CHRNA1 gene caused increased levels of extracellular dopamine due to the mutant CHRNA4 subunit 4 protein's failure to regulate dopamine release normally

Laboratory Evaluation

1. Normal EEG during an episode
2. Molecular genetic screening of the gene

Mixed Paroxysmal Dyskinesia

General Characteristics

1. The patients do not fall into the classic categories of paroxysmal dyskinesia

Clinical Manifestations

1. Patients have features of both paroxysmal kinesigenic and non-kinesigenic dyskinesia
2. Patients may respond to carbamazepine and clonazepam

Neuropathology

1. Not defined

Tardive Dyskinesia

General Characteristics

1. The usual cause is dopamine receptor antagonist or neuroleptic medication use
2. The most common drugs that are causative:

- a. Neuroleptics
- b. D2 dopamine receptor antagonists
- c. Metoclopramide
- d. Perphenazine
- e. Stelazine
- f. Promethazine
- g. Amitriptyline
- h. Butyrophenones

Clinical Manifestations

1. Abnormal movements occur:
 - a. During drug treatment
 - b. After drug withdrawal
 - c. May be permanent
2. Usually three months of exposure is required
3. Exacerbations of movements may occur with drug withdrawal; increasing the dose of the offending agent may dampen movements
4. Orofacial dyskinesia (the buccolingual masticatory syndrome)
 - a. Rhythmical involuntary movement of the tongue, face or mouth
 - b. Choreiform movements of the extremities
 - c. Abnormalities of gait, trunk and posture
5. Axial dystonias:
 - a. Patients > 50 years of age
 - b. May coexist with buccal lingual masticatory (BLM) syndrome and choreoathetosis
 - c. Neck flexion and lordosis
 - d. Pelvic rocking and thrusting
6. Respiratory dyskinesia with involuntary chest and diaphragmatic movements
7. Often accompanied by tardive akathisia:
 - a. Inner compulsion to move
 - b. Restlessness
 - c. Uncomfortable sensations of the body as a whole or specific body parts
8. Tardive dystonia:
 - a. Accompanied by tardive akathisia or tardive dyskinesia
 - b. Sustained and torsional movements
 - c. Facial dystonia with or without facial grimacing
 - d. Jaw deviation with sustained mouth opening (striking in DYT3 or Lubag)
 - e. Dystonic neck posturing (retrocollis)
9. Tardive dyskinesia variants:
 - a. Tardive akathisia
 - b. Tardive tics
 - c. Tardive dystonia
 - d. Tardive myoclonus
 - e. Generalized chorea
10. Associated tardive dyskinetic signs:
 - a. Respiratory dyskinesias
 - b. Body rocking
 - c. Pelvic thrusting

Neuropathology

1. The major putative hypothesis for the development of tardive dyskinesia is central blockade of dopamine receptors by dopamine antagonists that causes:
 - a. Striatal dopamine receptor supersensitivity
 - b. Reduction of D2 receptor blockade results in increased depolarization and firing of formerly blocked receptors even with less concentrations of striatal dopamine
 - c. Striatal disinhibition of the thalamocortical pathway (increased excitability of glutamatergic VL neuronal projections to the cortex) from imbalance of D1 and D2 receptors
 - d. Neurodegeneration of striatal neurons from excitotoxic or lipid peroxidative mechanisms
 - e. Abnormalities of D3, D4, and D5 receptors
 - f. There is a possible genetic vulnerability to tardive dyskinesia as demonstrated by the polymorphisms of the D3 receptor gene. The glycine allele of DRD3 is associated with neuroleptic-induced TD compared to both heterozygous and serine homozygous patients
 - g. A possible relationship between TD and nicotine agonists has been suggested
 - h. Lower levels of brain derived neurotrophic factor (BDNF) have been found in schizophrenic patients with tardive dyskinesia

Laboratory Evaluation

1. MRI:
 - a. Neuroleptic-naïve patients with schizophrenia:
 - i. Enlargement of the ventricles
 - ii. Decreased thalamic volume and decreased cortical gray matter that vary
2. In patients with tardive dyskinesia:
 - a. The volume of the caudate nuclei is smaller
 - b. Other studies demonstrate:
 - i. Usual antipsychotic medication may cause an increase of volume of the caudate nucleus while atypical antipsychotics do not change caudate volume

Differential Diagnosis of Tardive Dyskinesia

1. Tardive dyskinesia (TD) usually follows the long term use of any neuroleptic medication:
 - a. Two years of continuous use
 - b. Some patients have developed the syndrome within 3 to 6 months of use
 - c. The most common causative medications are phenothiazine, butyrophenones and antiemetic drugs
2. Schizophrenic patients (drug naïve):
 - a. Stereotyped and repetitive movements
 - b. Complex involuntary hyperkinetic dyskinesia
 - c. Isolated tics
3. Orofacial dyskinesia in normal patients:
 - a. The elderly
 - b. Early dementia
4. Huntington's disease:

- a. Protrusion of the tongue abnormally
5. Wilson's disease
6. Withdrawal emergent dyskinesia:
 - a. Usually seen in children
 - b. Dyskinesia that occurs transiently after withdrawal of neuroleptics
7. Unilateral striatal lesions may cause bilateral oral buccal dyskinesia

Differential Diagnosis of Orofacial Dyskinesia

1. Drug-induced:
 - a. Levodopa (associated chorea)
 - b. Triphenyl hexedine (dry mouth)
 - c. Antihistamines (neck muscle dystonia)
 - d. Stelazine (most potent of all drugs causing dyskinesias by milligram)
 - e. Tricyclic antidepressants (those with a basic phenothiazine structure)
2. Huntington's disease:
 - a. Associated dementia and choreatic eye movements
3. Hepatocellular degeneration:
 - a. In a setting of chronic liver failure
 - b. Dysarthria
 - c. Falling backwards
4. Cerebellar infarction:
 - a. PICA infarction
 - b. "Salt and pepper" facial pain
5. Edentulous patients:
 - a. Multiple "rodent-like" mouthing movements
6. Dystonia:
 - a. Meige's syndrome:
 - i. Dramatic associated blepharospasm
 - ii. Tardive dystonia:
 1. Associated choreiform movements
7. Tics:
 - a. Associated complex stereotyped extremity movements
8. Tremor:
 - a. Up-down head tremor; prominent chin tremor (basal ganglia)
9. Essential tremor (ET):
 - a. Side to side head tremor
10. Cerebellar tremor of the neck and head:
 - a. Associated postural kinetic tremor of the body > extremity intention tremor
11. Myoclonus:
 - a. Facial musculature (restricted)
12. Hemifacial spasm:
 - a. Large facial fasciculations
 - b. "Risus sardonicus" branch of the VIIth nerve may be the first affected muscle
13. Myokymia:
 - a. Seen around the soft tissue of the eye (may not be noticed by the patient)
14. Facial nerve synkinesia:

- a. Jaw winking
 - b. The mentalis muscle is often the most severely affected
 - c. Patients acquire a deep nasolabial fold (contractive) with nerve regeneration
15. Bruxism:
- a. Associated TMJ joint disease with atrophic masseter muscles
16. Epilepsia partialis continua:
- a. Thumb involvement (twitching) at the same rhythm as eye blinking
 - b. Cortically induced nystagmus on the contralateral side

Levodopa-Induced Dyskinesia

General Characteristics

1. After 4 to 6 years of continuous levodopa use, the therapeutic window narrows and patients suffer motor fluctuations and levodopa-induced dyskinesias

Clinical Manifestations

1. Dyskinesia most commonly occurs at the time of peak levodopa plasma concentrations (peak dose dyskinesia)
2. Diphasic dyskinesia occurs in advanced patients when the drug concentrations rises or falls

Neuropathology

1. An imbalance between the “direct” and “indirect” pathways that regulate the cortico-striatal-thalamic motor loops has been postulated
2. Underactivity of the indirect pathway and overactivity of the direct pathway
3. LIDs have more recently been associated with:
 - a. Presynaptic increased levels of dopamine
 - b. Postsynaptic gene and protein modifications
 - c. Abnormal function of other non-dopamine transmitter systems
 - d. Altered firing patterns and coherence between the basal ganglia and the cortex that leads to disinhibition of the thalamocortical neurons (projecting from VL to the premotor, motor and prefrontal cortices)

Laboratory Evaluation

1. Transcranial magnetic stimulation (TMS)
2. Demonstrates the presence of altered cortical excitability
 - a. Repetitive TMS over the supplementary motor area (SMA), the primary motor cortex (MI) induces a transient reduction in LIDs
3. Peak dose dyskinesia has been modified with theta burst stimulation delivered bilaterally to the lateral cerebellum
 - a. May modify the maladaptive sensorimotor plasticity of the motor cortex

Akathisia

General Characteristics

1. Definition:

- a. A subjective and objective motor restlessness
- b. It is most often a side effect of drugs, most often antipsychotic serotonin reuptake inhibitors and buspirone; it has also been seen with antiemetics, preoperative sedatives, calcium channel blockers and drugs for vertigo

Clinical Manifestations

1. Complex stereotyped movements of the extremities and trunk
2. Shifting weight, crossing and uncrossing the legs, rocking back and forth
3. Vocalizations: moaning, humming or groaning
4. Acute akathisia occurs with initiation of the triggering medication
5. Chronic treatment (tardive akathisia is increased by drug withdrawal)
6. Movements are present throughout the day
7. A compulsion to move
8. Occurs during any physical dependence drug withdrawal
9. May be associated with both Parkinson's disease and related syndromes
10. A sense of disquiet or anxiety
11. Many patients suffer neuropathic pain symptomatology
12. Patients may pace for hours
13. Insomnia
14. Some suggest that restless leg syndrome may be a form of focal akathisia

Classification of Akathisia

1. Acute akathisia
 - a. Duration of symptomatology for less than six months
 - b. Development:
 - i. It is induced with administration of antipsychotic medication or with increase of its dosage
 - ii. The use of high potency antipsychotic medication
 - iii. Anticholinergic withdrawal
 - c. Severe dysphoria
 - d. Awareness of restlessness and the compulsion to move
 - e. Complex, stereotyped and semi-purposeful movements
2. Chronic akathisia:
 - a. Continues for longer than six months after last dosage modification
 - b. Less sense of restlessness
 - c. Less dysphoria
 - d. Awareness of the sense of restlessness and compulsion to move
 - e. Stereotyped movement
 - f. May be associated with limb and orofacial dyskinesia
3. Tardive akathisia:
 - a. Delayed onset of approximately three months
 - b. Not related to either drug switching or dose modification
 - c. Associated with tardive dyskinesia
4. Withdrawal akathisia:

- a. Associated with change of antipsychotic medication
- b. The onset is usually within six weeks of discontinuation or decreased dosage of the drug
- c. May occur from anticholinergic discontinuation
- 5. Pseudoakathisia:
 - a. Motor manifestations without a sense of restlessness
 - b. Male predominance
 - c. No dysphoria
 - d. An overlap with limb and orofacial dyskinesia

Neuropathology

- 1. A putative imbalance between the dopaminergic/cholinergic or the dopaminergic/serotonergic transmitter systems
- 2. Some evidence to support dysfunction of D2/D3 occupancy in the ventral striatum (nucleus accumbens and olfactory tubercle)
- 3. A mismatch between the core and shell of the nucleus accumbens due to overstimulation of the locus coeruleus

Laboratory Evaluation

- 1. MRI (3 patients)
 - a. Both restless leg syndrome and akathisia were described after pontine infarction

Differential Diagnosis of Akathisia

- 1. Dopamine antagonists
- 2. Neuroleptic treatment
- 3. Parkinsonism/Parkinson's disease
- 4. Post-encephalitic parkinsonism
- 5. Tourette syndrome
- 6. Huntington's disease
- 7. Obsessive compulsive disorders
- 8. Miryachit (jumping Frenchman of Quebec)
- 9. Tic disorders
- 10. Oromandibular dystonia

Ballismus

General Characteristics

- 1. Definition:
 - a. Repetitive and varying large amplitude involuntary movements of the proximal portion of the extremities; hemiballismus is the flailing movements on one side of the body

Clinical Manifestations

- 1. Rapid large amplitude flinging movements of an extremity
- 2. Proximal girdle muscles are primarily involved
- 3. The face is usually spared
- 4. Sudden onset
- 5. Patients may restrain their affected extremity (their arm is placed under the belt or tied down)
- 6. It is often associated with hemichorea particularly if there is a metabolic cause (hyperosmolar state)

- 7. It is exhausting for patients but ceases during sleep
- 8. May occur bilaterally
- 9. Arms and legs often move together
- 10. Movement increases the disorder and relaxation dampens the involuntary movements

Neuropathology

- 1. Most often there is destruction of $\frac{2}{3}$ of the corpus Luysi (subthalamic nucleus)
- 2. Hemiballismus from lesions in the subthalamic nucleus is more severe than lesions in other brain regions
- 3. Other brain areas that are associated with ballismus include:
 - a. The globus pallidus:
 - i. Decreased output from the globus pallidus (normally produces GABA-ergic inhibition of the VL of the thalamus)
 - ii. Decreased firing rates from 70/s to 40/s of the internal segment of GPi have been demonstrated
 - b. The putamen:
 - i. Projects to the premotor cortex through the globus pallidus
 - c. Caudate nucleus:
 - i. Specific lesions have caused hemiballismus
 - d. Cortical motor areas:
 - i. Lesions of the cortex have caused hemiballismus
 - e. The usual artery that is infarcted in hemiballismus is the thalamoperforate artery whose origin is the P1 segment of the posterior cerebral artery (PCA). Infarction of the anterior choroidal artery (carotid) and the interpeduncular artery from the top of the basilar may also be causative:
 - i. Hemiballismus from stroke is seen in approximately 45 patients per one hundred thousand stroke patients
 - ii. Stroke is the most common cause of hemiballismus

Laboratory Evaluation

- 1. MRI:
 - a. P1 lesions of the PCA that primarily compromise the territories of the thalamoperforate and interpeduncular arteries (top of the basilar)
 - b. Lesions from any cause that compromise the striato-thalamocortical motor loop

Differential Diagnosis of Hemiballismus

- 1. Vascular lesions of the thalamoperforate, interpeduncular or anterior choroidal arteries
- 2. Traumatic brain injury
- 3. Non-ketotic hyperglycemia:
 - a. The second most common cause of hemiballismus
 - b. Putative subthalamic (STN) involvement or its efferents
 - c. MRI lesions are most conspicuous in the putamen with lesser involvement of the globus pallidus and caudate nucleus

- d. The ballistic movements are seen with high blood glucose levels and subside with attainment of normoglycemia. This occurs over hours
- 4. Neoplasm
- 5. Vascular malformations
- 6. Tuberculoma
- 7. Demyelinating disease
- 8. HIV infection complications
 - a. Hypoglycemia from pentamidine treatment of AIDS
 - b. Cerebral toxoplasmosis
- 9. Parkinson's disease surgery
- 10. Levodopa

Athetosis

General Characteristics

- 1. Definition:
 - a. A slow writhing involuntary large amplitude movement that primarily involves the distal extremity muscles. Facial and axial muscles may be involved
 - b. The term athetoid syndrome has now been changed to "dyskinetic cerebral palsy" and comprises a non-progressive but evolving disorder with:
 - i. Damage to the basal ganglia of the full term brain
 - ii. Impairment of postural reflexes
 - iii. Arrhythmical involuntary movements and dysarthria
 - iv. Spared sensation ocular movements and intelligence

Clinical Manifestations of Athetosis

- 1. Associated episodic hypertonic muscle contraction of affected muscle groups
- 2. Abnormal distal writhing movements may be unilateral or bilateral
- 3. Often associated with facial grimacing and dysarthria
- 4. Mixed with chorea and dystonia
- 5. The writhing movements involve the hands, toes and feet in addition to the arms, legs, neck and tongue
- 6. Kernicterus is now used to describe the clinical features of chronic bilirubin encephalopathy and includes:
 - a. Striatal movement disorder
 - b. Sensorineural hearing loss
 - c. Impaired upward gaze
 - d. Dental enamel dysplasia
- 7. Pseudoathetosis:
 - a. "Finger playing" sinuous movements of the outstretched upper extremity fingers
 - b. Updrift of the outstretched upper extremities
 - c. Severe proprioceptive deficits

Neuropathology

- 1. Neonatal asphyxia:
 - a. The loss of neurons and astrogliosis primarily affects the caudate nucleus and the putamen

- b. Bilirubin-induced neurologic dysfunction (BIND):
 - i. The risk for developing neurological deficits increases with elevated serum/plasma concentration of unconjugated bilirubin
 - ii. The risk is compounded by disorders of bilirubin-binding to albumin caused by:
 - 1. Reduction in serum albumin concentration
 - 2. Bilirubin-binding capacity and albumin affinity
 - 3. Infection
 - 4. Displacing agents
 - iii. Kernicterus occurs when unconjugated bilirubin crosses the blood-brain barrier (immature in infants)
 - 1. Bilirubin prevents the phosphorylation of many proteins; decreased phosphorylation of synapsin 1 interferes with vesicle transport at the presynaptic terminal by inhibiting exocytosis
 - 2. Neuronal loss, gliosis and demyelination of the corpus striatum is particularly severe in the globus pallidus
 - 3. Thalamic stroke:
 - a. Primarily in the distribution of the thalamogeniculate artery and portions of the thalamic perforate artery territory. There is often associated sensory loss and ataxia

Laboratory Evaluation

- 1. MRI: (infants with kernicterus)
- 2. Globus pallidus demonstrates increased signal in T1 sequences and T2 hyperintensity evolves over time
- 3. The subthalamic nucleus may be involved (FLAIR sequences)
 - a. White matter abnormalities have been described

Differential Diagnosis of Athetosis

- 1. Congenital anoxia with bilateral damage of the globus pallidus, red nucleus, midbrain tegmentum and descending periventricular corticospinal pathways
- 2. Kernicterus
- 3. Wilson's disease
- 4. Stroke or tremor that involves the striatum and thalamus which spans the cortex
- 5. Severe recovered traumatic brain injury
- 6. Post-anoxia

Differential Diagnosis of Pseudoathetosis

- 1. Large fiber 20–22 μ m finger (proprioceptive and vibratory modality) loss
- 2. Large dorsal root ganglion cell loss:
 - a. Sjögren's syndrome
 - b. Cisplatin chemotherapy
 - c. Neurosyphilis (dorsal root entry zone lesion)
 - d. Paraneoplastic antibodies that affect the DPG
 - e. Autoimmune (Richter's variant of GBS)

- f. Dorsal column and nuclear lesions
 - i. If from posterior medullary artery infarction there may be large flinging movements of the arms
 - ii. Loss of vibratory and proprioceptive sense which may also occur from lesions in the thalamic VPL nucleus

Hemifacial Spasm

General Characteristics

1. Definition:
 - a. Brief irregular, clonic twitches that may build up to a sustained contraction of facial muscles that usually lasts for seconds, but may continue for minutes

Clinical Manifestations

1. Movements may begin around the eye and later spread to the lower facial muscles
2. Persists in sleep
3. Contractures are desynchronous
4. Approximately 15% of patients have bilateral involvement
5. The orbicularis oculi is most often affected first and then there is spread to the corrugator, frontalis, orbicularis oris, platysma and zygomaticus

Neuropathology

1. In the majority of patients primary hemifacial spasm (HFS) is caused by compression of the facial nerve at its root exit zone (REZ) by a branch of AICA or the 8cA

Laboratory Evaluation

1. MRI:
 - a. Demonstrates vascular loops (most often from AICA and rarely from the superior cerebellar artery)
 - b. Intraoperative stimulation of the nerve to demonstrate abnormal muscle responses (lateral spread) often simulating a facial nerve branch and its absence after successful microvessel decompression
 - c. Neurophysiologic techniques to monitor changes in nerve excitability intraoperatively include:
 - i. Facial F-wave
 - ii. Blink reflex
 - iii. Facial corticobulbar motor evoked potentials

Differential Diagnosis of Hemifacial spasm

1. Aberrant branch of AICA (or the artery itself) that intermittently compresses the VIIth nerve
2. This diagnosis is especially likely if the patient is aware of a postural trigger or if there is a position that decreases the spasm
3. Bell's palsy
4. Neoplasm of the cerebellopontine angle
5. Cranial dystonia
6. Tic

Restless Leg Syndrome (RLS)

General Characteristics

1. Possibly 5–10% of the USA population suffers restless leg syndrome; moderate to severe RLS may affect up to 2–3% of adults; childhood restless leg syndrome occurs
2. The incidence is approximately 2× higher in women

Clinical Manifestations

1. Onset is usually middle age or older
2. Symptoms become more frequent and last longer with age
3. Patients feel uncomfortable sensations in their legs particularly when sitting or lying down
4. The abnormal sensations are accompanied by an irresistible drive to move the affected extremity. Rarely, the abnormal sensations can affect the arms, trunk and head
5. Patients may constantly move the affected extremity to prevent the sensations
6. Symptoms are worse at night; there may be a symptom free period in the early morning
7. Triggering events include:
 - a. Long car trips
 - b. Sitting for prolonged periods
 - c. Long distance flights
 - d. Immobilization in a cast
 - e. Sleep deprivation
8. The frequency of attacks varies widely among individuals but in severe patients occurs more than twice a week

Neuropathology

1. The most consistent neurophysiological finding is reduction in short interval intracortical inhibition
2. Resting motor threshold, active motor threshold, amplitude of motor-evoked potentials are typically normal
3. Conflicting results have been reported for short-interval intracortical facilitation and the contralateral silent period
4. RLS after stroke that involves the pyramidal tract and basal ganglia brainstem connections have been reported
5. Associated conditions:
 - a. Dysfunction of corticostriatal thalamic motor circuits that are dependent on dopamine
 - b. Iron deficiency
 - c. Parkinson's disease
 - d. 80% of patients have periodic limb movements of sleep that is characterized by:
 - i. Involuntary twitching or jerking movements during sleep
 - ii. May occur every 15 to 40 seconds (rarely throughout the night)
 - iii. Cause awakenings and severe disruption of sleep
 - iv. Most patients with PLMS do not have RLS
 - e. Kidney failure, diabetes and peripheral neuropathy
- f. Medications:
 - i. Prochlorperazine and metoclopramide (antipsychotics)

- ii. Haloperidol and phenothiazine derivatives (antipsychosis drugs)
- iii. Antidepressants that increase serotonin
- iv. Antihistamines
- g. Pregnancy
 - i. Primarily in the last trimester; usually ceases within 4 weeks of delivery

Laboratory Evaluation

1. Blood tests to detect iron deficiency, diabetes and vitamin deficiency and other causes of peripheral neuropathy
2. Polysomnography to evaluate for sleep apnea and PLMS
3. Transcranial magnetic stimulation for evaluation of motor cortical excitability (experimental and not validated)

Dystonia

General Characteristics

1. Definition
 - a. Slow, sustained involuntary movements and postures that involve both axial and proximal muscles

Clinical Manifestations

1. Slow and axial movements (athetosis/dystonia)
2. Superimposed involuntary jerks (myoclonic dystonia)
3. Dystonic postures:
 - a. Torticollis and tortipelvis
 - b. Scoliosis and lordosis
 - c. Dropped, inverted and plantar flexed foot
 - d. Dystonic tremor:
 - i. Fast distal tremulous movements
4. Excessive contraction of antagonist muscles during a voluntary movement
5. Spreading of contractions of muscles that are not needed for a specific movement
6. Spontaneous contraction of agonist and antagonist muscles
7. Distribution:
 - a. Generalized
 - b. Segmental (two contiguous areas)
 - c. Focal (one extremity or motor group)
 - d. Multifocal (two or more body parts)
8. Generalized dystonia is most often seen in young patients
9. Focal and segmental dystonia occurs in middle age to older patients
10. The muscle groups most frequently affected are:
 - a. Orbicularis oculi
 - b. Forearm flexors
 - c. Wrist flexors
 - d. Inverters of the foot
 - e. Sternocleidomastoid
11. Specific movements are repetitive
12. Sensory tricks to inhibit or dampen the involuntary movements
 - a. Finger to the eye to block blepharospasm

- b. Finger to the forehead to block torticollis
13. Action dystonia:
 - a. Early in the course of the disorder only the muscles that are used for a movement are affected
 - b. Over time dystonia spreads to other non-used groups of muscles
 - c. The abnormal movements are exacerbated by specific activities

Neuropathology

1. Autopsies of patients with DYT1 (GAG deletions) and those without GAG deletions demonstrated:
 - a. Larger and more compacted pigmented neurons in the substantia nigra of both forms
 - b. Smaller substantia nigra neurons have been described in Lesch-Nyhan syndrome patients with dystonia
 - c. A detailed morphometric study of 13 patients' substantia nigra who suffered various dystonia subtypes revealed:
 - i. Decreased pigmented SNpc neurons versus controls
 - ii. No volumetric changes in the cell body and nuclear or nucleolar structures
 - iii. In the majority of patients tau lesions were sparse
 - iv. It has been postulated that the reduced number of pigmented neurons represents a neurodevelopmental defect. It has been pointed out that other non-dopaminergic circuits and transmitter systems such as those utilizing acetylcholine or GABA may be involved
 - v. The somatopic neuronal organization and transmitter complexity may affect specific subregions of the SNpc that may be reflected clinically (segmental involvement)
 - vi. Rare patients have demonstrated neuronal loss in the dorsal caudate nucleus and putamen; two of the patients suffered Lubag or linked recessive dystonia-parkinsonism
 - vii. Brains from patients with spasmodic torticollis and Meige's syndrome (cranial dystonia) were normal; 2 brains from patients with Meige's have demonstrated SNpc degeneration (1 patient) and one patient had brainstem angioma
 - viii. Hemidystonia patients demonstrate:
 1. Lesions in the contralateral hemisphere that affect:
 - a. The caudate nucleus
 - b. The putamen and in some patients both the putamen and the globus pallidus or thalamus
 - ix. A possible bioamine dysfunction in dystonia has been suggested
 - x. Neurophysiological dysfunction within the corticostriato-pallido-thalamic and cerebello-thalamo-cortical loops are primarily involved in dystonia

Laboratory Evaluation

1. MRI:
 - a. Lesions of the contralateral cortex, striatum and thalamus have been identified in both focal and hemidystonia
 - b. Magnetic resonance diffusion imaging in genetic forms has demonstrated:
 - i. Reduced fractional anisotropy (FA) in white matter areas adjacent to the sensorimotor cortex and in the dorsal pons
 - ii. Reduced connectivity in cerebellar projections to the ventral thalamus in both affected and carrier dystonic patients
2. PET analysis reveals:
 - a. Abnormal disease related metabolic patterns in both clinically manifesting and non-manifesting carriers
3. Neurophysiological Evaluation:
 - a. EMG studies
 - i. Phasic bursts that predominate in antagonist muscles during movement
 - ii. Voluntary effort does not modulate involuntary activity of affected muscles; it precipitates contraction of neighboring segmental musculature ("overflow phenomenon") seen in action dystonia
 - iii. Activation of passively shortened muscles (a possible exaggeration of the shortening reflex)
 - iv. An abnormality of Ia inhibitory interneurons in the spinal cord that causes simultaneous contraction of antagonistic muscles
 - v. Hyperactivity of brainstem interneurons in patients with blepharospasm is demonstrated by:
 1. Increased amplitude and duration of the R2 component of the blink reflex
 2. Increased blink reflex recovery time in patients with blepharospasm
 3. Altered vagal reflexes in patients with spasmodic dysphonia
 4. Failure of exteroceptive suppression of cervical motor neurons in patients with spasmodic torticollis
 5. A generalized failure of reciprocal and inhibitory modulation of motor activity
 6. Serum and blood analysis for secondary causes of dystonia due to diseases with known or presumed metabolic defects

Differential Diagnosis of Primary Dystonias

1. At present there are 20 distinct primary dystonias 1–4, 5a, b, 6–8, 10–13 and 15–18
2. Loci are DYT1–4, 5a, b, 6–8, 15–18
3. DYT9, DYT19 and DYT20 map to regions in close proximity to known loci of DYT8, DYT10 and DYT18
4. There are 12 autosomal dominant, four autosomal recessive and 1 linked with recessive inheritance forms of dystonia

5. This group of movement disorders comprises pure dystonias and dystonia plus syndromes as well as paroxysmal dystonias
6. Pure dystonias may have tremor
7. Dystonia plus syndromes:
 - a. Dystonia is the primary sign
 - b. May have concurrent myoclonus and parkinsonism
8. In some dyskinesias, dystonia may occur as a paroxysmal sign and may be associated with other movement abnormalities and rarely seizures
9. The disease genes of autosomal dominant dystonias include:
 - a. DYT1-gene (TOR1A)
 - b. DYT5a (GCH1)
 - c. DYT6 (THAP1)
 - d. DYT8 (PNKD1/MRI)
 - e. DYT11 (SGCE)
 - f. DYT12 (ATPIA 3)
 - g. DYT18 (SLC 2)
10. The disease genes of autosomal recessive dystonias are:
 - a. DYT5 (TH)
 - b. DYT16 (PRKRA)
11. One chromosomal recessive form:
 - a. DYT3 (TAF1)

DYT1*General Characteristics*

1. Torsion dystonia 1 is caused by heterozygous mutation in the TOR1A gene that maps to chromosome 9q34.11; AD inheritance
 - a. Encodes the ATP-binding protein torsin-A

Clinical Manifestations

1. DYT1 is an early onset primary dystonia with onset in childhood or adolescence; very rarely in adulthood
2. Older age of onset may occur among relatives of affected individuals; late onset family members may have arm dystonia manifested as writer's cramp
3. Dystonia usually has its onset in a leg (average is 9 years); if it starts in the arm the average age is 15 years
4. Foot inversion or eversion, abnormal flexion of the knee or hip
5. Difficulty with writing
6. Rarely the onset is in the neck or a cranial muscle
7. If onset is in the leg, the dystonia progresses over years, becomes less action-specific and can occur at rest
8. The dystonia spreads to the other body regions including the trunk
9. In patients whose dystonia started in an arm, progression is more variable and generalizes in approximately 50% of patients
10. Patients with onset in the neck or a cranial muscle may have variable progression
11. Variable features:

- a. 20% of DYT1 patients have dystonia of only 1 body region (usually writer's cramp)
- b. Cranial muscles are involved in 11–18% of patients
- c. Early onset brachial dystonia
- d. Isolated blepharospasm
- e. Fluctuating unilateral myoclonic dystonia
- f. Asian patients have segmental dystonia with more frequent onset of axial dystonia as compared to Caucasians
- g. Pain is uncommon in DYT1 except with torticollis
- h. Increased rate of major depression
- i. The vast majority of patients have onset prior to 26 years of age

Neuropathology (Few Autopsies)

1. Larger dopaminergic neurons
2. 4 brains have demonstrated perinuclear inclusion bodies in the midbrain reticular formation and periaqueductal gray

Laboratory Evaluation

1. MRI:
 - a. Diffusion tensor imaging (DTI):
 - i. Microstructural abnormalities of the subcortical white matter of the sensorimotor cortex and the dorsal pons (region of the superior cerebellar peduncle) suggestive of dysfunction of the cerebello-thalamocortical motor circuitry
 - b. PET evaluation: Decreased striatal D2 receptor binding
2. Differential Diagnosis of DYT1
 - a. Dopa-responsive dystonia (GCH1)
 - b. DYT6 (THAP1)
 - c. DYT25 (GNAL)
 - d. Dramatic improvement with levodopa administration is most suggestive of dopa-responsive dystonia from heterozygous mutation of the GCH1 gene which codes cyclohydrolase 1; early onset dystonia that is also responsive to levodopa is juvenile-onset Parkinson's disease from mutation of PARK2 which encodes parkin
 - e. Genetic disorders in which dystonia is prominent include:
 - i. Wilson's disease
 - ii. Huntington's disease
 - iii. Some spinocerebellar ataxias
 - iv. Rapid-onset dystonia parkinsonism
 - v. Pantothenate kinase deficiency
 - f. Acquired dystonia that includes:
 - i. Neuroleptic exposure
 - ii. Dopamine blocking agents (tardive dystonia)
 - iii. Perinatal stroke
 - iv. Traumatic brain injury
 - v. Encephalitis
 - vi. Clinical features against a diagnosis of DYT:
 1. Onset in adulthood (>40 years of age)
 2. Isolated focal or segmental cervical-cranial dystonia that includes:

- a. Spasmodic torticollis
- b. Spasmodic dysphonia
- c. Blepharospasm
- d. Oromandibular dystonia

DYT5a

General Characteristics

1. DYT5a also known as Segawa syndrome or hereditary progressive dystonia with marked diurnal fluctuation
2. Caused by mutations in the GCH1 gene that maps to chromosome 14q22¹-q22.2 that encodes the enzyme GTP cyclohydrolase 1 (GTPCH1)

Clinical Manifestations

1. Onset occurs in childhood (the average age is 6)
2. Females are 2–4 times more frequently affected than males
3. Most often onset is with equinovarus posture of the foot that disturbs gait
4. Diurnal fluctuations; symptoms are worse in the evening and improve with sleep
5. Exercise aggravates symptoms
6. Variable features:
 - a. Arm dystonia
 - b. Postural tremor of the hands
 - c. Bradykinesia
 - d. Cervical dystonia
 - e. Brisk reflexes
 - f. Striatal toe
 - g. The disorder progresses to generalized dystonia
 - h. Patients with onset in adolescence or adulthood may develop parkinsonism (bradykinesia, rigidity and postural tremor)
7. Patients with late onset may have a milder phenotype
8. Rarely patients develop depression, anxiety, sleep disruption and obsessive-compulsive disorder
9. Dramatic response to levodopa therapy

Neuropathology

1. GTP cyclohydrolase 1 (GTPCH1) is essential in the biosynthesis of tetrahydrobiopterin which is the essential cofactor for tyrosine hydroxylase, the rate-limiting enzyme in the biosynthesis of dopamine

Laboratory Evaluation

1. Decreased levels of biopterin and neopterin are found in the CSF

GTPCH1

1. Reduced GTPCH1 activity in blood cells can be demonstrated

Differential Diagnosis

1. Autosomal recessive DRD
2. Early onset torsion dystonia
3. Myoclonic dystonia

4. Hyperphenylalaninemia
5. Spastic paraplegia
6. Young adult-onset Parkinsonism

DYT6*General Characteristics*

1. DYT6 is autosomal dominant and is caused by heterozygous mutation in the THAP1 gene that maps to chromosome 8p11

Clinical Manifestations

1. Described in Mennonite families
2. Approximately 50% of patients present with cranial or cervical involvement
3. The mean age at onset in one kindred was 16 years of age
4. Dystonia may start in an arm
5. Many patients may have first symptoms in the larynx, tongue, facial muscles, or the neck
6. Most patients have some degree of progression to other body regions

Neuropathology

1. Missense, nonsense and frameshift mutations have been reported in all three exons of the gene
2. THAP1 binds to the core promoter of Torsin A and represses its expression
3. The function of the protein is unknown

Laboratory Evaluation

1. PET:
 - a. Bilateral hypermetabolism in the presupplementary motor cortex and parietal association cortices
 - b. Hypometabolism in the putamen and hypermetabolism in the temporal cortex
 - c. Decreased availability of DRD2 in the caudate and putamen. There was no difference between manifesting and non-manifesting mutation carriers
 - d. Voxel-based analysis demonstrated that the lateral putamen and right ventrolateral thalamus are primarily affected

DYT8 (Paroxysmal Non-Kinesigenic Dyskinesia 1)*General Characteristics*

1. DYT1 (Mount-Reback disease) is caused by heterozygous mutation in the myofibrillogenesis regulator-1 gene that maps to chromosome 2q35

Clinical Manifestations

1. Mount-Reback disease has autosomal dominant inheritance
2. Symptom onset is in early childhood in many kindreds
3. Attacks of paroxysmal choreoathetosis that last a few minutes, occur several times per day and are not associated with altered mental status
4. Alcohol, coffee, hunger, fatigue and tobacco are triggering factors for attacks

5. Patients with MR1 mutations have a homogeneous phenotype with earlier onset than those that do not carry the mutation
6. Premonitory sensations (focally in the limbs) are reported in approximately 40% of mutation carriers
7. Lessened during pregnancy
8. Patients without MR1 mutations differed from mutation carriers by:
 - a. Exercise as a precipitating factor
 - b. Alcohol is not precipitant
 - c. Ballismus (18%)
 - d. Seizures (23%)

Neuropathology

1. Putative function in a pathway to detoxify methylglyoxal which is present in coffee and alcoholic drinks and is also a byproduct of oxidative stress

Laboratory Evaluation

1. MRI:
 - a. Normal

DYT11 (Myoclonic Dystonia Syndrome)*General Characteristics*

1. DYT11 is caused by heterozygous mutation in the epsilon-sarcoglycan gene (SGCE) that maps to chromosome 7q21; it is autosomal dominant in inheritance

Clinical Manifestations

1. The onset is variable but may start in early childhood
2. Myoclonic jerks of proximal muscles
3. Dystonia is manifest by torticollis or writer's cramp in most kindreds; it may be the only manifestation of the disorder
4. Psychiatric disorders occur in some kindreds as does cognitive impairment
5. Symptoms are alcohol responsive
6. Tremor and jerky movements may occur in association with head, neck and arm myoclonus
7. Variable features:
 - a. Usually the myoclonus is triggered by complex motor tasks, it is rarely seen at rest
 - b. Rarely the legs and larynx can be affected
 - c. Isolated torticollis

Neuropathology

1. The only causative gene is the epsilon-sarcoglycan (SGCE) that encodes a transmembrane protein which is part of the dystrophin-associated glycoprotein complex of skeletal and cardiac muscles
2. The epsilon-sarcoglycan protein is also expressed in monoaminergic neurons, Purkinje cells, hippocampus and cortex. Its function in these areas is unknown

Laboratory Evaluation

1. MRI:

- a. Negative
- b. Genetic molecular testing confirms the diagnosis

DYT12*General Characteristics*

1. Rapid-onset dystonia-parkinsonism is caused by heterozygous mutation in the ATP1A3 gene that maps to chromosome 19q13.2
2. It encodes the alpha-3 subunit of the NaK-ATPase
3. Heterozygous mutations of the gene also cause:
 - a. Alternating hemiplegia of childhood
 - b. CAPOS syndrome
4. Inheritance is autosomal dominant

Clinical Manifestations

1. The onset is in childhood or early adulthood (range from 4–58 years)
2. Abrupt onset of dystonia and Parkinsonism (bradykinesia and postural instability)
3. A rostrocaudal gradient:
 - a. Dysarthria and dysphagia
4. Symptoms may progress over several minutes to up to 30 days and then stabilize
5. Onset may be triggered by exertion, fever, extreme heat, childbirth, excessive alcohol or stress
6. Some patients note upper limb dystonia (primarily in the hands) and cramping prior to disease onset
7. Most patients stabilize but a few suffer a second episode of clinical deterioration 1–9 years following the initial onset
8. Variable features:
 - a. Seizures
 - b. Anxiety and depression
9. Variant phenotype in infants with:
 - a. <4 years of age
 - b. Episodic hypotonia
 - c. Gait ataxia
 - d. Motor delay
 - e. Speech and swallowing dysfunction

Neuropathology

1. Several missense mutations in the sodium/potassium-transporting ATPase subunit alpha-3 protein are causative
2. The protein is essential for maintaining the electrochemical gradients of potassium and sodium across the plasma membrane

Laboratory Evaluation

1. Low homovanillic acid concentration in the CSF
2. Normal brain imaging
3. PET and SPECT demonstrate normal dopamine reuptake in dopamine transporters

DYT18*General Characteristics*

1. GLUT1 deficiency syndrome-2 (GLUT1DS2) or dystonia-

18 is caused by heterozygous mutation of the SLC2A1 gene that maps to chromosome 1p34

2. Allelic disorders include:
 - a. GLUT1 deficiency syndrome-1
 - b. Dystonia 9
 - c. Idiopathic generalized epilepsy 12
3. Inheritance is autosomal dominant

Clinical Manifestations

1. Childhood onset
2. Transient paroxysmal exercise-induced dyskinesia that includes:
 - a. Dystonia
 - b. Choreoathetosis
 - c. Affects the exercised limbs
3. Some patients have seizures, the most common of which is childhood absence epilepsy
4. Variable features:
 - a. Cognitive impairment
 - b. Hemolytic anemia (one family)
 - c. Fasting, stress, vibration may also precipitate attacks
 - d. Involuntary flexing and extending movements that alternate with athetotic twisting movements
 - e. Migraine
 - f. Abnormal head and eye movements
 - g. In one kindred seizure types include:
 - i. Absence (64%)
 - ii. GTCS without focal onset (50%)
 - iii. Complex and simple partial seizures (14%)
 - h. PED and epilepsy may improve with age in some patients
 - i. Hand tremor was documented in one family (action tremor)
 - j. A 3 generation family with exertion-induced dystonia, choreoathetosis and ballistic movements with a monocytic hemolytic anemia
 - k. Some patients improve with the ketogenic diet

Neuropathology

1. Decreased CSF glucose metabolism in corticostriate pathways from a defect in the GLUT1 glucose transporter

Laboratory Evaluation

1. Decreased CSF glucose concentration
2. Decreased glucose uptake into erythrocytes
3. EEG:
 - a. Findings are variable but include synchronous and hypersynchronous spike-wave complexes, sharp waves and rhythmic theta- and delta-activity

Other Autosomal Dominant Dystonias*DYT7 (Adult Onset Focal Primary)*

1. AD that maps to chromosome 18pter-p11.32
2. Clinical manifestations:
 - a. Adult onset of focal dystonias that include cervical dystonia, writer's cramp, dysphonia, or blepharospasm

DYT8 (Paroxysmal Non-Kinesigenic Dyskinesia)

1. Autosomal dominant that maps to chromosome 2q34
2. Clinical manifestations:
 - a. Attacks of dystonia that are precipitated by stress, fatigue, alcohol and chocolate

DYT9 (Paroxysmal Choreoathetosis with Spasticity)

1. Autosomal dominant with a locus that maps to 1p34-p22
2. Clinical manifestations:
 - a. Attacks of dystonia, episodic ataxia and paresthesias
 - b. Double vision
 - c. Attacks are precipitated by exercise, stress and chocolate
 - d. Patients demonstrate spastic paraplegia between attacks

DYT10 (Paroxysmal Kinesigenic Dyskinesia)

1. Autosomal dominant locus that maps to chromosome 16p11.2-q12.1
2. Clinical manifestations:
 - a. Dystonic attacks precipitated by sudden movement
 - b. Paroxysmal kinesigenic choreoathetosis

DYT13

1. Autosomal dominant; locus that maps to chromosome 1p36.32-p36.12.13
2. Clinical manifestations:
 - a. Early and late onset
 - b. Focal or onset in cranial cervical distribution
 - c. A focal or segmental dystonia most often in the upper limbs
 - d. Mild course

DYT14

1. Autosomal dominant locus that maps to chromosome 14q13
2. Clinical manifestations:
 - a. Early onset with gait and postural signs
 - b. Generalized dystonia
 - c. Later in disease course parkinsonism

DYT15

1. Autosomal dominant with the locus mapping to chromosome 18p11
2. Clinical manifestations:
 - a. Onset in the first or second decade with jerky movements (myoclonus) of the upper limbs, hands and axial muscles
 - b. Alcohol responsive
 - c. Dystonia of the upper limbs primarily
 - d. Incomplete penetrance

DYT20

1. Autosomal dominant that maps to chromosome 2q31
2. Clinical manifestations:

- a. Paroxysmal non-kinesigenic dyskinesia 2
- b. Attacks of involuntary movement and dystonia that occur spontaneously at rest
- c. Attacks may be precipitated by caffeine, alcohol and stress
- d. Attacks last from minutes to hours and can occur several times/day

DYT21

1. Autosomal dominant
2. Maps to chromosome 2q14.3-q21.3
3. Clinical manifestations:
 - a. Adult onset generalized or multifocal dystonia
 - b. May start as blepharospasm

DYT23

1. DYT23 is caused by heterozygous mutation in the CACNA1B gene that maps to chromosome 9q34; inheritance is autosomal dominant
2. Clinical manifestations:
 - a. Adult onset dystonia usually during the fourth and fifth decades
 - b. Torticollis and hypertrophy of the sternocleidomastoid muscles
 - c. Head and limb tremor
 - d. Cervical dystonia
 - e. Dutch kindred (3-generation):
 - i. Writer's cramp, dysphonia, torticollis
 - ii. Generalized myoclonus (2 patients)
 - iii. Other patients with myoclonus of the voice, face, trunk or limbs
 - iv. Variable features included panic attacks and hyperventilation syndrome

DYT24

1. DYT24 is caused by heterozygous mutation in the ANO3 gene that maps to chromosome 11p14
2. Clinical manifestations:
 - a. Adult onset of dystonia
 - b. Focal dystonia that affects the neck, laryngeal muscles as well as muscles of the upper extremities
 - c. Mean age of onset is 29 (range of 19 to 40 years)
 - d. Variable features:
 - i. Blepharospasm
 - ii. Voice tremor
 - iii. Head and arm tremor
 - iv. Writing tremor
 - v. Dystonic arm posturing

DYT25

1. DYT25 is caused by heterozygous mutation in the GNAL gene that maps to chromosome 18p11
2. Clinical manifestations:
 - a. Adult onset
 - b. Focal dystonia is initially in the neck

- c. The dystonia progresses to involve the face and laryngeal muscles and less often axial and extremity musculature

Autosomal Recessive Dystonia

DYT5b

General Characteristics

1. DYT5b is caused by mutations in the tyrosine hydroxylase (TH) gene that maps to chromosome 11p15.5
2. Inheritance is autosomal recessive

Clinical Manifestations

1. The clinical phenotypes comprise:
 - a. TH-deficient dopa-responsive dystonia (DRD)
 - b. TH-deficient infantile Parkinsonism with motor delay
 - c. TH-deficient progressive infantile encephalopathy (the very severe form)
2. TH-deficient DRD:
 - a. Onset is between 12 months and six years
 - b. Initial symptoms are lower-limb dystonia with an abnormal gait and difficulty walking
 - c. Diurnal fluctuation with worsening symptoms in the evening and sleep benefit
 - d. Psychomotor development is normal
 - e. Gradual progression to generalized dystonia
 - f. Some patients demonstrate bradykinesia and primarily postural tremor
 - g. Rigidity in affected extremities
 - h. Postural instability
 - i. Some patients demonstrate pyramidal signs with:
 - i. Hyperreflexia
 - ii. Extensor plantar response
 - iii. Spasticity
 - j. Rare oculogyric crisis
 - k. Excellent response to levodopa therapy

Neuropathology

1. No autopsies have been reported
2. Tyrosine hydroxylase is the rate-limiting enzyme for catalyzing the conversion of L-tyrosine to L-dopa, the precursor of dopamine
3. There is a suggestion that mutations in the promoter region may be associated with a milder phenotype

Laboratory Evaluation

1. Brain MRI is normal in DRD
2. In patients with progressive infantile encephalopathy there may be mild to moderate cerebral and/or cerebellar atrophy
3. CSF pattern:
 - a. Reduced homovanillic acid (HVA)
 - b. Normal 5-hydroxyindoleacetic acid (5-HIAA)

- c. Reduced HVA/5-HIAA ratio
- d. Reduced 3-methoxy-4 hydroxy-phenylethyleneglycol (MHPG)
- e. Normal total biopterin (BP) primarily tetrahydrobiopterin (BH4)
- f. Normal total neopterin (NP)
4. Molecular genetic testing of the coding region and the cAMP response element region

Differential Diagnosis of Tyrosine Hydroxylase (TH) Deficiency

1. GTP cyclohydrolase 1-deficient dopa-responsive dystonia (GTPCH1-deficient DRD)
2. Autosomal recessive sepiapterin reductase (SR-deficient DRD)
3. Early-onset primary dystonia
4. Early-onset Parkinsonism
5. Cerebral palsy
6. Spastic paraplegia
7. Primary and secondary deficiencies of CSF neurotransmitter metabolites

DYT16

General Characteristics

1. DYT16 is caused by homozygous mutation in the PRKRA gene that maps to chromosome 2q31.2
2. It encodes the protein kinase interferon-inducible double-stranded RNA-dependent activator

Clinical Manifestations

1. Childhood onset
2. Early signs are gait abnormalities and leg pain
3. Dysphagia and laryngeal dystonia
4. Spasmodic dysphonia
5. Torticollis
6. Upper limb dystonia
7. Orofacial dystonia
8. Speech and language impairment
9. Some patients have mild Parkinsonism

Neuropathology

1. PACT is a stress-modulated activator of interferon-induced double-stranded RNA-activated protein kinase (PKR)
2. PKR activation induces the phosphorylation of translation initiation factor eIF2alpha inhibition of protein synthesis and apoptosis
3. It is hypothesized that altered activation of PKR enhances apoptosis in dystonia cells that cause a mutation in the PKR activator protein PACT
4. Homozygous missense mutation P222L in PACT (the activator of PKR) that leads to dysfunction of the endoplasmic reticulum stress response

Laboratory Evaluation

1. Molecular genetic testing

X-Chromosome Recessive Dystonia**DYT3***General Characteristics*

1. DYT3 ("Lubag") is caused by a retrotransposon insertion in an intron of the TATA-binding protein-associated factor-1 gene TAF1 that maps to chromosome Xq13.1
2. Primarily found in the Philippine Island of Panay

Clinical Manifestations

1. The mean age of onset is early adulthood (average age of onset is the late 30s); range 12–56 years
2. Generalized dystonia occurs approximately 7 years after onset
3. Parkinsonism may occur concomitantly or precede dystonia
4. Manifestations may begin in the head and neck
5. In a large kindred Parkinsonism was reported early in approximately 1/3 of patients
6. Approximately 50% of female carriers are symptomatic; the average age of affected women is 52 years. It has been suggested that extreme X-inactivation is the cause of the disorder in women carriers

Neuropathology

1. Post-mortem evaluation in 7 male patients revealed:
 - a. Patients with dystonia demonstrated patchy areas of preserved neurons in the striosome and relative sparing of the matrix
 - b. Parkinsonian patients had:
 - i. Severe depletion of the striosomal and matrix-based pathways
 - c. Goto hypothesized that early stage disease is dominated by loss of striosomal GABA-ergic projection neurons and disinhibition of nigral dopaminergic neurons causing the hyperkinetic symptomatology. In later stages, Parkinsonism predominates; there may be greater involvement of the matrix-based projection system
 - d. Some transcripts of DYT3 may regulate the INXG and C154 genes on the opposite strand of DYT3. Mutation in DYT3 may interfere with this regulation
 - e. Atrophy of the caudate nucleus and the putamen with mild to severe neuronal loss and gliosis
 - f. Genetic sequencing of the critical region of Xq13.1 reveals:
 - i. SVA (short interspersed nuclear element, variable number of tandem repeats and Alu composite) retrotransposon insertion in an intron of the TAF1 gene
 - ii. This mutation may reduce neuron expression of the TAAF1 isoform in the caudate nucleus and interfere with transcription of many genes including those that code for the dopamine 2 receptor
 - iii. An abnormal pattern of DNA methylation in the retrotransposon of the genome from a patient's caudate that has been hypothesized to cause decreased expression of TAF1

Laboratory Evaluation

1. Molecular genetic sequencing

Differential Diagnosis of Primary Dystonia

1. Isolated dystonia (with dystonic tremor):
 - a. DYT1 (TOR1A)
 - b. DYT4 (TUBB4)
 - c. DYT6 (THAP1)
 - d. DYT16 (PRKRA)
 - e. DYT23 (C1Z1)
 - f. DYT24 (AN03)
 - g. DYT25 (GNAL)
2. Combined dystonias with parkinsonism or myoclonus:
 - a. Persistent:
 - i. DYT5 (GCH1)
 - ii. DYT11 (SGCE)
 - iii. DYT12 (ATP1A3)
 - iv. DYT3 (TAF1)
3. Paroxysmal:
 - a. DYT8 (PNKD)
 - b. DYT10 (PRRT2)
 - c. DYT18 (SLC2A1)

Secondary Dystonia*The Requirements of the Diagnosis of Primary Dystonia*

1. Isolated dystonic movements and postures without other neurologic abnormalities (may have dystonic tremor)
2. Normal perinatal and early developmental history
3. No exposure to drugs that cause dystonia
4. The medical and neurological examination and laboratory evaluation should not be linked to any etiology of dystonias
5. Abnormally rapid progression, sudden onset, hemidystonia or generalization in an adult favors a secondary cause
6. The diagnosis of secondary dystonia is made if there is deviation from the requirements of primary dystonia

Differential Diagnosis of Dystonia with a Known Metabolic Defect

1. Wilson's disease:
 - a. Kayser-Fleischer ring
 - b. Tremor, dysarthria, clumsiness of the hands and psychiatric disorder
 - c. Dystonia is a late manifestation
2. Variant of GM1 gangliosidosis:
 - a. AR GLB1 gene that maps to chromosome 3p22.3
 - b. Dystonia, upper motor neuron signs and symptoms, rigidity and ataxia
 - c. Corneal clouding
 - d. Dystonia may begin in adulthood and be restricted to a focal or segmental region
3. GM2 gangliosidosis

4. Lesch-Nyhan syndrome
5. Homocystinuria
6. Glutamic acidemia type I
7. Metachromatic leukodystrophy
8. Methylmalonic acidemia
9. Triosephosphate isomerase deficiency

Differential Diagnosis of Dystonia with Known Disorders

1. Pantothenate kinase deficiency
2. Calcification of the basal ganglia
3. Bilateral necrosis of the basal ganglia (mitochondrial cytopathy)
4. Ataxia telangiectasia
5. Neuronal ceroid lipofuscinosis
6. Neuroacanthocytosis
7. Ferritinopathy
8. Aceruloplasminemia
9. Hartnup's disease
10. Dystonic lipidosis (Niemann-Pick disease)
11. Neuronal intranuclear inclusion disease

Differential Manifestations of Disorders with Dystonia

1. Pantothenate kinase deficiency:
 - a. In approximately 25% of patients, it is the presenting feature
2. Calcification of the basal ganglia:
 - a. Disordered calcium metabolism (hypoparathyroidism and pseudohypoparathyroidism)
 - b. HIV in children
 - c. May be autosomal dominant or recessive
 - d. Dystonia is seen in combination with cognitive impairment and psychiatric disorders, seizures, spasticity, ataxia, Parkinsonism and chorea
3. Bilateral causes of striatum and/or globus pallidus necrosis:
 - a. Wilson's disease
 - b. Leigh's disease
 - c. Mitochondrial cytopathy (cytochrome oxidase deficiency)
 - d. Dystonia with striatal lucency and optic neuropathy
 - e. Hanging with survival (most often globus pallidus necrosis)
 - f. Carbon monoxide (severe globus pallidus involvement)
 - g. Cyanide poisoning, prolonged hypotension and anoxia:
 - i. Associated cortical (layer III–V) necrosis
 - ii. Purkinje cell damage
 - iii. Vth nerve nuclear involvement
 - iv. Renshaw spinal cord cell damage
 - h. Hemolytic uremia syndrome
 - i. Sickle cell disease (associated large and small vessel strokes)
 - j. Infantile striatal necrosis (following a febrile illness)

- k. Methylmalonic acidemia
 - l. Wasp sting encephalopathy
- m. Methanol (concurrent severe hemorrhagic optic neuropathy)
- n. Carbon disulphide
- o. Disulfiram intoxication

Differential Diagnosis of Dystonia in Neurodegenerative Diseases

1. Parkinson's disease
 - a. As a complication of levodopa therapy (usually > than 5 years)
 - b. Early morning plantar flexion and inversion of the foot
 - c. Rarely seen in untreated patients but does occur in the upper extremity or foot
 - d. Dystonia is very prominent in DYT6 (Segawa disease) and DYT3 ("Lubag")
2. Progressive supranuclear palsy
3. Huntington's disease
4. Ferritinopathy
5. Aceruloplasminemia
6. Pallidal degenerations
7. Machado-Joseph disease
8. Olivopontocerebellar atrophies

Differential Diagnosis of Dystonia from Structural Lesions, Toxins and Drugs

1. Perinatal anoxia:
 - a. Abnormal motor development
 - b. Onset within the first decade
 - c. May be greatly delayed > 2 decades
2. Focal lesions:
 - a. Putamen and thalamus; rarely the caudate nucleus
 - b. Cause hemidystonia contralateral to the lesion (may or may not involve the face)
 - c. Causes of hemidystonia include:
 - i. Cerebral infarction (often with resolution of the hemiparesis)
 - ii. Arteriovenous malformations
 - iii. Brain tumors
 - iv. Multiple sclerosis (paroxysmal form)
 - v. Traumatic brain injury
 - vi. Post-thalamotomy
 - vii. Chronic regional pain syndrome (CRPS); may start focally and then generalizes; always in a setting of severe pain, edema and difficulty initiating movement
 - viii. Drugs
 1. Manganese intoxication of miners and welders
 2. Often preceded by severe depression
 3. Acute dystonic reactions:
 - a. At initiation of therapy
 - b. Involves cranial and axial musculature
 - c. Oculogyric crises

- d. Resolves rapidly with intravenous anticholinergic or antihistamine IV treatment; spontaneous resolution occurs in two days
- 4. Tardive dystonia:
 - a. Chronic disorder
 - b. Follows prolonged neuroleptic use or may occur after up to three months from drug withdrawal
 - c. Focal, segmental or generalized dystonia may occur but most often the cranial and cervical muscles are involved
 - d. May respond to a degree with anticholinergic administration
 - e. Psychogenic dystonia:
 - i. More common to have true dystonia diagnosed as psychogenic
 - ii. Characteristically there is paroxysmal variation in the clinical manifestation and its severity
- 2. Focal, segmental and multifocal:
 - a. Cranial dystonia (oculo-omandibular)
 - b. Spasmodic torticollis
 - c. Writer's cramp
 - d. Spasmodic dysphonia
 - e. Musicians dystonia
 - f. Overuse syndromes
- 3. Secondary dystonias:
 - a. Metabolic defects
 - b. Neuronal degenerations
 - c. Associated with known movement disorders
 - d. Psychogenic dystonia

Focal, Segmental, or Multifocal Dystonia

- 1. Spasmodic torticollis:
 - a. General characteristics
 - i. Usually the sternocleidomastoid and trapezius muscles are most affected; the scalene muscles are often affected early
 - ii. More frequent in women than men
 - iii. Tonic or clonic contraction of neck musculature:
 - 1. Fixed and spastic deviation of the head to an awkward position (retro, latero or anterior)
 - 2. Named by the contracting sternocleidomastoid muscle
 - 3. Movements are jerky early in the course of the disease
 - 4. Sensory tricks:
 - a. Touching the forehead
 - b. Resting the back of the head on an object
 - c. Early in the course of the disorder they lessen the specific dystonia but their effect is lost with time
 - d. Pain and tension are noted in the absence of head turning (associated cervical spondylosis and disc disease)
 - e. Possibly higher incidence of postural and essential tremor
 - f. Usually progresses for approximately 5 years and then stabilizes; a small minority of patients improve
 - g. If remissions occur they are < 5 years from onset
 - h. Sustained remissions are approximately 10%
 - i. May start in the 4–5th decade; familial loss has been reported with onset
 - j. Rarely it is caused by compression of the XIth nerve by an artery (or trauma) in the posterior triangle of the neck

Differential Diagnosis of Paroxysmal Dystonia

- 1. Genetic causes:
 - a. Paroxysmal kinesigenic dystonia
 - i. PRRT2 gene; chromosome 16p11; AD
 - ii. Paroxysmal non-kinesigenic dystonia
 - 1. MRI gene; chromosome 2q35; AD
 - iii. Paroxysmal hypnogenic dystonia
 - 1. Now classified as a frontal lobe seizure disorder
 - 2. CHRNA4 gene; chromosome 20q13.33; AD
 - b. Structural lesions and drugs
 - i. Seizures
 - ii. Cerebral palsy (anoxia, intrauterine stroke)
 - iii. Multiple sclerosis
 - iv. Transient ischemia:
 - 1. Interpeduncular artery (top of the basilar)
 - 2. Thalamoperforate artery (P1 of the PCA)
 - 3. MCA branches to M1; ACA to SMA
 - v. Traumatic brain injury:
 - 1. Interruption or damage to the cortico-pallido-thalamic and cerebellothalamic motor circuitry
 - 2. 2/3 injury of the STN (hemiballismus)
 - vi. Drugs
 - 1. Tardive dyskinesias
 - 2. Acute dystonic reactions
 - vii. Metabolic causes:
 - 1. Hypoparathyroidism
 - 2. Hyperthyroidism
 - 3. Hartnup's disease
 - 4. Pyruvate decarboxylase deficiency
 - 5. Glutaric acidemia
 - viii. Rarely Parkinson's disease and supranuclear palsy

Differential Diagnosis of Dystonia by Etiology

- 1. Primary genetic dystonias

Differential Diagnosis of Torticollis

- 1. Mechanical cervical spine defects:
 - a. Rotational atlantoaxial subluxation
 - b. Spondylosis

- c. Rotary facet subluxation
- d. Spondylolisthesis
- e. Disc herniation
- 2. Klippel-Feil syndrome:
 - a. Congenital fusion of cervical vertebra (often at C4–C5)
 - b. Metameric Sprengel's deformity may be associated with elevated shoulder and scapula
- 3. Syringomyelia
- 4. Chronic regional pain syndrome:
 - a. Often initiated by cervical posterior root traction injury (C2–C4)
- 5. Posterior fossa tumor:
 - a. Dural initiation or direct trauma to C2–C4 roots
- 6. Lesions of the lenticular or caudate nucleus
- 7. Arnold-Chiari malformation:
 - a. Downward displacement of the cerebellar tonsil with traction on cervical nerve roots
- 8. Posterior pharyngeal infection:
 - a. Tonsils and adenoid involvement (Vincent's angina)
- 9. Oromandibular dystonia:
 - a. Forced dystonic mouth opening
 - b. Tongue protrusion
 - c. Mutilation of lips and tongue
 - d. Impaired swallowing due to dystonia of the pharyngeal muscles
 - e. Very prominent in DYT3 ("Lubag"-Panay Islands in the Philippines)
- 10. Writer's cramp
 - a. Dystonia of the hand and arm develops only on attempting to write
 - b. It is a pure action dystonia
 - c. Deterioration in handwriting, increased finger pressure on the writing instrument and abnormal hand postures have been described
 - d. Some patients complain of aching in the hand and fingers but actual pain is unusual
 - e. The onset is in the second to fourth decade
 - f. Symptoms start as soon as the writing instrument is grasped
 - g. Increased pressure, abnormal extension of the fingers or hyperpronation of the forearm
 - h. Over time there may be spread to other skilled motor functions
 - i. Specific action dystonias occur with:
 - i. Musicians
 - ii. Typists
 - iii. Athletes
 - iv. Any activity that requires skilled motor activity
- 11. Laryngeal dystonia (Spasmodic dysphonia)
 - a. Adductor spasm of the vocal cords
 - i. The voice is harsh and strained with a superimposed tremulous component
 - b. A minority of patients have abductor spasm of the vocal cords that causes:
 - i. Intermittent aphonia
 - ii. Breathlessness
 - iii. Sudden drops in pitch
- c. Mixed spasmodic dystonia
- d. Manifestations of all spasmodic dysphonias:
 - i. Hoarseness
 - ii. Pitch breaks
 - iii. Poor intensity range and control
- 12. Blepharospasm
 - a. Usually is initiated as an increased frequency of blinking that gradually progresses to clonic and then tonic forced eyelid closure
 - b. It is bilateral
 - c. Severity interferes with vision:
 - i. Some patients believe they are blind
 - d. Sensory tricks are common:
 - i. Dark glasses may be helpful
 - ii. Singing, talking, neck extension, reading, chewing may either increase or decrease its occurrence
 - iii. Prying one eye open breaks bilateral blepharospasm
 - e. Blepharospasm and oromandibular dystonia (Meige's syndrome)
 - i. Often associated with spasmodic torticollis
 - f. Patients with blepharospasm demonstrate other cranio-cervical involvement that includes lower facial, masticatory, lingual, pharyngeal and cervical dystonia

Myoclonus

Overview

Myoclonus is a movement disorder that manifests with sudden, brief shock-like jerks due to a brief burst of muscular activity (positive myoclonus) or from a brief cessation of ongoing muscular activity (negative myoclonus). It may originate from several levels of the neuraxis which includes the cortex, basal ganglia, brainstem (nucleus gigantocellularis) and spinal cord. Movements may involve small muscles or the entire body and may be discrete and non-random. They are produced by a brief muscle contraction and in some instances are precipitated by sensory stimulation. Rhythmic myoclonus is most often caused by brainstem or spinal cord disease. Positive myoclonus is generally more common than negative myoclonus and is most often caused by toxic-metabolic disorders. Both may occur concomitantly in the same illness.

Myoclonus is classified in several ways. It may be focal, multifocal or generalized. If classified by provoking factors it is spontaneous or reflex. Anatomically its source is cortical, subcortical, spinal or peripheral. Its classification has been proposed by activity in which it occurs: 1. postural 2. during action or 3. at rest. More than one form of myoclonus may occur in a given patient.

Physiological Classification of Myoclonus*Cortical Myoclonus***General Characteristics**

1. Cortical myoclonus is commonly encountered in both out-patient and hospital settings

Clinical Manifestations

1. Primarily affects the distal upper limbs and face (large cortical representation of these body regions)
2. It may be focal, multifocal, or generalized due to intracortical and transcallosal spread
3. It most often occurs with action and affects speech and gait
4. It is stimulus sensitive, most frequently to touch but has been described with visual stimuli
5. In cortical myoclonus, patients may have both positive and negative myoclonus which may manifest independently or concomitantly
6. Prolonged cortical myoclonus that lasts for days or weeks is a rare form of focal epileptic status

Neuropathology

1. Focal cortical myoclonus is most often caused by an underlying lesion that produces hyperexcitability and includes:
 - a. Cerebral vascular pathologies (stroke, hemorrhage or malformation)
 - b. Post-hypoxic myoclonus (the Lance-Adams syndrome)
 - c. Progressive myoclonic epilepsies
 - d. Progressive myoclonic ataxias
 - e. Neurodegenerative diseases

Laboratory Evaluation

1. MRI:
 - a. Identifies the cortical pathology
 - b. EEG
 - c. Somatosensory evoked potentials
 - d. Evaluation of the neurodegenerative process
 - e. Molecular genetic analysis

*Negative Myoclonus (NM)***General Characteristics**

1. Is a sudden interruption of ongoing muscle contractions
2. It may be cortical or subcortical in origin

Clinical Manifestations

1. A non-specific shock-like involuntary jerky movement
2. If the trunk or lower extremities are involved the patient may fall
3. Epileptic negative myoclonus:
 - a. Interruption of tonic muscle activity
 - b. Time-locked to an epileptic EEG abnormality without evidence of antecedent positive myoclonus
 - c. It occurs in symptomatic and idiopathic epilepsy
 - d. It occurs in association with other types of seizures such as partial motor seizures (often of the Rolandic type), absence or atonic seizures

- e. It is never an isolated sign
- f. It may have a subcortical origin
- g. Lance-Adams syndrome:
 - i. Most often seen as a complication of successful cardiopulmonary resuscitation
 - ii. Associated with action myoclonus
 - iii. May affect the trunk and lower extremities that cause patients to fall
 - iv. May develop days or weeks after the event
 - v. There is no myoclonus at rest or during sleep
 - vi. There is no consistent correlation with EEG abnormalities
 - vii. PET evaluation demonstrates:
 1. Increased glucose metabolism in the pontine tegmentum, mesencephalon and ventrolateral thalamus
 2. SPECT analysis has demonstrated hypoperfusion of the temporal lobe
 3. Serotonin and GABA acid are thought to be the involved neurotransmitters
- h. Asterixis:
 - i. Subcortical origin
 - ii. Occurs in toxic metabolic encephalopathies
 - iii. Most often it is bilateral and rhythmic
 - iv. Unilateral asterixis has been described with thalamic and cortical lesions

*Subcortical Myoclonus***Non-Segmental Subcortical Myoclonus**

1. General characteristics:
 - a. Hyperekplexia and reticular reflex myoclonus are classic examples of brainstem myoclonus
 - b. Myoclonic dystonia and drug-induced myoclonus have no correlation with cortical myoclonic jerks and are therefore postulated to have a subcortical origin
2. Clinical manifestations of brainstem myoclonus:
 - a. Generalized jerks
 - b. Sensitivity to auditory stimuli
 - c. The two major types of brainstem myoclonus are:
 - i. The startle response that is physiologic or can be pathologic as in hyperekplexia
 - ii. Reticular reflex myoclonus

Physiologic Startle Response

1. Triggered by an unexpected stimulus
2. Sensitivity to somatosensory stimuli applied to the head, face and upper chest as well as visual stimuli
3. Places the body into a defensive position
4. EMG activity demonstrates an orderly spread of activity that starts in the sternocleidomastoid muscles and then engages the face, trunk and limbs (brainstem and spinal cord spread)
5. Proximal and distal muscles are involved synchronously and bilaterally that cause:
 - a. Brief, shock-like movements
 - b. Grimacing, arm abduction and flexion of the neck, trunk, elbows, hips and knees

Hyperkplexia

1. General Characteristics
 - a. Hyperkplexia may be caused by heterozygous, homozygous, or compound heterozygous mutation in the GLPA1 gene that maps to chromosome 5q33.1. Both AD and AR inheritance occurs
2. Clinical manifestations:
 - a. Congenital form:
 - i. Episodic and generalized stiffness after birth that subsides during the first years of life
 - ii. Apnea attacks
 - iii. Delayed speech
 - iv. Cognitive impairment
 - v. Excessive startle reflexes to unexpected stimuli (particularly auditory or tactile)
 - vi. Persistent startle attacks throughout life
 - vii. Increased incidence of umbilical hernia
 - b. Adult form:
 - i. Forced eye closure
 - ii. Rising of bent arms over the head
 - iii. Flexion of the neck, trunk, elbows, hips and knees
 - iv. Consciousness is maintained throughout the episode which distinguishes these episodes from seizures
 - v. Nocturnal myoclonus
 - vi. Falling with episodes
3. Neuropathology:
 - a. Loss of motor neuron inhibition due to mutation in the alpha 1 subunit of the glycine receptor
 - b. Other causes of hyperkplexia are brainstem encephalitis, vascular lesions and multiple sclerosis
4. Laboratory evaluation:
 - a. In some patients, EMG demonstrates contiguous activity at rest with normal motor unit action potentials which are abolished by diazepam (during episodes)
 - b. In one kindred, electrophysiological studies demonstrated a prominent C response 60–75 ms after median and peroneal nerve stimulation; it was hypothesized that hyperactivity of long-loop reflexes is responsible for the increased startle response

Brainstem Reticular Myoclonus

1. General characteristics:
 - a. A rare generalized myoclonus
2. Clinical manifestations:
 - a. Spontaneous myoclonus
 - b. Sensitivity to somatosensory stimuli applied to the distal limbs rather than the mantle or face
3. Neuropathology:
 - a. Post-hypoxic encephalopathy
 - b. Brainstem encephalitis
 - c. Ischemia
4. Laboratory evaluation:
 - a. MRI (patient was born after 35 weeks of gestation) with severe myoclonus

- i. High intensity lesions in the Rolandic area of the cortex, the thalamus, basal ganglia and brainstem
- ii. MRI in follow up at 1 month demonstrated great improvement of the pontine lesion as the patient was remitting from the myoclonus

Segmental Subcortical Myoclonus*Palatal Myoclonus***General Characteristics**

1. Essential palatal myoclonus (EPM) or symptomatic palatal myoclonus is classically thought to occur from a lesion in the Guillain-Mollaret triangle. The triangle comprises connections between the dentate nucleus, red nucleus and the inferior olivary nucleus

Clinical Manifestations

1. The palatal myoclonus is rhythmic (1–2 Hz) contractions of the tensor veli palatini muscle
2. An audible click may be heard by the patient from repetitive opening and closing of the eustachian tube in essential palatal myoclonus (EPM). It remits in sleep
3. In symptomatic palatal myoclonus:
 - a. There may not be clicking and it may persist during sleep
 - b. SPM occurs more frequently than EPM

Neuropathology

1. Lesions that cause symptomatic palatal myoclonus include:
 - a. Vascular disease (stroke)
 - b. Multiple sclerosis
 - c. Brainstem tumors
 - d. Progressive ataxia palatal tremor syndrome (PAPT)
 - i. May be sporadic or familial
 - ii. Marked brainstem and spinal cord atrophy
 - iii. No olivary hypertrophy
 - iv. Some familial patients with PAPT have adult onset Alexander disease from mutation of the GFAP (glial fibrillary acidic protein) gene
 - v. AD neuroferritinopathy due to ferritin light chain (NFL) gene mutation may cause palatal myoclonus
 - vi. Lesion-induced disease causes olivary hypertrophy

Laboratory Evaluation

1. MRI
 - a. Identifies structural lesions of Mollaret's triangle
 - b. Olivary hypertrophy

*Spinal Myoclonus***General Characteristics**

1. Most often secondary to a spinal cord structural lesion
2. Reflects the segmental organization of the spinal cord

Clinical Manifestations

1. May persist in sleep

2. Present at rest
3. May or may not be stimulus-sensitive
4. Affects one or a few contiguous myotomes
5. May occur irregularly or appear to be quasi-rhythmic

Neuropathology

1. Syringomyelia
2. Autoimmune causes of myelitis
3. Spinal cord trauma
4. Vascular malformations
5. Malignancy

Laboratory Evaluation

1. MRI:
 - a. Evaluates spinal cord structural lesions
2. EMG:
 - a. Motor unit action potential discharges of 1–2 per minute to 100–200 per minute
 - b. Myoclonic bursts may last up to 1000 ms

Propriospinal Myoclonus

General Characteristics

1. Propriospinal myoclonus affects spinal segments that are connected by propriospinal pathways rostrally and caudally from a spinal generator

Clinical Manifestations

1. Axial flexion jerks that involve the neck, trunk, and hips
2. It is initiated from a specific myelomere and then spreads to contiguous spinal segments rostrally and caudally
3. It most often occurs spontaneously but can be elicited by tapping the abdomen or eliciting deep tendon reflexes
4. It is exacerbated in the supine position
5. It may be exacerbated in sleep-wake transition

Neuropathology

1. Propriospinal myoclonus has been described with cervical and thoracic trauma, spinal cord tumor, and myelitis. In a significant number of patients, no clear etiology may be determined. It is often labeled as psychogenic

Laboratory Evaluation

1. MRI:
 - a. Specific spinal cord lesions; recently patients have been studied with diffusion tractography
2. EMG:
 - a. Polymyography which may delineate the generator muscle, the extent of propagation through propriospinal pathways, and slowed spinal conduction velocity from the latencies of the EMG bursts
3. Bereitschaftspotentials have been documented in some patients with a psychogenic etiology

Differential Diagnosis of Asterixis

1. Hepatic failure

2. Renal failure
3. Respiratory failure
4. Acidotic states:
 - a. Diabetic ketoacidosis
 - b. Poisoning (large anion gap)
5. Hyperosmolar states:
 - a. Usually a very high blood sugar (1500–2000 mg%); non-ketotic diabetic ketoacidosis
 - b. Severe hyperlipidemia

Differential Diagnosis of Spinal Myoclonus

1. Hyperosmolar states (most commonly non-ketotic diabetic ketoacidosis)
2. HZ infection
3. Trauma (spinal cord)
4. Paraneoplastic syndrome
5. HS
6. HIV
7. Spinal arteriovenous malformations
8. Arteriography of thoracic intercostal arteries

Differential Diagnosis of Propriospinal Myoclonus

1. Spinal cord tumor
2. Demyelinating disease
3. Viral myelitis
4. Alpha-interferon therapy (renal cell carcinoma)
5. Spinal anesthesia
6. Cervical hemangioblastoma

Peripheral Myoclonus

General Characteristics

1. Hemifacial spasm is the most common form

Clinical Manifestations

1. Rhythmic or quasi-rhythmic jerks

Neuropathology

1. Plexus, nerve or root lesions are causative; rarely described with anterior horn cell disease
2. Almost universal myoclonus with longstanding CRPS I and II (>1 year); associated neurogenic inflammation, edema, hyperalgesia to mechanical and thermal stimuli; frequently seen in a mirror distribution

Myoclonus Classification by Etiology

Physiologic Myoclonus

General Characteristics

1. Occurs in normal individuals

Clinical Manifestations of Sleep Myoclonus

1. Sleep is the most common cause of physiologic myoclonus

- a. Sudden jerks during sleep or sleep transition states
- b. Massive myoclonic jerks (hypnic)
- c. Partial jerks:
 - i. Multifocal
 - ii. Affects only distal musculature
- d. Hypnic jerks:
 - i. Affects the trunk and proximal extremities
 - ii. May be generalized
 - iii. May be noted prior to a major motor seizure
 1. May increase 1–2 weeks prior to a major motor tonic-clonic seizure
- e. Nocturnal myoclonus:
 - i. Repetitive stereotyped dorsiflexion of the toes and foot
 - ii. Flexion of the knees and hip
 - iii. May be associated with restless leg syndrome
 - iv. Occurs during non-REM sleep
 - v. Lasts 1.5–2.5 seconds
 - vi. Increased incidence in patients with daytime drowsiness or insomnia

Other Forms of Physiologic Myoclonus

1. Hiccough (diaphragmatic myoclonus)
2. Provoked by anxiety or exercise

Essential Myoclonus (Myoclonus Dystonia)

General Characteristics

1. Myoclonus is the sole manifestation or the major feature of the disorder
2. Patients suffer some disability
3. The myoclonus may be hereditary or sporadic

Clinical Manifestations (DYT11)

1. Inheritance is AD; 50% of patients have mutations in the epsilon-sarcoglycan gene that maps to chromosome 7q21
2. The disorder is most often inherited paternally with variable penetrance
3. Onset is in childhood
4. “Lightning jerks” (myoclonic) in association with mild dystonia
5. No other neurologic deficits
6. A subset of patients have anxiety, depression, and obsessive-compulsive disorder
7. Myoclonus and dystonia:
 - a. Affects the head, neck and arms
 - b. Rarely there is prominent leg involvement with falls
 - c. Dramatic response of the myoclonus to alcohol
 - d. Minimal stimulus sensitivity

Neuropathology

1. A putative subcortical myoclonus generator that involves the cerebellum
2. Subtle metabolic increases in the superior parietal cortex suggests this as the underpinning of the dystonic component (FDG)

Laboratory Evaluation

1. [¹⁸F]-fluorodeoxyglucose PET evaluation:
 - a. Increased metabolism in the inferior pons and posterior thalamus
 - b. Reduced metabolism in the ventromedial prefrontal cortex
 - c. Increased metabolism in the parasagittal cerebellum
2. Cortical somatosensory evoked potentials are normal

Epileptic Myoclonus

General Characteristics

1. Definition:
 - a. Disorders in which myoclonus occurs in the setting of epilepsy
2. Epileptic myoclonus may be positive or negative (lapse of postural tone)
3. Epileptic myoclonus is associated with generalized epileptiform EEG activity, but the myoclonus itself may be focal, segmental, or generalized
4. May occur as one component of the seizure or as its only manifestation
5. Myoclonus may be one seizure type among several in the individual patient

Clinical Manifestations

1. Older children and adolescents:
 - a. Photosensitive epileptic myoclonus
 - b. Myoclonic absences
 - c. May be associated with primary generalized epilepsy
2. Adults:
 - a. A proportion of adults with primary generalized epilepsy have morning myoclonic jerks
 - b. Myoclonus may be interictal in primary generalized epilepsy
 - c. Myoclonic jerks increase (particularly nocturnally) in 25% of patients prior to seizures
 - d. As a component of epilepsy:
 - i. Isolated epileptic myoclonic jerks
 - ii. Photosensitive myoclonus
 - iii. Stimulus-sensitive myoclonus
 - iv. Epilepsia partialis continua
 - e. Focal myoclonus can occur in lesional epilepsy from infection, vascular disease trauma, and tumor

Neuropathology (Causes of Myoclonic Epilepsy)

1. Childhood myoclonic epilepsy:
 - a. Infantile spasms
 - b. Lennox-Gastaut syndrome
 - c. Aicardi syndrome
 - d. Benign familial myoclonic epilepsy
 - e. Myoclonic epilepsy of Janz
2. Adult myoclonic epilepsy:
 - a. Progressive myoclonic epilepsy of Unverricht-Lundborg (ULD) (Baltic myoclonus)

- b. Lafora body disease
- c. Ceroid lipofuscinosis
- d. Tay-Sachs GM2 gangliosidosis
- e. Sialidosis
- f. Familial cortical tremor (benign autosomal dominant familial myoclonic epilepsy (BADFME))
- g. Mitochondrial disease
- h. DRPLA

Secondary Myoclonus

General Characteristics

1. Myoclonus that occurs in the setting of an underlying neurological or non-neurological disorder
2. The most common form of myoclonus
3. The major categories of etiology include:
 - a. Post-hypoxic
 - b. Drug-related
 - c. Toxic-metabolic
 - d. Lesions of the CNS (central nervous system)
 - e. Neurodegenerative disease
 - f. Hereditary metabolic diseases

Clinical Manifestations

1. Symptomatic myoclonus may be cortical, focal or multifocal, is sensitive to stimuli, and may be associated with asterixis and brainstem reticular myoclonus

Neuropathology

1. Metabolic abnormalities:
 - a. Renal failure
 - b. Hepatic failure
 - c. Respiratory failure
 - d. Electrolyte abnormalities
 - e. Acidosis or alkalosis
 - f. Hypoxia
 - g. Hyperosmolar states
2. Endocrine abnormalities:
 - a. Hashimoto's encephalopathy
 - b. Hyperthyroidism
 - c. Hypoglycemia
3. Vitamin deficiency:
 - a. Vitamin E deficiency
 - b. Thiamine deficiency
4. Myoclonus due to toxic-metabolic causes is most often associated with ataxia, seizures, and altered mental states
5. Toxins:
 - a. Alcohol and its withdrawal
 - b. Following dialysis (possible aluminum toxicity)
 - c. Methyl bromide
 - d. Gasoline sniffing (huffer's syndrome)
6. Post-anoxic myoclonus (Lance-Adams syndrome)
 - a. Severe hypoxia from cardiac arrest and resuscitation, respiratory arrest
 - b. May have delayed onset

- c. Myoclonus is most often cortical and multifocal, but may be associated with asterixis and reticular reflex myoclonus
- d. Action myoclonus
- e. Exaggerated startle reflex
- f. Seizure (some patients)
- g. Cognitive impairment (some patients)
7. Myoclonus of the progressive myoclonic epilepsies manifests as:
 - a. Multifocal involvement
 - b. Involves the distal extremities and face
 - c. Is provoked by posture or action
 - d. May be triggered by touch, noise, or light
 - e. Often has associated severe action myoclonus
8. Action myoclonus renal failure syndrome:
 - a. Caused by mutation of the SCARB2 gene that encodes liposomal integral membrane protein-2 (LIMP-2); inheritance is autosomal recessive (AR)
 - i. Onset is in early adulthood (age 17–26 years)
 - ii. Initial tremor that is followed by action myoclonus
 - iii. Infrequent seizures
 - iv. Cerebellar ataxia
 - v. Progression from proteinuria to renal failure
9. Progressive myoclonic ataxias (Ramsay Hunt syndrome)
 - a. Prominent myoclonus and ataxia
 - b. Seizures and cognitive impairment are less prominent
 - c. The progressive myoclonic ataxias include:
 - i. Celiac disease
 - ii. Some mitochondrial cytopathies
 - iii. Vitamin E deficiency
 - iv. Some patients with Unverricht-Lundborg disease
10. Neurodegenerative diseases:
 - a. Cortical myoclonus occurs in approximately 15% of patients with Lewy body disease and Parkinson's disease dementia
 - b. Multiple system atrophy:
 - i. May demonstrate small amplitude myoclonic movements of the outstretched fingers (polymyoclonus)
 - ii. The myoclonus is stimulus sensitive and increases with movement
 - iii. A cortical origin has been demonstrated by back-averaging
 - iv. May have "giant" somatosensory potentials
 - c. Myoclonus is demonstrated in 50% of patients with corticobasal degeneration:
 - i. It occurs in the affected arm
 - ii. Early in the course of the illness, it is repetitive and rhythmic in attempted movement or often with somatosensory stimulation. It may later occur spontaneously. There is associated apraxia, rigidity, dystonia, and the alien hand in the affected extremity
 - iii. It has a putative cortical origin

- d. Huntington's disease:
 - i. Myoclonus may occur in patients with a juvenile onset and in those with longer CAG repeats
- e. Alzheimer's disease may demonstrate multifocal myoclonus in its middle or late stages. In early-onset genetic forms it occurs earlier
- f. Myoclonus is prominent in sporadic, familial, and new variant Creutzfeldt-Jakob disease:
 - i. Early in the course of the disorder, myoclonus is limited and sporadic. Later in the illness it becomes generalized and rhythmic (0.6–1.5 Hz)
- g. Psychogenic myoclonus is characterized by:
 - i. Spontaneous occurrence or following a trauma
 - ii. It may be restricted to a few muscles or be generalized
 - iii. Distractible
 - iv. Inconsistent over time
 - v. Sudden onset and offset
 - vi. Day-to-day variability

Laboratory Evaluation

1. Routine evaluation:
 - a. Electrolytes, glucose, liver, renal and thyroid function
- b. MRI:
 - i. Brain and spinal cord imaging
- c. EEG:
- d. Additional evaluation depending upon the history and examination:
 - i. CSF
 - ii. Paraneoplastic antibody panel
 - iii. Genetic evaluation
 - iv. Enzyme activity assays

Neurophysiology

1. Electrophysiological tests are helpful in determining if the myoclonus is cortical, subcortical, or spinal
2. An EMG that determines duration, distribution, and stimulus sensitivity of the affected muscles
3. EEG-EMG back-averaging
4. Averaging and recording somatosensory evoked potentials (SSEPs)

Tic Disorders

General Characteristics

1. Definition: repetitive intermittent stereotypic movements that include the following features:
 - a. Sudden and rapid
 - b. Predominantly clonic
 - c. Temporarily suppressible for variable lengths of time
 - d. Preceded by a strong urge to make the specific movement
2. Spectrum of tics:
 - a. Simple blinks or jerks
 - b. Complex coordinated movements and vocalizations:
 - i. Clonic
 - ii. Choreic
 - iii. Dystonic

Clinical Manifestations

1. Simple motor tic: one group of muscles is involved
 - a. The movement often starts around the eyes or mouth, then spreads to the neck and shoulders, and then generalizes
 - b. The tic or simple movement may consist of:
 - i. Eye blinking
 - ii. Nose twitch
 - iii. Jerking extension of the head
 - iv. Shoulder shrug
2. Complex motor tic: a stereotypic series of movements that involves different groups of muscles; a coordinated series of movements that includes:
 - a. Neck turning, snorting and hand movements
 - b. Linguistically meaningful utterances
3. Chronic tic
4. Tonic or dystonic:
 - a. Slower in onset
 - b. Prolonged
5. Vocal tics:
 - a. Motor tics that involve respiratory, laryngeal, pharyngeal, oral and nasal musculature
 - b. Complex vocalizations:
 - i. Coprolalia
 - ii. Echolalia
6. Premonitory sensations:
 - a. Frequently present
 - b. Occur in the shoulder girdle, palms, midline abdomen, ventral thighs, feet, and eyes
 - c. The abnormal movement may relieve the provoking sensation. These are voluntary movements, whereas in other hyperkinetic movement disorders (the movements) are involuntary
 - d. Disturbed sleep patterns (some patients)
 - e. Tics are variably present during sleep

Neuropathology

1. In Gilles de la Tourette syndrome there may be caudate and putamen atrophy and cortical thinness
2. Most tic disorders have negative studies
3. Dopaminergic hypothesis is supported by:
 - a. DA receptor antagonists are effective in dampening tics
 - b. Tics are exaggerated by agents that enhance dopamine neurotransmission (for example, amphetamines)
4. Recent MRI (fMRI/PET) activation studies reveal:
 - a. Overactivation of prefrontal and premotor cortices including the supplementary motor cortex
 - b. Resting state functional connectivity studies reveal:
 - i. Abnormal connectivity of cortico-subcortical circuits
 - ii. Abnormalities in the limbic-cortico-basal ganglionic loops that include altered baseline neuronal activity patterns and specific tic-related movements
5. Deep brain stimulation has been utilized to stimulate the globus pallidus internus, the thalamic motor nuclei, and the nucleus accumbens with success

Laboratory Evaluation

1. MRI:
 - a. Specific deficits have been detected in GTS (detailed below)

Gilles de la Tourette Syndrome (GTS)*General Characteristics*

1. There are mutations in several genes that cause Gilles de la Tourette syndrome. Linkage to:
 - a. Chromosomes 3q, 4q, 5, 7p21, 7, 11 and 17q25 have been established

Clinical Manifestations

1. Childhood onset (usually prior to age 22)
2. Simple or complex motor tics
3. Vocalizations:
 - a. Sniffing, throat clearing, spitting
 - b. Complicated motor activity:
 - i. Jumping, kicking, bizarre gait
4. Coprolalia (obscene language)
5. Coprapraxia (obscene gesturing)
6. In severe GTS:
 - a. Elaborate sequential multiple complex movements
 - b. Echolalia and coprolalia
7. Mild GTS:
 - a. Tics are primarily in the face
 - b. Minor vocalizations
8. Associated disorders:
 - a. Attention deficit hyperactivity disorder
 - b. Obsessive compulsive disorders
 - c. Behavior disorders

Neuropathology

1. Structural changes of clinical phenotypes of GTS:
 - a. Determined by 3T high resolution T1-weighted images
 - b. Cortical thickness measurements
2. Patients with GTS and simple tics:
 - a. Cortical thinning was demonstrated in the primary motor cortex
3. Patients with GTS that manifested both simple and complex tics:
 - a. Cortical thinning extended into premotor, prefrontal and parietal areas
4. In patients with GTS and associated obsessive compulsive disorder:
 - a. Reduced cortical thickness in the anterior cingulate cortex
5. Altered hippocampal morphology
6. Decreased volume of the putamen and caudate nuclei have been reported
7. Local field potentials (3 patients that underwent DBS):
 - a. Thalamic synchronization and thalamocortical cross-coherence was noted in time-locked and prior to onset of spontaneous motor tics

8. Recording from 3 patients that were not time-locked to motor tics:
 - a. Increased intrathalamic coherences in the 1–8 Hz frequency band was noted
9. Spontaneous tics in GTS are preceded by repetitive coherent thalamocortical discharges
10. Thalamic recordings from patients with GTS reveal:
 - a. Power in low-frequency oscillations (2–15 Hz) is higher than power in high frequency oscillations (>45 Hz)
 - b. Activity in gamma band increases with patient improvement

Laboratory Evaluation

1. MRI:
 - a. As noted above
2. Functional:
 - a. Overactivation of prefrontal and premotor cortices including SMA
 - b. Abnormal connectivity of cortico-subcortical motor circuitry
3. CSF HVA:
 - a. Reduced baseline and turnover
 - b. D1 and D2 receptor binding:
 - i. Inconsistent bindings or minimal changes
 - c. Normal noradrenalin levels in the cortex and basal ganglia
4. MicroRNA (miR-H29) is underexpressed in GTS patients

Differential Diagnosis of Tic Disorders

1. Drugs:
 - a. Levodopa
 - b. Neuroleptics
 - c. Carbamazepine
 - d. Phenytoin
 - e. Lamotrigine
 - f. Phenobarbital
2. Basal ganglia diseases:
 - a. Neuroacanthocytosis
 - b. Encephalitis lethargica
 - c. Vascular disease
3. Toxins:
 - a. Carbon monoxide
 - b. Carbon disulfide
4. Trauma
5. Gilles de la Tourette syndrome
6. Obsessive compulsive disorders
7. Attention deficit disorder

Exaggerated Startle Reflexes*General Characteristics*

1. Syndromes with exaggerated startle can be divided into 3 major categories:
 - a. Hyperekplexia
 - b. Stimulus induced disorders
 - c. Neuropsychiatric disorders

Clinical Manifestations

1. Hyperekplexia:
 - a. An exaggerated motor startle reflex
 - b. Combined with stiffness
 - c. Mutations in the gene that encodes the glycine receptor
 - d. Preserved consciousness distinguishes it from startle epilepsy
 - e. Clonazepam responsiveness
2. The jumping Frenchmen of Maine:
 - a. Described in French Canadian lumbermen from the Moosehead Lake region of Maine; many come from the Bearce region of Quebec
 - b. The condition is often familial
 - c. A sudden sensory stimulus elicits an abnormal reaction while a sudden quick command elicits an appropriate response
 - d. The words of command would often be echoed (by the patient)
 - e. Onset ranges from 12–20 years of age
3. Latah:
 - a. A culture-specific startle syndrome described from Indonesia and Malaysia
 - b. Startle response with vocalizations and echolalia
 - c. Late behavioral response

Neuropathology

1. Two phases in the startle response have been described:
 - a. A short latency motor startle initiated from the lower brain stem (>100/120 ms)
 - b. A second phase:
 - i. Influenced by psychological factors (the “orienting reflex”)
 - ii. 100/120–1000 ms

Laboratory Evaluation

1. EMG:
 - a. Evaluates recruitment pattern latency and habituation
2. EEG:
 - a. Evaluates myoclonus

Painful Legs and Moving Toes Syndrome*General Characteristics*

1. Most often affects the lower extremities but may also be seen in the arm and fingers
2. Most often occurs in middle-aged women (66% in one large series)

Clinical Manifestations

1. Pain is more distressing to the patients than the chronic wiggling movement of the toes
2. Pain is most frequently described as neuropathic (lancinating, burning, tingling)
3. The initial movements start in one limb and then become bilateral

Neuropathology

1. Most often associated with a radiculopathy or at a peripheral nerve level that may induce a generator at the spinal cord or brain stem level from maladaptive neuroplasticity

Laboratory Evaluation

1. MRI:
 - a. Brain and spine to rule out a spinal lesion
2. EMG:
 - a. MUAP discharge is concomitant with digit movements. They are irregular or semi-rhythmic microphasic bursts with muscle contraction. Bursts duration (40 milliseconds to two seconds). The rates of motor unit discharge are from 1.5 to 30 Hz

Differential Diagnosis of Hyperkinetic Movement Disorders

The hyperkinetic movement disorders are the choreas, myoclonic disorders, tics, some dystonias and tremors. The diagnostic difficulty most often is not in distinguishing the categories, but in correctly diagnosing the entities within a specific category.

Huntington's disease is probably the most common hereditary chorea that will be encountered. The severity of the dementia, choreatic eye movements and lurching gait are dramatic. Family history at times is difficult to obtain, but when elicited is clearly autosomal dominant.

Sydenham's chorea is not hard to diagnose in childhood (although now rare in developed countries). As an adult it may be associated with old rheumatic heart disease, is often familial, and may not have an antibody response to streptococci. Rarely, it is associated in an adult with Jaccoud's arthritis. Autoimmune causes of basal ganglia disease both from infection and cancer are being increasingly defined in both children and adults. Benign familial chorea is not associated with cognitive decline and has a normal lifespan.

Medications, particularly D2 agonists, anticonvulsants, steroids and neuroleptics cause chorea. “Crack dancing” is not unusual. Patients that have chorea on birth control pills often returned with pregnancy. As noted earlier, many systemic diseases, particularly SLE with antiphospholipid antibodies, hyperthyroidism and metabolic derangements such as renal failure are associated with chorea.

Post-pump chorea and CHAP syndrome (choreoathetosis, orofacial dyskinesia, hypotonia and pseudobulbar palsy) declare themselves by the circumstances. However, hypoxia induced movement disorders may have a delayed onset.

Hereditary diseases in which chorea may be a component of the symptom complex all have striking seminal features exemplified by: Niemann-Pick type 2C (failure of vertical gaze), Pelizaeus-Merzbacher (Nystagmus), Wilson's disease (Kayser-Fleischer ring), Lesch-Nyhan syndrome (mutilated lower lip), ataxia telangiectasia (ataxia and scleral telangiectasia), the mitochondrial encephalopathies

(hearing loss, short stature, cardiomyopathy) and paroxysmal kinesigenic choreoathetosis (chorea and dystonia). Neuroacanthocytosis, Huntington's disease-like 2, PANK2 and Bassen-Kornzweig all have a complex of akinetic rigid features, tics, seizures and rarely vertical gaze deficits. DR-PLA also has a gamut of other movement disorders and seizures, cognitive dysfunction as well as acanthocytes on blood smear.

Hemichorea is most often seen with congenital disease of the striatum (severe hemiplegia) with atrophy of the affected side. Infarction of the thalamus (thalamoperforate artery), trauma, post-VIM thalamotomy for tremor, hemorrhages and tumor or vascular malformation are causative.

Hemiballismus is an instant diagnosis. The proximal flinging movements require the arm to be restrained (often under the belt). Usually it is secondary to infarction of the interpeduncular artery from the top of the basilar or occlusion of the P1 segment of the PCA that infarcts the thalamoperforate artery.

Tardive dyskinesias almost always have an oral lingual buccal component. The extremities, axial musculature and diaphragm may develop rhythmic movements over time. Akathisia, dystonic sustained movements (tardive dystonia) as well as facial dystonia, blepharospasm, mandibular dystonia and neck dystonia occur.

Neuroleptic induced oculogyric crisis (formerly common with von Economo's encephalitis) associated with myoclonus and tremor is encountered.

Abdominal dyskinesias usually occur after trauma and may be difficult to distinguish from propriospinal myoclonus. The clue is surgery in the former and exacerbation by the prone position and progressive waves of spreading axial myoclonus in the latter.

Athetosis is immediately recognized by its slow, sinuous writhing quality that primarily affects distal musculature. Pseudoathetosis is an updrift of the outstretched upper extremities with sinuous "piano playing" finger movements. It is usually seen in the context of congenital stroke, birth trauma, anoxia, kernicterus or Wilson's disease.

The dystonias are easily diagnosed because of the obvious abnormally held postures. The features that are peculiar to the diagnosis are sensory "tricks," dystonic spasms and unusual stereotyped maintained postures (dropped plantar flexed and inverted foot retrocollis or torticollis). Dystonic spasms and tremor may be confusing.

The dystonia of chronic regional pain syndrome (CRPS I and II) is very common, often associated with severe allodynia and neurogenic edema. It is invariably misdiagnosed.

Movement-specific, athletic and musicians' dystonias are easily diagnosed by their task-specific triggering movement, possibly caused by maladaptive neuroplasticity of the SMA, MC, or PMC. Rarely, peripheral surgery such as dissection in the neck causes axon rewiring or ephaptic conduction such that intended extension of the wrist results in hand flexion.

Spasmodic dysphonia is differentiated from lesions of components of the Xth nerve by its intermittent nature. These patients also demonstrate other neurologic abnormalities such as tremor.

The paroxysmal dyskinesias cannot be missed as a group due to their spectacular onset. Paroxysmal kinesigenic dyskinesia is composed of choreoathetosis, ballism and dystonic postures. Interruption of speech, rigidity and falls may be confusing. The attacks usually last for seconds to minutes.

Spontaneous paroxysmal non-kinesigenic dyskinesia is not initiated by movement and lasts from minutes to hours. This form of dyskinesia is triggered by stress, alcohol and caffeine. Specific paroxysmal dyskinesia is defined by initiating triggers, such as sleep or exercise and whether they are short lasting (less than five minutes). Paroxysmal ataxia and tremor has now been designated as a spinocerebellar degeneration (SCA7).

The differential diagnosis of myoclonus is wide. The setting in which it occurs most often determines the diagnostic possibilities. Hospital settings suggest metabolic or toxic etiologies. Renal failure and post-dialysis states often are accompanied by action myoclonus. Hyperosmolar states are most often from non-ketotic hyperglycemia. They cause segmented myoclonus. Hepatic insufficiency is accompanied by asterixis, lethargy and hyperreflexia. Mitochondrial disease that causes myoclonus should be suspected in a short patient with deafness, oculomotor paralysis, fatigue with minimal exercise and cardiomyopathy.

The Lance-Adams syndrome of post-hypoxic myoclonus, is more often seen with respiratory rather than cardiac arrest and should be suspected following any severe hypoxic episode. The intentional action myoclonus and postural kinetic components of the syndrome are seminal. It may be delayed up to two weeks following the anoxic event.

Most poisonings that cause myoclonus are accompanied by nausea, vomiting, and have a large serum anion gap.

The hereditary progressive myoclonic epilepsies are rare. Seizures and cognitive impairment predominate. Neuronal ceroid lipofuscinosis and Lafora body disease are most often seen in adults. Visual hallucinations and occipital lobe symptomatology occurs in 50% of patients with Lafora body disease. Cognitive impairment and severe ataxia are the seminal features of Ramsay Hunt syndrome.

Myoclonus may be a feature of all of the basal ganglia degenerations. Most present with akinetic rigid signs. Low blood pressure and cold hands suggest multiple system atrophy (MSA). Severe dysarthria, a wing-beating tremor and a Kayser-Fleischer corneal ring is pathognomonic of Wilson's disease. The "eye of the tiger" in the globus pallidus by IS MRI diagnostic of PANK2 (however, it may also be seen in other iron accumulation and neurodegenerative disorders).

Rapid dementia with myoclonus in an adult is Creutzfeldt-Jakob disease until proven otherwise. The 14-3-3 protein, elevation of neuron-specific enolase as well as a characteristic EEG support the diagnosis. PRNP is the only gene

in which mutations cause genetic prion disease. Late severe Alzheimer's disease may demonstrate myoclonus, but the loss of memory and general cognitive impairment have made the diagnosis long before myoclonus is prominent. Both Creutzfeldt-Jakob disease and Alzheimer's disease may have anterior horn cell involvement. Diffuse Lewy body disease may be associated with myoclonus, but visual hallucinations, transient episodes of altered mental status, falls and fluctuations in cognitive abilities are its most prominent manifestations.

Palatal myoclonus cannot be missed if the soft palate is examined. Rhythmic contractions of the platysma muscle, tensor veli palatini, clicking in the ears (opening and closing of the eustachian tubes) and ocular and diaphragmatic movements secure the diagnosis. Rhythmic palatal myoclonus is associated with torsional and rotary nystagmus, while pendular nystagmus is noted in the midline form.

The spinocerebellar ataxias, particularly SCA3/Machado-Joseph disease, have myoclonus as a minor component of the movement disorder. Bulging eyes and amyotrophy are prominent (in SCA3).

Propriospinal myoclonus is striking with axial and extremity arrhythmic jerks. The myoclonus of the abdomen is predominant.

Myoclonus diagnosed in the office is primarily a hereditary form, part of an ataxic syndrome or rarely a fragment of a seizure disorder.

Further Reading on Basal Ganglia and Movement Disorders

General Movement Disorders

Parkinson's Disease

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Chapter 12

The Cerebral Cortex

Overview

Clinical anatomical correlations, studies with functional MRI, PET, SPECT and magnetoencephalography reveal that widely distributed brain networks form the basis of behavioral neurology. In essence, a lesion in varied areas of the brain may destroy a functional network which may then cause a specific deficit. Patterns or modes of distributed activity underlie functional connectivity. An eigenmode of functional connectivity, a covariance among regions or nodes, is the same as the eigenmodes of the underlying effective connectivity if it is restricted to symmetrical connections. The principal modes of functional connectivity correspond to dynamically unstable modes of effective connectivity that decay slowly and demonstrate long term memory. Dynamic instability underlies intrinsic brain networks. Cognitive flexibility and executive function require dynamic integration between brain areas. Should the previous sentence read as: The linking of brain regions (nodes) by their interactions (time-dependent edges or connections) groups brain region clusters together into densely interconnected structures (distributed networks) that change when a task is executed.

It is still clinically useful to assign major functions to specific anatomical areas of the brain with the understanding that this one area may be only one link in a distributed network. Another aspect of distributed networks is diaschisis of Von Monakow that must be borne in mind when performing pathological, anatomical and clinical correlations. This concept demonstrates that anatomical connections of a distributed network have metabolic and neurotransmitter concomitants that may cause a neurological deficit at a distance from the site of injury.

Electrical discharges from one area of the brain may damage homologous areas of the contralateral hemisphere or another component (node or edge) of the distributed network by:

1. Glutamate-NMDA excitotoxicity mechanisms
2. Induction of apoptosis from intracellular calcium dysregulation
3. Maladaptive neuroplasticity induced by immediate early response genes

In general, the anatomical, pathological and the clinical correlates of classic neurology have stood the test of time, but basic mechanisms have been more fully elaborated particularly on a molecular level.

Functional MRI has established the nodes and edges of the CNS connectome that comprise the major distributed networks that underlie higher cortical function and include:

1. The default mode network (DMN)
2. The salience network

3. Arousal and consciousness
4. Motor-sensory circuits
5. Executive function
6. Auditory and visual networks
7. Language networks
8. Memory and learning

Neurophysiological techniques such as EEG, magnetoencephalography and evoked potentials are able to evaluate spatial and time dimensions of a specific task.

PET radiotracers are able to evaluate the function of transmitter systems, microglial activation and neurochemical aggregate accumulation.

The Left Frontal Lobe

Executive function is a constellation of cognitive abilities that guide goal-oriented behavior and is comprised of working memory, inhibition, set shifting and fluency. These processes underlie planning and effective behavioral choices given specific options and are a major function of the left frontal lobe. Broca's aphasia and transcortical motor conduction aphasia occur with area 44 and superior Broca's area lesions. Immediately anterior to area 44 are the frontal operculum and the area triangularis. Lesions of this area cause a particular lack of facility with writing (out of proportion to hand weakness) and cortical negative variant grammatical mistakes.

Various apraxias occur with frontal lobe lesions. An apraxia is the inability to perform an isolated or sequential task in the face of normal motor, sensory and coordinative abilities. A specific motor function is first conceived and is denoted as an engram. The electrophysiological correlate is the *Bereitschaft* (readiness) potentials which are recorded over the prefrontal and supplementary motor cortices. They are then effected by the distributed motor circuitry of the cortico-pallido-thalamic cortical and cerebellar circuitries. Disorganization of simple or sequential engrams is the core of apraxia. Various apraxias are seen with left frontal lobe lesions. An ideomotor apraxia (the engram is encoded in area 6) is an inability to perform a single command such as saluting or using a comb. A patient with a callosal apraxia (right handed, left brain dominant) is unable to perform a simple task with the leg and hand. The command is decoded in Wernicke's area (posterior 1/3 of the superior temporal gyrus) and is projected to the left premotor area, crosses the corpus callosum (anteriorly) to synapse in the right prefrontal area which then engages the circuitry of the distributed motor loop. If the patient is able to perform the simple motor task, but does so with a lack of facility, it is a limb-kinetic apraxia (motor function has to be normal).

Major behavioral deficits of left frontal lobe lesions:

1. Poor planning
2. Poor behavioral choices
3. Poor executive function
4. Broca's aphasia

5. Acute mutism
6. Bilateral frontal opercular lesions
7. Anterior alien hand syndrome (intermanual conflict)
8. Callosal apraxia
9. Limb-kinetic apraxia – paracentral lobule
10. Writing apraxia (Exner's area)
11. Eyelid opening apraxia
12. Ideomotor apraxia
13. Constructional apraxia
14. Right-directional apraxia (hypokinesia)
15. Visual neglect of right hemispace
16. Imitation-utilization behavior (environmental-dependency)
17. Undue fatigue during the completion of a task
18. Paratonia (inability to change position once the extremity is placed)
19. Gait apraxia

Minor behavioral deficits:

1. Executing sequences
2. Inability to follow consecutive hand movements
3. Inability to copy facial movements
4. Difficulty following multiple commands
5. Inability to pair blink responses with voluntary saccades (the loop involved is from the posterior parietal cortex to the second frontal convolution)
6. Echopraxia
7. Sitting apraxia

The Primary Motor Cortex (M1)

Recent retrograde transneuronal transport of rabies virus from single muscles of rhesus monkeys has suggested a new organization of M1. The primary motor cortex is the major origin of descending motor commands for voluntary movement. The output from M1 of the corticospinal projections is from layer V. The corticospinal neurons are of two types. The axons from CST neurons that originate from the convexity of the precentral gyrus constitute approximately 5–10% of the CST neurons and synapse with interneurons of the intermediate zone of the spinal cord (Rexed layer VII). A proportion of these interneurons connects with motoneurons of Rexed layer IX and mediate a component of the descending command for movement. The major component of M1 cells that make direct contact with motoneurons of Rexed layer IX (termed corticomotoneuronal (CM)) cells take origin from the caudal portion of M1 in the anterior bank of the central sulcus. A few monosynaptic cells are also located in the rostral portion of M1 on the convexity of the precentral gyrus. Most single finger muscles are innervated by CM neurons from the caudal M1.

The new organization of M1 (as experimentally supported by tracing experiments in macaques) supports the view that M1 is subdivided into rostral and caudal zones that is based on the differential distribution of CM cells. The rostral zone

is on the crest of the precentral gyrus and the caudal zone is in the anterior bank of the CS. A great proportion of the CST neurons monosynaptically projects to interneurons of the ventral spinal cord. The CST neurons of the caudal region monosynaptically project to motoneurons in Rexed layer IX of the ventral spinal cord. In addition to distal forelimb muscles, shoulder and elbow musculature is also innervated by CST neurons from the caudal zone. The caudal zone directly synapses with motoneurons that control proximal and distal musculature. The direct monosynaptic connection from M1 to spinal motoneurons permits the development of more complex patterns of muscle activity and enhanced manual dexterity. The overlap of CM cells for different hand muscles and the muscles that control the elbow and shoulder enable the motor cortex to effect muscle synergies and multi-joint movement. The direct caudal zone connections are not present at birth and develop over the first months of life which parallels the development of new motor skills and the capacity for fractionated independent finger movement. Physiologic studies support a functional distinction between rostral and caudal subdivisions of M1. Neuronal activity in the rostral zone of M1 is correlated with the general direction and kinematics of hand movement while the caudal region controls the pattern of force production and the dynamics of the motor output. M1 has been shown to contain neurons that encode abstract movement parameters and others that discharge in concert with specific patterns of muscle activity.

The Premotor Cortex (PMC)

The premotor cortex is a complex mosaic of interconnected frontal lobe regions that are subdivided into lateral and medial components. The lateral component is located in Brodmann's area BA6 on the surface of the hemisphere rostral to the primary cortex M1. It has extensive reciprocal connections with M1 as well as axons that project through the corticobulbar and corticospinal tracts that modulate lower motor neurons of the brainstem and spinal cord. Approximately 30% of the axons in the CST originate from the PMC.

The structural distinctions between the PMC (area 6) and M1 (area 4) are:

1. Giant pyramidal cells (Betz cells) in layer V in M1 while there are fewer and smaller Betz cells in the PMC
2. The primary motor cortex is agranular; it lacks layer IV (that is composed of granular cells). Thus there is a transition between the agranular motor cortex (M1) and the six-layered PMC

The PMC is divided into four subregions based on cytoarchitecture, histochemistry and physiological properties. The studies delineating the specific anatomy and physiology of the PMC have been done in monkeys. If the correlation is congruent in humans is not known. The PMC utilizes projections and afferences from other cortical areas to select specific patterns of movement (an engram) that are appropriate for a

specific task. The neurophysiological correlate of this PMC function is the Bereitschafts- or readiness potentials that can be recorded over the PMC prior to movement. Their presence signifies voluntary intent for a specific movement.

Approximately 65% of neurons in the lateral premotor cortex are time locked to movement and increase their discharge frequency when the movement is made in a specific direction. The major connectivity of the PMC (BA6) is reciprocal with M1, the supplementary motor cortex (BA8, the medial component of the PMC), the superior and inferior parietal cortices and the prefrontal cortex (PFC). The premotor cortex has been divided into four fields, 2 dorsal and two ventral based on cytoarchitectonics based on experimental work in monkeys:

1. The premotor dorsal caudal field PMDc(F2):
 - a. A role in guiding and preparing movements
 - b. Neurons are active during preparation for the reach and during its execution
 - c. Respond most actively during one direction of reach
 - d. Stimulation of the area provokes a complex movement simulating reach
2. PMDr(F7):
 - a. This area may associate sensory stimuli with specific movements. It may also be associated with cortical control of eye movements
3. PMVc(F4):
 - a. This area is important for the sensory guidance of movement. Its neurons respond to tactile, visual and auditory stimuli. It may also be involved in object identification in peripersonal space (that immediately surrounding an individual)
4. PMVr(F5):
 - a. This region shapes the position of the hand during grasping and in interactions between the hand and the mouth

There are at least three representations of the hand in the motor cortex that are located in the primary motor cortex as well as one each in the ventral and dorsal PMC which suggests a specific function for each in control of hand movements.

It is presently thought that the lateral motor cortex is a mosaic of multiple subregions that includes M1 and several premotor fields that have specific functions. An alternative principle of organization for the primary motor cortex and the caudal portion of the premotor cortex is organization as a map of a behavioral repertoire in which different parts of the movement repertoire are located in different cortical subregions. Complex movements that require coordination among different body parts, the processing of complex variables, monitoring of objects in peripersonal space and control variables occur in the anterior portion of the motor map. The anterior motor map may also control complex movements that involve multisegments of the limb as the area also modulates the musculature of the neck and back which is a coordinating link between body parts. Simpler parts of the motor repertoire that controls the distal musculature are controlled by the primary motor cortex while more complex movements are initiated from the caudal premotor cortex.

The Medial Premotor Cortex (Supplementary Area BA8)

The supplementary motor cortex along with the lateral areas of the PMC are involved in selecting a specific movement or sequence of movements from a movement repertoire. Pathologic clinical correlations have demonstrated that the supplementary motor cortex is instrumental in coordinating muscle activation of both sides of the body, in speech, and the generation, temporal sequence and preparation of movements.

1. Motor function:
 - a. Initiates movements specified by internal cues. Experimental removal of this cortex in the monkey reduces self-initiated or spontaneous movement while the animal is able to execute movements in response to external cues
 - b. PET scans have demonstrated that activation of the SMA occurs in humans when subjects perform motor sequences from memory
 - c. Neuronal recordings demonstrate firing in the premotor cortex one to two seconds prior to the onset of self-paced movement
2. Aphasia (similar to Broca's)
3. Other motor functions:
 - a. Coordinating movements of both sides of the body during a task (walking, swing phase and stance phase)
 - b. Generation of engrams of movement
 - c. Temporal sequence of a motor task
 - d. Entrainment of motor sequences
 - e. Mirror movements may be seen with SMA lesions
 - f. Priming (encoding of consciously inaccessible knowledge)
 - g. Sequentially memory guided saccadic eye movements

The Major Motor Loops Derived from the Cortex

The major motor circuits arise from specific areas of the cerebral cortex, project to the basal ganglia and thalamus to return to their areas of origin in the frontal lobe. These circuits are characterized as:

1. Motor
2. Oculomotor
3. Prefrontal
4. Limbic

They have a segregated organization that facilitates parallel processing of cortical inputs through separate distributed networks. The separation of functional domains permits the targeting of specific nodes within a circuit without compromise of other circuit function. This is particularly true in the internal segment of the globus pallidus. Modulation of the subthalamic nucleus is less specific because of:

1. Its small size
2. The spatial proximity of its subdivisions
3. Wide dendritic fields
4. The overlap of adjacent terminal fields of corticothalamic projections

Movement disorders result from dysfunction within specific motor circuits. The motor circuit arises and terminates in cortical pre- and post-central motor areas that include M1, the premotor cortex (PMC), the cingulate motor area (CMA) and the supplementary motor area (SMA). These motor cortical areas project in a topographic organization to the motor portion of the striatum, putamen and post-commissural caudate nucleus and the motor component of the subthalamic nucleus (STN). The corticostriatal projections synapse on dendrites of striatal medium spiny projection neurons. Specific clusters of gamma-amino butyric acid (GABA-ergic) neurons connect the striatal motor nuclei to the external segment of the GPe, the internal segment of the GPi and the substantia nigra pars reticulata (SNr). The GPi and SNr are the primary output nuclei of the basal ganglia and project to the motor thalamus (VL_a, VL_m, VAp_c) and the brainstem. The topographic and parallel organization of connections is maintained from the cortex through the basal ganglia and thalamus.

The direct pathway from the striatum to GPi and SNr originates from medium spiny neurons that express D1-like receptors. The indirect pathway takes origin from striatal medium spiny neurons that synapse in the external segment of the globus pallidus (GPe) and express D2-like receptors. The external segment of GPe projects directly to GPi and via the STN. The hyperdirect pathway links frontal cortical areas to the STN. It is uncertain if this projection is from collaterals of corticobulbar and corticospinal fibers or takes origin from cortical neurons. The corticosubthalamic projection and that from the STN to the GPi constitute the hyperdirect pathway. This pathway facilitates cortical input to the STN and GPi at a faster latency than that which synapses in the striatum.

In the thalamus, projections of the motor circuit components synapse in the anterior ventrolateral thalamic nucleus, while projections from the associative circuit (primarily from SNr) synapse in the ventral anterior thalamic nucleus. The thalamic projections to the motor cortex fields (primarily glutamatergic) arise from the anterior ventrolateral and the ventral anterior thalamic nuclei to close the motor circuit. Clinical and experimental evidence indicate that the motor circuit has multiple non-overlapping parallel subcircuits centered on the delineated motor fields. There are collateral projections from both the pallidofugal and nigrothalamic (SNr) to the intralaminar nuclei. The centromedian nucleus (demonstrated in primates) receives afferents from the motor components of GPi and SNr which in turn project to the motor areas of the putamen and STN. The afferents to the parafascicular nucleus and its efferent output belong to the associative and limbic circuitry.

Axon collaterals of GPi and SNr synapse in the brainstem as well as the pedunculopontine nucleus and the superior colliculus. The pedunculopontine nucleus is heterogeneous and projects widely utilizing acetylcholine as its neurotransmitter to the thalamus, cerebellum and the brainstem. It has non-cholinergic projections to the SNpc, STN and globus pallidus as well as descending projections to the pons, medulla and

spinal cord. It is a component of the brainstem locomotor area and may be important for gait ignition. Experimental lesions in primates decrease spontaneous movement. There are subcortical anatomical and physiological interactions between the cerebellum and basal ganglia circuitries making a pure lesion of each unlikely. Dysfunction in either network may affect the other. Examples of this type of subcortical interaction have been hypothesized to occur in the rest tremor of Parkinson's disease and some forms of dystonia.

Functional interactions between the direct, indirect and hyperdirect motor circuitries determine the amplitude, speed, extent and duration of movement. The output of the GPi and SNr is inhibitory due to the release of GABA on brainstem and thalamic motor projection neurons. The activity of the direct and indirect motor circuitries facilitates or decreases movement respectively.

Cortical phasic activation of medium spiny neurons of the direct pathway directly decreases GABA-ergic output from the GPi and the SNr. Thus the thalamocortical motor projection neurons (utilizing glutamate) stimulate the motor neurons of M1, PMC and SMA that facilitates movement. Activation of the medium spiny neurons of the indirect pathway induces increased GABA-ergic output from the basal ganglia that suppresses glutamatergic stimulation of the motor cortex with consequent bradykinesia and reduced movement. The balance between activation of the direct and indirect circuitries determine the parameters of movement. It has been hypothesized that the hyperdirect pathway prevents premature reflexive responses to external stimuli by increasing inhibitory output to thalamocortical projection neurons. This mechanism would increase the time to select a more appropriate motor program. It may also play a role in switching from automatic and habitual motor programs to voluntary control.

A great deal of cortical and basal ganglion physiology is based on dopaminergic transmission. Corticostriatal transmission over the direct pathway is facilitated by dopamine release. It inhibits corticostriatal transmission over the indirect pathway. Its net effect, striatal dopamine release, would be a reduction of inhibitory basal ganglia output which would facilitate movement. Dopamine acts directly on receptors in the STN, the pallidum, thalamus and cortex that influence discharge patterns and rates in these nuclei and motor areas.

Phasic activation of dopamine receptors and medium spiny neurons induces long term potentiation or depression of corticothalamic neurotransmission which are mechanisms that are thought to be essential for reinforcement learning. The prefrontal associative cortex appears to be important for the learning of a motor task while the motor cortex executes the learned motor sequences.

Modulation of the motor circuit components of the STN, GPi and thalamus is effective for different movement disorders by disrupting abnormal projections from the basal ganglia which may allow intact portions of the motor circuit to function normally.

The Dorsolateral Prefrontal Cortex (DLPFC)

The DLPFC is generally thought to comprise the lateral part of Brodmann's areas BA9 and BA46 of the middle frontal gyrus. Some scientists have included BA8, BA9 and BA10. Its principal connections are the orbitofrontal cortex, the thalamus, the dorsal caudate nucleus, the hippocampal formation and primary and secondary association areas of the posterior temporal, parietal and occipital lobes. The DLPFC receives afferences from the dorsal visual stream. The ventrolateral prefrontal cortex receives visual afferences from the ventral pathway that identifies the characteristics of a visual stimulus.

A primary function of DLPFC is executive function that involves the higher cognitive processes of working memory, cognitive flexibility and planning. These functions had been extensively studied neuropsychologically utilizing the A-not-B task, the delayed response and object retrieval tests. The A-not-B/delayed response task requires the patient to find a hidden object after a time delay. This test utilizes working memory that is not required for memory of a single item (recognition memory). The DLPFC is required if two objects have to be compared from memory. Patients with DLPFC lesions are unable to identify objects they have seen after a time delay. Patients fail the Wisconsin card-sorting test as they are unable to maintain the current rule and organize their cards according to the previous correct rule. The DLPFC plays a major role in mood, emotional processing, and attentional processing of emotional information. The major functions of the DLPFC are in:

1. Decision evaluation:
 - a. The DLPFC is activated when subjects have to decide risk and moral attributes of a situation (how to distribute limited resources)
 - b. Cost benefit analysis of alternate choices
2. Working memory:
 - a. Working memory allows the individual to utilize transitory information to perform a task. It may be involved in computational mechanisms for monitoring and manipulating material
 - b. Analyzing visuospatial information to mentally represent coordinates within the spatial domain
3. Specialized DLPFC behavior functions include:
 - a. Act of deception and lying
 - b. Conflict-induced behavioral adjustments (what to do within conflicting rules that require action)
 - c. Associated with intelligence:
 - i. Involvement in deductive syllogistic reasoning
 - d. Threat-induced anxiety:
 - i. Theorized to be related to deficits in problem solving
 - e. Social cognition:
 - i. The DLPFC may be involved in:
 1. Inferring the intentions of other people
 2. Suppression of selfish behavior
 3. Commitment in a relationship

The DLPFC is important as a store of knowledge to solve problems that are immediate, to perform internally generated motor tasks and to perform motor functions that require multiple sequences. It is important in memory retrieval that is pivotal for working memory. The frontal eye fields are located in the DLPFC which initiate saccadic eye movements and are important for ocular fixation.

Major clinical behavior deficits in patients with DLPFC lesions

1. Pseudodepression syndrome:

- a. Psychomotor inhibition
- b. Indifference
- c. Lack of drive
- d. Decreased emotional reactivity

General clinical deficits with DLPFC lesions:

1. Decreased procedural learning
2. Decreased ability to index events in time
3. Failure to develop internal references
4. Apraxia:
 - a. Defective performance of purposive acts
5. Deficits in working memory
6. Deficits in awareness of near extrapersonal space:
 - a. Space that is within the grasp of the patient
7. Switching motor programs
8. Abulia
9. Post-stroke depression:
 - a. The severity of depression is related to the proximity of the lesion to the frontal pole
10. Release of approach behavior

Left Ventrolateral Prefrontal Cortex (VLPFC)

The ventrolateral prefrontal cortex is located in the inferior frontal gyrus that is bounded superiorly by the inferior frontal sulcus and inferiorly by the lateral sulcus. It includes Brodmann's area BA44, BA45 and BA47. It has anterior, mid and posterior subdivisions that have specific functional differences between the right and left VLPFC.

The left VLPFC is important in the cognitive control of memory. The anterior division (BA47; inferior frontal gyrus pars orbitalis) is involved with controlled access to stored conceptual representations. The mid VLPFC (BA45; inferior frontal gyrus pars triangularis) functions in a domain-general selection process that is involved in a post-retrieval process to resolve competition between active representations.

BA47 (left side) may also be involved in syntax processing in oral and sign language, musical syntax and semantic aspects of language.

Right Ventrolateral Prefrontal Cortex (VLPFC)

The right VLPFC is a functionally heterogeneous area. The prefrontal cortex in general has been shown to exert top-down

control of cognition in the execution of a desired task by utilizing multiple specific mechanisms. There are two prominent hypothesis of right VLPFC function:

1. The VLPFC putatively is involved in motor inhibition that stops or overrides a motor program. This function is supported by neuroimaging studies during tasks that require inhibition and clinical studies in patients with damage to the inferior portion of the right VLPFC that take longer than controls to override a motor task
2. It has also been proposed that the right VLPFC is a component of a right-lateralized ventral attention network that controls reflex reorienting. The area functions in concert with a region of the right temporoparietal junction (TPJ) and the inferior parietal lobule to reorient attention to stimuli that abruptly occur outside of the current focus of attention
3. The right VLPFC is active during the updating of action plans
4. The right middle VLPFC (BA45) is activated during decision uncertainty
5. The VLPFC is the termination of the ventral pathway of vision that is engaged in the determination of the characteristics of an object
6. The right VLPFC may be important in the mirror motor neuron system. These neurons respond both to the execution of an action and during the observation of performance of the same action. This system may be involved in imitation, empathy and social cognition. Neuroimaging studies have demonstrated bilateral activation of the VLPFC in concert with other regions during the observation of an action and imitation. The inferior frontal junction and the posterior and mid-VLPFC are prominently activated during these tasks. The orbital frontal cortex is Brodmann's areas BA10, BA11 and BA47. Anatomically it is usually considered to be synonymous with the ventromedial prefrontal cortex. It has widespread connections with primary and secondary association cortices, the limbic system and receives afferents from the magnocellular medial nucleus of the mediodorsal thalamus. It has extensive corticocortical connections with other prefrontal areas that include motor, limbic and sensory cortices. Its projections support a major role in the integration for executive motor control. All sensory cortices are reciprocally connected with the orbitofrontal cortex. There is extensive innervation from regions associated with olfaction and taste. Its somatosensory innervation from SI and SII is particularly dense in areas associated with innervation of the hand and trigeminal complex

The orbitofrontal cortex receives a rostral stream for auditory phonetic processing and a caudal stream that terminates just posterior to it in the periarculate prefrontal cortex that is associated with auditory-spatial processing. (There is overlap with OFC in this area.) Both the dorsal and ventral visual streams terminate in orbitofrontal cortical regions. There are dense reciprocal connections to the temporal pole, an area that

is important for integration of spatial and object processing. The OFC is reciprocally connected with limbic areas that include the granular, dysgranular and agranular insular cortex, the parahippocampal gyrus, the hippocampus, the amygdala and the hypothalamus.

Its striated projections are dense to the ventral reward-related areas. It has connectivity with thalamic and periaqueductal areas posited to be involved with autonomic functions.

Clinical pathologic and neuroimaging associated with specific tasks support a role for the OFC in decision selection, emotional control and reward expectation. Disruption of the striato-thalamo-orbitofrontal circuitry may be involved in drug addiction and substance abuse. Neural reward circuitry may also be involved with attention deficit hyperactivity disorder (ADHD). This circuitry is putatively involved in motivation, reward and impulsivity.

The medial component of the OFC is primarily connected to the hippocampus and associated areas of the cingulate, retrosplenial and entorhinal cortices, the anterior thalamus and the septal diagonal band of Broca. The lateral component of the OFC is characterized by its anterior section connectivity with the granular insula association cortex, mediodorsal thalamic nucleus, inferior parietal lobule and the dorsolateral PFC. Its most caudal sector has dense connections with the amygdala, midline thalamus, non-isocortical insula and the temporal pole.

Functionally the medial OFC is putatively involved in stimulus-reward selection and reinforcement of behavior. The lateral OFC is putatively involved in stimulus-outcome associations. The evaluation and possible reversal of behavior.

Activation and involvement of the lateral OFC occurs:

1. During the encoding of new expectations in regard to punishment and social reprisal
2. Approach avoidance contexts (suppressing negative emotions)
3. Conflict resolution:
 - a. Inappropriate anger and inappropriate response to anger in others
 - b. LOFC lesions have been associated with defensive personality traits
4. Machiavellian personality traits are seen if the medial OFC is activated with:
 - a. Monitoring, learning and memory of the reward value of reinforcers

In general, more complex or abstract reinforcers of value are represented more anteriorly in the OFC. There is a suggestion that the OFC mediates subjective hedonic experience.

The OFC is the termination of the olfactory cortex, the piriform cortex, amygdala and entorhinal cortex without a thalamic relay.

The OFC, nucleus accumbens and amygdala are thought to be major components influencing addictive behavior. A proposed mechanism is dopaminergic activation of reward circuits. The OFC may also be associated with compulsive,

repetitive behavior and drive via dysfunction of the striato-thalamo-orbitofrontal circuitry. The OFC projects to the nucleus accumbens via the mediodorsal nucleus of the thalamus that is thought to be important in reinforcing the effects of an administered drug of abuse. There are reciprocal nucleus accumbens projections to the OFC which also receives afferences from the dopaminergic ventral tegmental area (A10). The VTA has been posited with reinforcing the effect of drugs. Limbic regions of the hippocampus, cingulate gyrus, and amygdala project to the OFC which may function to integrate this information to modulate the response of limbic areas to the rewarding effects of drugs of abuse.

Addictive patients have deficits in orbitofrontal, striatal, and thalamic nuclei. It is posited that conscious mechanisms involve craving that is associated with loss of control and subconscious mechanisms that include anticipated conditioned responses to the addicting drug and impulsivity. Neuroimaging studies of cocaine withdrawal demonstrate increased glucose metabolism in the OFC that correlates to the degree of drug craving. During protracted withdrawal (3–4 months), there is decreased metabolism in the OFC of cocaine addicts as compared to healthy non-addicted subjects. There is a similar decreased metabolic activity in the OFC during withdrawal. This response is confounded due to the fact that detoxified alcoholics have lower levels of benzodiazepine receptors in the OFC (compared to healthy subjects) as well as decreased OFC metabolism in response to serotonergic and GABA-ergic stimulation. The role of these transmitter systems is not fully determined in cocaine addiction.

Other orbitofrontal cortex associated behaviors:

1. Pseudopsychopathic behavior
 - a. Disinhibition
 - b. Facetiousness
 - c. Sexual/perverted behaviors
 - d. Lack of concern for the effects of behavior
2. Bilateral lesions cause retrograde amnesia
3. Failure to break previously learned associations
4. Medial orbitofrontal lesions are associated with confabulation (similar to mediodorsal thalamic lesions that project to the OFC are seen with Korsakoff's syndrome)
5. Mania
6. Autonomic regulation of vagal tone

The Right Frontal Lobe

The distributed functions of the right frontal lobe are most involved with emotional control and inhibitory control of the limbic system. Deficits in the right frontal lobe are associated with disinhibition of personal behaviors, hygiene and sexual conduct. Patients frequently demonstrate "witzelsucht" (inappropriate jocularity) as well as impersistence.

Major right frontal lobe deficits:

1. Disinhibition:

- a. Personal behavior
 - b. Poor hygiene
 - c. Sexual dysfunction
 2. Inappropriate jocularity; "witzelsucht"; a drive to tell bad jokes
 3. Impersistence of a motor task
 4. Neglect of left hemisphere
 5. Stimulus familiarity and novelty abnormalities
 6. False recognition syndrome with confabulation
- Minor right frontal lobe deficits:
1. Understanding and mediating negative emotions
 2. Area 6 and 8 lesions are associated with simultanapraxia (inability to coordinate both sides of the body to accomplish a motor function)
 3. Right frontal eye fields direct bilateral search of the visual landscape
 4. Retrieving the temporal order of stimuli

The Parietal Lobe

The parietal lobe is central to somatosensory function. It contains the primary somatosensory cortex, Brodmann areas BA3, BA1 and BA2. It is somatotopically organized such that the lower extremity is at the top of the post-central gyrus and the mouth is inferior. The amount of primary somatosensory cortex representing a body part is proportional to the relative density of the cutaneous tactile receptors of that body part and the degree of sensitivity of that area. Thus the lip and hands have the largest representation.

BA3 is subdivided into areas 3a and 3b. 3a has pyramidal cells in layer V and layer IV is less granular than in 3b. Its cortical connections are with BA4, BA1 and BA5 and SII. It has a heavy muscle spindle input which responds during movement. It has some cutaneous sensitivity.

3b receives dense input from the major sensory nucleus of the thalamus (VPL). Its neurons respond to somatosensory stimuli (rarely to other stimuli), lesions impair somatic sensation and its electrical stimulation elicits somatic sensations. Its cortical connections are with BA1, BA2, BA3a, BA5 and SII. Its primary cutaneous afference is from rapidly adapting (RA1) and slowly adapting (SA) cutaneous receptors whose origin is from VPL. The projections from 3b to area 1 primarily are associated with texture information and that to area 2 relays information in regard to size and shape.

BA1 has granular layers III, IV and V which are less dense than in 3b. Its cortical connections are with BA2, BA3a, BA4, SII and reciprocally with 3b. Its afferences are from cutaneous RA1 and RA11 receptors whose origin is the VPL.

BA2 has a more dense granular IV than BA1. It receives projections from muscle and joints, some cutaneous receptors and contains direction sensitive, multidigit complex receptive fields. Its BA connections are with BA4, BA5, BA6, BA3a and SII. It provides feedback to 3b and 1.

Each of the four cytoarchitectonic regions contains a functionally distinct map of the peripheral body schema. Thala-

mic inputs project into layer IV that then project into other layers. S1 neurons are organized into vertical columns that have similar inputs and responses and extend through all of the cortical layers. Area 3a is at the top of the central sulcus followed in ascending order (towards the apex) by 3b, 1 and 2. The homunculus is organized somatotopically. The legs and trunk are at the top of the parietal convexity, the arm and leg are mid convexity, and the face is most inferior.

The functional organization of the posterior parietal cortex (PPC) has been extensively investigated in both humans and macaques both neurophysiologically and with functional MRI. The PPC contains specific clusters of neurons that are involved with goal-directed arm and eye movements needed for reaching, grasping and ocular fixation and saccadic eye movement. Functional MRI studies in patients have begun to delineate the role of the PPC in attention, planning, execution of movement and the control of rapid eye movements. The posterior parietal area is subdivided into the superior parietal lobule (Brodmann areas BA5 and BA7) and the inferior parietal lobule (BA39 and BA40) by the intraparietal sulcus (IPS). These areas integrate neural afferents from different sensory modalities to guide and control movements in space. They are arranged modularly, are reciprocally interconnected and comprise a series of neural circuits that involve both the frontal lobe and visual areas of the occipital cortex. The neurons of a specific IPS area encode the spatial coordinates of objects, the position of a body part in space, eye movement parameters and the shape, size and orientation of objects. The IPS is an anatomically constant sulcus in humans but has complex folding and branching patterns that have made it difficult to study in humans. The macaque monkey intraparietal sulcus has been studied on a cellular electrophysiological level and is thought to be relevant to its human counterpart.

Anterior parts of the IPS function in sensorimotor processing while its posterior parts are involved in visual information processing. Neurons in the IPS that are located in its medial bank are responsive to arm movements while those located in the lateral bank are involved with eye movements. Each area of the IPS receives and processes information from more than one sensory modality.

Anterior Intraparietal (AIP) Cortex

Clinical pathological correlation in patients with lesions of the anterior intraparietal cortex has demonstrated its importance for manipulating objects and grasping movements. PET studies in healthy subjects have shown that the anterior IPS is a component of a tactile shape-processing network that discriminates objects from changes in their 3D structure. Both areas in the anterior and posterior IPS are activated during the construction or recognition of 3D shapes by finger manipulation. The same area may be important for the discrimination of the orientation of a visual stimulus. The anterior

intraparietal cortex functions in tactile and visual object processing.

The Putative Ventral Intraparietal Area (VIP)

In macaques the VIP encodes polymodal motion processing primarily in head-centered coordinates. Visual, auditory and tactile motion detection and vestibular processing have been shown to activate modality-specific and supramodal areas of the VIP. These studies have demonstrated involvement of the PPC that supports this part of the parietal cortex as a component of a polymodal information-processing neural circuit. Lesion studies in patients demonstrate that the PPC is involved in the clinical phenomena of neglect or extinction that affects multiple modalities that are often organized in a head-centered frame of reference. It has been suggested that lesions of a putative human VIP may cause a component of visuospatial neglect.

The Putative Human Medial Intraparietal Area (IPA)

The human medial IPA is essential for visuomotor coordination of hand movements that require adjustment for dynamic grasp and the abrupt switches between grip apertures for different target sizes. Thus the medial intraparietal area is necessary for online-control and the correction of movement errors. Patients with optic ataxia (most often under-reaching the target) have lesions of the medial intraparietal cortex or contiguous areas. Functional MRI data support that the medial intraparietal cortex transforms visual coordinates into motor programs and is essential for the online control of goal-directed precision movements.

Putative Lateral Intraparietal Cortex (LIP)

In macaques LIP is located in the lateral wall of the IPS (intraparietal sulcus) and is a component of the saccadic network. It receives afferences from several areas of the visual cortex and projects to the frontal eye field (FEF) and the superior colliculus. These neurons discharge during the detection of a salient visual stimulus, during the delay period when the location of the stimulus is memorized and during the saccade to the intended location. Some studies demonstrate that the LIP is involved in the representation of the motor programs for saccadic movements. Other studies suggest that LIP neurons discharge at the locus of attention and therefore represent a salience map. This function may contribute to the maintenance of a spatially accurate representation of the visual field during eye movements.

Functional MRI studies in human subjects have shown that the IPS is involved in attention and the control of eye movements. Shifts in visuospatial attention activate the IPS as does detection of the target. In humans, the activation is in the medial rather than the lateral wall of IPS as occurs in the macaque.

The Putative CIP Area in Humans

Both PET and functional MRI studies demonstrate that posterior areas of the IPS are activated during the analysis of surface and pattern orientation. The human equivalent of CIP is located in the medial bank of the IPS and not lateral which is its location in the macaque.

The combined use of functional MRI and diffusion tensor imaging demonstrates that posterior IPS connects to retinotopically defined visual regions and the superior temporal gyrus while anterior IPS regions have higher connection probabilities to the prefrontal cortex. All IPS regions have interhemispheric connections to homologous areas of the contralateral hemisphere and connections to the thalamus and striatum.

Multiple visual maps exist within the intraparietal sulcus that are essential for encoding visuospatial information. Each hemisphere symmetrically represents contralateral visual space. The two major forms of hemispheric asymmetry occur in the parietal cortex ventrolateral to areas that are functional for visuotopic discrimination in the IPS. Attentional processes are localized in the right lateral parietal cortex primarily in the temporoparietal junction and long-term memory retrieval processes are localized to the cingulate gyrus of the left parietal cortex.

A frontoparietal attention network consisting of the IPS, the inferior parietal lobe and the dorsal premotor cortex that includes the frontal eyelids controls the selection of sensory targets by attention. The nodes of this network are connected by edges (sensory fibers) that form the superior longitudinal fasciculus.

The functional characteristics of the posterior parietal cortex include:

1. Feature-independent coding
2. Enhancement of activity by attention
3. Representation of task-related signals
4. The posterior parietal cortex comprises multiple reference frames that compute features and modality maps of the environment. It is postulated that the priority map integrates information from the sensory cortex with behavioral goals and expectations from the dorsolateral prefrontal and premotor cortex. The frontoparietal attention network has a decisive role in the selection of relevant environmental information
5. The PPC is activated in the planning and control of goal directed-action. Electrophysiologic studies in macaques have delineated reach-specific areas in the PPC. The reach modules (forearm and hand) in the human PPC area are the superior parietal cortex, the occipital cortex, the mid-posterior intraparietal cortex and the cingulate gyrus. A functional framework for the human PPC has been proposed and includes:
 - a. Encoding of reach goals in the posterior-medial PPC
 - b. Reach movement vectors are processed in anterior-lateral PPC areas

- c. Integration within a broader cortical framework for reach grasp and eye-hand coordination that enables the spatial information in the parietal reach region to influence eye control pathways

In summary, the posterior parietal cortex is essential for the production of planned movement. It receives afferents from sensory systems that localize the body in space (visual, somatosensory and auditory). Its major output is the frontal motor cortex, the dorsolateral prefrontal cortex, the secondary motor cortex and frontal eye fields. It is composed of a mosaic of small modules that guide the movements of the eyes, head, and extremities.

The primary deficits in patients from PPC injury are in:

1. Perception and memory of spatial relationships
2. Hand movements, particularly reaching and grasping
3. Control of saccadic eye movements
4. Attention
5. Hemispatial neglect

General Parietal Lobe Sensory Function (Similar in Each Hemisphere)

1. Two point discrimination
2. Localization of extremities and objects in near and far space (outside of the examiner's grasp)
3. Graphesthesia
4. Stereognosis
5. Point localization
6. Perceptual rivalry of double simultaneous stimuli. Non-perception of the damaged side
7. Posterior parietal cortex:
 - a. Reach and grasping (the modules in the intraparietal cortex)
8. Anterior intraparietal sulcal cortex:
 - a. Manipulation or active touch
9. Posterior superior parietal cortex:
 - a. Inability to utilize stereoscopic vision for hand movements
 - b. Optic ataxia (area 5)
10. Gesture representations:
 - a. Bilateral ventral medial parietal lobe
 - b. Inability to recognize objects (BA7)
11. Inferior parietal lobule:
 - a. Memory or recognition of spatial position
12. Medial parietal lobe:
 - a. Deficient sense of direction
13. Intraoral sensation (parietal operculum)

Right Parietal Lobe

1. Visuospatial processing
2. Asomatognosis (denial of a body part)
3. Denial of illness (anosognosia)
4. Asimultagnosia:

- a. Inability to synthesize parts of an object into a whole (eyes, ears and nose can be recognized but the patient cannot synthesize these individual parts to perceive a face)
- 5. Left visual inattention (hemineglect)
- 6. Aprsody:
 - a. Flat speech without the proper intonations appropriate for the circumstances
- 7. Constructional apraxia
- 8. Dressing apraxia
- 9. Pressure of speech
- 10. Inability to judge the directional orientation of lines (right posterior parietal areas)
- 11. Inability to discriminate faces
- 12. Right superior parietal cortex:
 - a. Poor visual-manual coordination
 - b. Optic apraxia
 - c. Inability to judge a previously bisected line
- 13. Responding to a question posed to an adjacent patient
- 14. Gourmand syndrome:
 - a. Eating disorder
- 15. Decreased short term memory
- 16. SII involvement:
 - a. Asymbolia for pain
 - b. The entire body is represented
 - c. Located at the foot of SI with the head dorsal and foot ventral
 - d. A sensation of heat that may rise and envelope the entire body (a seizure aura)
- 17. Topographic disorientation:
 - a. Right medial parietal lobe
- 18. Topographic amnesia:
 - a. Inability to remember shapes and locations
- 19. Alloesthesia
 - a. Touch on the abnormal side is transferred to a homologous position on the normal side
 - b. Impulse control disorder

Left Parietal Lobe Function

- 1. Gerstmann's syndrome:
 - a. Right-left confusion
 - b. Inability to cross the midline
 - c. Finger agnosia
 - d. Conduction aphasia
 - e. Dyslexia with or without agraphia
- 2. Bilateral deficits in point localization
- 3. Alexia without agraphia (BA39, 40 & 41)
- 4. Conduction aphasia:
 - a. Disconnection of Wernicke's and Broca's area
 - b. Damage to the arcuate fasciculus
- 5. Inferior left posterior parietal lobule:
 - a. Deficits in auditory verbal short term memory
- 6. Superior parietal lobule:
 - a. Appreciation of detail
- 7. Parietal-occipital function:

- a. Bálint's syndrome:
 - i. Most often the lesions are bilateral for the full blown syndrome
 - ii. Deficit in visual scanning
 - iii. Optic ataxia (undershooting an object on attempted grasp)
- 8. Color anomia
- 9. Anomic aphasia:
 - a. Lesion of the supramarginal gyrus
- 10. Posterior alien hand:
 - a. Posterior parietal areas 5 and 7
 - b. Ideational apraxia:
 - i. Inability to complete a sequence of commands
 - ii. Lesions of the supramarginal and L superior lobule

The Temporal Lobe

The temporal lobe's distributed functions include receptive speech that is involved in processing sensory input into language comprehension that occurs primarily in Wernicke's area and in the basal temporal language areas. The right temporal lobe processes visual memory. The middle temporal gyrus visual area is vital to recognition and tracking of moving objects. The dorsal visual stream of the parietal lobe is most important for delineating the salience and position of objects. Medial temporal lobe structures are pivotal for the registration and consolidation of short term memory. The temporal lobes are one of the anatomical substrates of personality in and of itself and due to its anatomical projections to the limbic system and frontal lobes (the uncinate fasciculus is a major projections tract).

The medial temporal lobe is critical for declarative memory or explicit memory which is conscious memory that is divided into semantic memory for facts and episodic memory for events. The hippocampus, perirhinal, parahippocampal and entorhinal neocortical areas are fundamental for this memory function. Areas of the prefrontal and visual cortices are also activated during explicit memory. The hippocampus is essential for the inscription of memory (the first thirty seconds) and the encoding of short term memory (those that last for less than 3 minutes). The lateral temporal lobe is involved in primary auditory perception as it contains the primary auditory cortex in the superior temporal gyrus.

The ventral visual stream terminates in the inferior temporal gyrus where object and complex stimuli such as faces (fusiform gyrus) and scenes (parahippocampal gyrus) are decoded.

The inferior temporal cortex has been extensively studied both electrophysiologically and with functional MRI. The inferior temporal cortex (ITC) contains multiple color-biased areas that are ventral to regions activated by face perceptions. Both color and face areas are located anteriorly in the ITC. The ITC areas comprise parallel and multi-stage processing networks that are organized as a coarse map of eccentricity

similar to the retinotopic map in the visual cortex. Peripheral representations of objects overlap with regions that respond to the place of the object. Some functional MRI experiments have suggested that the ITC is not retinotopically organized but reflects an organization based on size. Regions of ITC that are activated by images of large objects are separated from areas activated by images of small objects.

Activity in the face-selective fusiform cortex is enhanced by emotional (usually fearful) expressions.

Left Temporal Lobe

1. Wernicke's aphasia (BA22, BA23)
2. Rostral Pole (proper name anomia)
3. Sensory conduction aphasia
4. Short term memory loss
5. Basal temporal language area:
 - a. Receptive speech/anomia
 - b. Deficits in confrontational naming
6. Color anomia:
 - a. Medial temporal lobe
 - b. Fusiform gyrus
7. Temporal/occipital junction:
 - a. Dorsal
 - i. Pure alexia
8. Semantic memory:
 - a. Left inferior temporal gyrus
9. Superior temporal gyrus:
 - a. Consolidation of memory
10. Grammatical comprehension:
 - a. Anterior temporal lobe
11. Temporal parietal junction:
 - a. Object word naming

Right Temporal Lobe

1. Anterior temporal lobe:
 - a. Anxiety/panic attacks
 - b. Amnesia
 - c. Apraxia
 - d. Agitated delirium:
 - i. Superior and middle temporal gyrus
 - e. Aura of hunger
 - f. Priming for memory
 - g. Non-verbal amnesia
 - h. Pathologic crying
 - i. Right hippocampus:
 - i. Non-verbal task processing:
 1. Spatial information
 2. Less readily verbalizable visual stimuli
 - j. Parahippocampal gyrus:
 - i. Encoding of spatial information for long-term storage
 - k. Prosopagnosia:
 - i. Impairment in the recognition of faces and of unique individual facial features
 - l. Visual agnosia:
 - i. Impairment in the identification of familiar objects

Bilateral Temporal Lobe Dysfunction

General Characteristics

1. Causes of bilateral temporal lobe disease
 - a. The major pathologies are complex partial seizures that induce temporal lobe dysfunction contralateral to the seizure focus (excitotoxicity)
 - b. Head trauma
 - c. Temporal lobectomy:
 - i. The contralateral temporal lobe is defective
 - d. Herpes simplex (Klüver-Bucy syndrome)
 - e. Urbach-Wiethe disease
 - f. Irradiation of the pituitary
 - g. Pick's disease
 - h. Frontal temporal dementia
 - i. Korsakoff's syndrome

Clinical Manifestations

1. Deafness
2. Apathy and personality change
3. Impaired learning and memory
4. Amnesia

Neuropathology

1. Klüver-Bucy syndrome:
 - a. General characteristics:
 - i. It is most often incomplete
 - ii. A dangerous complication of lesioned temporal lobectomy
 - b. Clinical manifestations:
 - i. Most often associated with bilateral damage or removal of the temporal lobes that contain the amygdale
 - ii. Hypersexuality
 - iii. Hyperorality
 - iv. Hypermetamorphopsia (excessive explanation, attention and manipulation of visual stimulus)
 - v. Visual agnosia
 - vi. Apathy
 - vii. Severe memory deficits
 - c. Neuropathology:
 - i. Dependent on the pathologic process that affects the medial temporal lobe structures
 - d. Laboratory Evaluation:
 - i. MRI:
 1. Destruction of medial temporal lobe structure including the amygdala
 2. EEG
 3. Neuropsychological testing

Urbach-Wiethe Disease

General Characteristics

1. Lipoid proteinosis (Urbach-Wiethe disease) is caused by homozygous or compound heterozygous mutation in the ECM1 gene that maps to chromosome 1q21

2. It is autosomal recessive in inheritance
3. The extracellular matrix protein 1 (ECM1) gene encodes for a glycoprotein that appears to be involved in skin adhesions, epidermal differentiation, wound healing and scarring, endochondral bone formation, tumor biology, endothelial cell proliferation and angiogenesis

Clinical Manifestations

1. Dermatological:
 - a. Changes of the skin have onset in infancy with thickening of the skin and mucous membranes
 - b. Thickening of the vocal cords with hoarseness
 - c. Lesions and scars occur on the face and distal extremities from poor wound healing
 - d. The skin is dry and wrinkled, it may appear waxy
 - e. White or yellow infiltrates occur in the lips, buccal mucosa, tonsils, uvula and epiglottis
 - f. Beading of papules around the eyelids is common
 - g. Rare dermatological and other signs include:
 - i. Hair loss
 - ii. Parotitis
 - iii. Dental abnormalities
 - iv. Corneal ulceration
 - v. Focal macular degeneration

Neurological Manifestations

1. 50–70% of patients have calcification of the amygdala and the periamygdaloid gyri
2. Abnormal fear response
3. Complex partial seizures (temporal lobe origin)
4. Partial or complete Klüver-Bucy signs and symptoms

Neuropathology

1. Accumulation of hyaline-like material in the dermis and thickening of the skin basement membrane. The hyaline material is periodic acid-Schiff (PAS) positive
2. Calcium deposits within the amygdala blood vessels with gradual ischemic infarction
3. Staining of skin lesions with antitype I collagen antibodies or antitype VII collagen antibodies is positive at the dermoepidermal junction

Laboratory Evaluation

1. Genetic testing for identification of the ECM1 gene
2. Skin biopsy
3. MRI:
 - a. Calcification of the amygdala

Amygdala Seizures

Clinical Manifestations

1. Seizure semiology:
 - a. Freezing response
 - b. Autonomic response (paleness)
 - c. Lack of emotional expression

- d. Slow contralateral turning (may occasionally be ipsilateral turning)
- e. Automatism:
 - i. Lip smacking or chewing
2. Medial amygdala nuclear discharge:
 - a. Ictal fear
 - i. Abdominal location
 - ii. Free-floating; cannot be linked with an expected or past event
 - iii. Associated with excessive anxiety
 - iv. Feeling of impending doom

The Cingulate Cortex

The cingulate cortex includes the enteric cingulate gyrus, is located above the corpus callosum and extends into the cingulate sulcus. It is part of the limbic lobe. Its major afferences are from the thalamus and the neocortex and it projects to the entorhinal cortex via the cingulum. It is essential for emotional formation and processing, learning, memory, pain, motivation and emotional components of movement. It is on the medial surface of the hemisphere and is composed of Brodmann's areas BA23, BA24, BA26, BA29, BA30, BA31, BA32 and BA33. BA26, BA29 and BA30 are its retrosplenial components.

1. The anterior cingulate cortex:
 - a. Is composed of Brodmann's areas BA24, BA32 and BA33; its anterior continuation is located below the genu of the corpus callosum (BA25)
 - b. Cytoarchitectonically it is agranular
 - c. It is divided further into the pregenual anterior cingulate cortex that is near the genu and the mid-cingulate cortex

Clinical Manifestations

1. The pregenual regions are associated with affective experience
2. A major component of autonomic regulation
3. Electrical stimulation of the dorsal pregenual cortex elicits fear, pleasure and agitation
4. Electrical stimulation of BA24 and BA25 evokes:
 - a. Increases and decreases of respiratory rate and blood pressure
 - b. Mydriasis and piloerection
 - c. Facial flushing
 - d. Visceral responses (nausea, vomiting, epigastric sensations and bowel and bladder evacuation)

Neuropathology

1. Connections of the pregenual ACC that regulate autonomic activity include:
 - a. The nucleus solitarius
 - b. Dorsal motor nucleus of the vagus
 - c. Sympathetic thoracic intermediolateral column

- d. The periaqueductal gray
- e. Reciprocal connections with the amygdala
- f. The PACC (Posterior anterior cingulate cortex) is involved in emotionally relevant autonomic activity through its connections to BA25 that in turn activates brainstem autonomic nuclei

The Mid Cingulate Cortex (MCC)

General Characteristics

1. Has a major role in motor response selection derived from the motivational relevance of a particular situation

Clinical Manifestations

1. Attention for action response selection
2. Error detection
3. Anticipation
4. Working memory

Neuropathology

1. The MCC is composed of two subdivisions:
 - a. The dorsal MCC (dMCC) in the sulcal cortex that extends into the superior cingulate gyrus
 - b. An area on the surface of the cingulate gyrus
2. The dMCC:
 - a. Has large layer Vb neurons that project to the spinal cord, supplementary motor, primary motor and limbic cortices
 - b. Electrical stimulations of dMCC evokes:
 - i. Gestures; touching, kneading and rubbing the hands together; lip puckering or sucking
 - ii. These gestures can be modified by sensory input and at times voluntary control
 - iii. Blood flow studies have demonstrated modifiable changes in this area of the cingulate cortex by altering the reward qualities of particular outcomes

The MCC in addition to selection and regulation of motor actions and motivation also has a role in cognitive processes associated with divided attention.

The Posterior Cingulate Cortex (PCC)

General Characteristics

1. The PCC consists of BA23 and BAB1
2. It is granular

Clinical Manifestations

1. The PCC and retrosplenial cortex are involved in topographic and kinetic memory
2. Focal lesions (experimental lesions in macaques) impair memory of spatial positional relationships

Neuropathology

1. The afferents to the PCC are from the thalamus (lateral dorsal and anterior nuclei)
2. Direct afferents from the subiculum

3. BA23 projects to the dorsolateral prefrontal cortex (BA9), the anterior prefrontal cortex (BA10), the orbitofrontal cortex (BA11), the parahippocampal gyrus and the posterior part of the inferior parietal lobule, the presubiculum, the superior temporal sulcus and the retrosplenial area
4. Deep brain stimulation (DBS) of the subcallosal cingulate cortex (SCC) is now being assessed for treatment resistant depression. To date, it has been found to be efficacious for transient changes in mood, attention and social connectedness which have also been shown by DBS of the medial forebrain bundle and the nucleus accumbens. The effectiveness of DBS for treatment-resistant depression requires inclusion of:
 - a. The forceps minor of the anterior corpus callosum which connects the two ventromedial frontal cortices
5. The cingulum bundle that connects the ipsilateral subcallosal cingulate (SCC) to the rostral and dorsal anterior cingulate cortices
6. The uncinate fasciculus that connects the SCC to the ventromedial frontal cortex
7. The frontal-subcortical fibers connect the SCC to the basal ganglia, thalamus and brainstem. All components of the cingulate gyrus may be involved in vascular disease, head trauma, tumors and viral encephalitides. Immune-mediated processes particularly affecting NMDA and AMPA receptors, as well as anti-Hu paraneoplastic diseases frequently affect the cingulate gyrus. It frequently herniates under the tentorium during increased intracranial pressure from mass lesions and is a component of central brain herniation

Laboratory Evaluation

1. MRI:
 - a. Evaluates mass lesions and MRA evaluates the vascular supply to the gyrus
 - b. Antibody studies evaluate paraneoplastic processes and those that affect NMDA and AMPA receptors
 - c. EEG in confusional states

Summary of the Cingulated Cortex

The cingulate gyrus is an integral component of the limbic system. It is a major component of Papez' loop that consists of the mammillary bodies, the mamillothalamic tract, anterior ventral thalamic nuclei, cingulate gyrus, prefrontal cortex and hippocampus. Its distributed functions are associated with attention, motivation, the affectual components of movement, and the "suffering" component of pain. It has a major function in the control of the autonomic nervous system particularly in response to emotional states.

1. The ACC:
 - a. Affective states and the control of the ANS
2. MCC:
 - a. Selection of movement and motivation
 - b. Divided attention
3. PCC:
 - a. Topographic and topokinetic memory

The Occipital Lobe

Overview

The primary visual cortex is Brodmann's area BA17. It is located on the medial side of the occipital lobe within the calcarine sulcus. It is named the striate cortex due to a large stripe of myelin, the Stria of Gennari that is visible.

The primary visual cortex (V1) encodes the orientation, spatial frequency and chromatographic features of small receptive fields of the visual field. V1 projects to V2 and V4 of the visual ventral stream. The dorsal stream V3, MT (V5) and dorsomedial area also receives projections from V1. In general, the ventral stream processes visual information for object recognition while the dorsal stream is involved with object movement and its spatial location. Each visual area maintains a map of the visual field. "Low-level" representations of edges, color and lights are built into "high-level" of semantic representations that include the perceptions of objects, faces and environmental scenes.

The occipital lobe is central to all aspects of vision. Knowledge of occipital lobe function has been meticulously accrued from elegant physiological and anatomical studies in primates that have been buttressed by pathological correlation in patients and by recent functional imaging studies with PET, SPECT, functional MRI and neurophysiologic studies.

Stimulation of the calcarine cortex BA17 in awake patients evokes non-colored, non-moving flashes of light with occasional geometric designs. Stimulation more anteriorly in BA18 produces moving, colored geometric figures in the contralateral visual field. Stimulation in the junction of the temporo-parietal-occipital cortex causes visual distortion, phosphenes, photopsia (moving geometric patterns), complex visual hallucinations and palinopsia (visual perseveration). Occasionally a fixed visual hallucination may be seen or a positive bright yellow scotoma is noted with lesions in this area. Color naming may be lost with lesions of the fusiform gyrus and visual agnosia supervenes with bilateral lesions of the junction of the temporo-occipital cortex. Word blindness occurs with a left posterior cerebral artery occlusion that destroys the splenium of the corpus callosum which isolates Wernicke's area (for decoding graphemes) from the right occipital lobe (the left occipital lobe is infarcted). Visual memory may be disturbed with lesions of the inferior longitudinal fasciculus such that visual images cannot be compared with prior images stored in hippocampal circuitry. Metamorphopsia, unusual interest in all visual objects, occurs with lesions of the occipital-parietal cortex as well as lesions in the retina, chiasm, optic radiations and retrosplenial areas.

Disorders of Complex Visual Processing

Visual Agnosia

1. Definition: Visual agnosia is a disorder of higher behavior in which an alert, intelligent, non-aphasic patient with normal visual perception does not recognize a visual stimulus

2. There is specificity for the types of stimuli for which patients are impaired. They include:
 - a. Agnosia for objects
 - b. Propagnosia (faces)
 - c. Words ("pure word blindness")
 - d. Colors
 - e. Environment (including landmarks)
 - f. Simultagnosia (an inability to see more than one object at a time)
3. Functional imaging demonstrates that specific regions of the brain process different classes of visual stimuli
4. Specific visual information is segregated at the retinal level and different afferent visual input is processed in parallel. Color, angle, motion, depth orientation, and length are processed in different brain regions in parallel
5. "Boundary marking", a low-level visual process groups different stimuli that lead to visual forms. These processes are automatic, not requiring attention or effort and group visual characteristics that are essential for objective cognition
6. Visual attributes are processed in parallel but have to be integrated that is "binding" of visual feature information that is "visual attention."
7. Imaging studies support the fusiform gyri and the lateral occipital cortex as the anatomical substrate for the integrated feature representation and structural description systems
8. Familiar objects are recognized across a wide range of angles and perspectives that is termed the view normalization system

Visual Object Agnosia

These patients are unable to recognize the generic class to which an object belongs. A defect of visual naming is common as is alexia. Some patients with object agnosia may recognize the object when it is moved or rotated. These patients may complain of "unclear" or "blurred" vision, possibly related to a selective defect of low spatial frequency vision that impairs appreciation of static, low contrast stimuli. Moving, high contrast stimuli may be appreciated. Visual object agnosia patients have bilateral lesions in the ventral and mesial part of the occipital temporal visual areas that extend dorsally and laterally.

Disorders of Low-Level Vision

The primary deficit in these disorders is impairment of processing of different types of visual feature information.

Achromatopsia

Achromatopsia is an acquired impairment of color perception that manifests as an inability to distinguish color. It varies widely in its clinical expression from a mild loss of intensity or richness of color (e.g. "red desaturation"—red looks brownish) to a complete loss of color sense. If severe, patients may see the world as black or white or shades of gray. The de-

fect may affect only one visual field. Lesions generally involve the lingual or fusiform gyrus. It may be associated separately or associated with prosopagnosia, alexia, and superior visual field deficits. Rarely is it associated with visual object agnosia.

Motion perception deficit (akinetopsia) results from damage to cells that are biased to discharge by motion are localized in the retina, lateral geniculate body, primary visual cortex, and the MT (medial temporal gyrus). Pure disorders of motion perception are rare. One patient extensively studied with profound impaired motion perception suffered bilateral infarcts of the posterior portions of the middle temporal gyri that extended into the occipital lobe and adjacent subcortical white matter. Movement was not perceived as a continuous process – objects jumped from one position to the next. Moving objects would appear static.

Patients have been described in which object recognition is influenced by motion. This manifests as failure to recognize static stimuli (“static form agnosia”) but ability to recognize the object when it is moved. The posterior portion of the middle temporal gyrus (V5) is specialized for motion processing.

Visual Form Agnosia

Visual form agnosia has been postulated to be a deficit in the segregation of coherent regions of visual input. Patients are unable to discriminate shape although there is no impairment in cognitive function or the recognition in differences in luminance, wavelength, area or motion. The two patients described also had difficulties recognizing drawings, letters, or faces. MRI revealed bilateral lesions of the lateral occipital lobes.

Definition of Visual Attention

Simultanagnosia

Simultanagnosia is the inability to see more than one object at a time. Patients may also have difficulty with recognizing single objects. This impairment is usually a deficit in the ability to appreciate the entire visual stimulus. Dorsal simultanagnosia is associated with a visual field deficit and has been described with bilateral posterior parietal-occipital lesions. It has been postulated that this is an impairment of visual attention allocation that is required for the integration of visual feature information. These patients incorrectly combine visual features.

Deficits in the View Normalization System

These patients have difficulty identifying objects from different angles, perspectives or views. Several patients have been described with lesions of the posterior portion of the non-dominant hemisphere. It has been suggested that patients are unable to generate a representation of the object in its canonical principal axis.

Associative Agnosia

Associative agnosia refers to the failure to name an object although the patient may be able to copy it. Patients are able

to describe the object visually, but are unable to do so verbally or by touch. This differentiates the disorder from loss of knowledge of the object which is a semantic deficit. These patients have difficulty sorting complex non-object figures.

Prosopagnosia

Prosopagnosia is a visual agnosia characterized by an inability to recognize previously known human faces and to learn new ones. Recognition through other sensory channels is intact. These patients are unable to recognize stimuli that belong to a group that have numerous subcomponents. Patients can perform generic recognition. They recognize the class to which the stimulus belongs, but are unable to identify a specific member within the generic class. The deficit lies in the appropriate retrieval of contextual memory (one possible mechanism). Lesions associated with prosopagnosia are usually bilaterally in the temporo-occipital area although they have been described with lesions only in the right hemisphere. Functional MRI has delineated a region of the fusiform gyrus bilaterally designated as the “fusiform face area” that is activated by the presentation of faces. The argument is primarily whether prosopagnosia should be considered a cortical module for the processing of faces or is part of the visual recognition system that is biased for the stimulus properties that characterize faces. Additional deficits that have been described with prosopagnosia include achromatopsia, visual field loss, topographical memory loss and object agnosia. Most patients described have suffered emboli to the distal branches of the posterior cerebral arteries that may have occurred at different times. Some patients have had bilateral tumor involvement. It has also been described as an epileptic phenomenon.

Pure Alexia

Alexia without agraphia or “word blindness” is a disorder of visual pattern recognition. These patients can copy what they cannot read, have normal visual acuity and have normal recognition of non-verbal visual stimuli. They are unable to evoke the appropriate associated material when confronted with words. Speech, writing, auditory comprehension is normal.

The necessary lesions to cause the syndrome must disconnect both visual association cortices from the dominant language area. Lesions of the splenium of the corpus callosum cause interhemispheric disconnection and combined with a lesion of the left occipital cortex cause disconnection of visual association cortex with the language areas. A lesion of the tapetum, beneath the occipital horn can disrupt both callosal and left visual association fibers and thus cause pure alexia. Patients may have alexia and visual agnosia with additional right visual association cortex lesions.

Disorders of Spatial and Topographic Orientation

These patients demonstrate an acquired inability to locate a familiar room in their house, a common public building

and are unable to utilize verbal directions to locate a specific place. This type of deficit may occur secondary to unilateral hemispatial neglect or from a global amnesic syndrome. These specific defects underlie a lack of visuospatial memory whereby the architectural or topography detail cannot trigger the retrieval of stored memories that could be utilized to plan a route to the desired destination. Bilateral lesions of the inferior and superior visual association cortices especially the right occipital parietal area cause this deficit. Patients with prosopagnosia may have impaired ability to learn new topographic paradigms. These patients may also be unable to identify cities on a map, to draw a state or country and suffer geographical orientation deficits.

Disorders of Color Perception

There are acquired disorders of color perception that involve all or part of the visual field with preservation of formed vision. Patients with central achromatopsia lose color vision in a portion or all of their visual field. They report the deficit most often as a dulled or washed out but distinguishable color or as a complete loss of color so that the patient only sees objects as black or white. Patients otherwise see accurately in the colorless portion of their visual field. Patients with full visual field achromatopsia often have impairment in portions of their visual field with visual agnosia, and blindness for form. A lesion of the left inferior occipital temporal cortex may cause pure right hemi-achromatopsia alexia from damage to intra- and interhemispheric visual pathways within the left occipital cortex. These lesions are often embolic to the terminal branches of the posterior cerebral artery that supply the fusiform and lingual gyri.

Disorders of Color Naming

These patients can match colors, but are unable to name them. They are not aphasic and have no deficit of color perception. They have concomitant right homonymous hemianopsia, intact color perception in the left visual field and pure alexia. The lesion responsible for this color-naming deficit is in the left hemisphere between the occipital and temporal lobe. The right homonymous deficit is from a lesion in the geniculate body, optic radiation or visual cortex. Some patients demonstrate more difficulty in naming colors to confrontation than on pointing to them. In general, disorders of hue and color perception are associated with prosopagnosia and those of color naming are associated with alexia and word blindness. Some patients suffer the inability to associate a specific color with a specific object which is easily accomplished by patients with an isolated color naming defect.

Disorders of Spatial Analysis

Bálint's Syndrome

Bálint's syndrome is an acquired inability to perceive the visual field as a whole and to perform visually guided move-

ments, and to shift gaze to new stimuli in the visual fields. They have visual disorientation, optic ataxia, and apraxia. Visual disorientation and optic ataxia can occur concomitantly with one of the other two components of the syndrome.

Patients most often see only the macular component of the visual field, but even this fragment of the visual field moves erratically from quadrant to quadrant. These patients fail to orient to new stimuli that appear in the peripheral field unless the erratic movements of the macular component settles on it. They often have simultagnosia, the inability to report more than one or two components of a scene which may suddenly vanish as the center of vision shifts. Patients also complain that moving objects are difficult to see. Patients concomitantly suffer optic ataxia which is the inability to grasp an object using visual guidance. They can point to objects in their own body and to the origin of sounds. They frequently undershoot the grasp of the intended object. Patients have ocular apraxia and are unable to generate a saccade that will fix gaze on a new stimulus that enters the periphery of the visual field. Bálint's syndrome is most often encountered following damage to bilateral occipital parietal watershed regions between the anterior and posterior cerebral arteries and the middle cerebral artery. In the complete syndrome, there is frequent involvement of BA7, BA19 and BA39. Most lesions that cause Bálint's syndrome are in the parietal-occipital cortex. Patients that have visual disorientation in isolation have bilateral lesions of the supracalcarine cortex that spares the parietal cortex.

Area 7 of the parietal lobe contains cells that discharge to and direct gaze to new stimuli that appear in the peripheral visual field and are important for visually guided hand movements. The superior occipital striate and peristriate cortex are important for perception of the visual field as a whole. Patients with Bálint's syndrome have impaired perception of spatial information outside of their own body. They often cannot locate an object and cannot tell if an item is moved towards or away from them. Bálint's syndrome has been suggested as a type of double neglect. They may neglect both sides of a room, but can see a single object. In hemineglect from a right parietal lesion, there is inattention to the left side of visual environment as well as the left side of objects. They (Bálint's patients) see complete objects and neglect both sides of the room.

Deficits of Stereopsis

The ability to discriminate depth from binocular visual cues is stereopsis. Two-dimensional projections of these dimensional objects are projected to slightly different portions of the left and right retinas. This horizontal disparity provides the anatomic basis of stereopsis. There seems to be stereoptic function in each hemisphere. Both the striate and peristriate cortex have cells that respond to binocular stimuli. The disparities are processed by these cells which produces depth perception. The perception of depth and 3-dimensional structure can be performed with one eye from differences in object

size and motion parallax although not as accurately as that derived from bilateral disparities.

Course stereopsis is used to estimate stereoscopic motion in the environmental periphery. It provides the sense of localization in one's environment and is important for orientation in space while moving. Fine stereopsis is required for the completion of delicate motor tasks (i.e., threading a needle). Fine stereopsis requires good visual acuity in each eye to be able to detect small spatial differences. Coarse stereopsis is associated with the magnocellular visual pathway that processes low spatial frequency disparities and motion. Fine stereopsis is processed by the parvocellular pathway that processes high spatial frequency retinal disparities.

Cortical Blindness (Anton's Syndrome)

Most patients have suffered bilateral damage to both visual cortices and to the optic radiations.

They have:

1. Inability to see
2. Often are euphoric
3. Have normal pupillary responses
4. Deny blindness
5. Confabulate vision
6. Patients may be able to move around a room without hitting large objects possibly related to preserved islands of retinal rod vision

The Insular Cortex (IC)

General Characteristics

1. The insular cortex is a portion of the cerebral cortex located deep within the lateral sulcus. It is divided into two parts:
 - a. The anterior insula and the posterior insula
2. The cortical operculum overlies the insula which is formed from components of the frontal, temporal and parietal lobes
3. The anterior insula has an agranular cytoarchitecture while the posterior IC is granular
4. The anterior insular cortex contains von Economo neurons that are large bipolar neurons found only in the great apes and humans. They have a simple dendritic structure which has been posited to enable them to process information rapidly. They are selectively lost in the early stages of frontotemporal dementia that supports their involvement in empathy, social awareness and self-control
5. The anterior insula afferences are primarily from:
 - a. Basal ventral medial nucleus of the thalamus
 - b. The central nucleus of the amygdala with which it is reciprocally connected
6. The posterior insula:
 - a. Connects reciprocally with the secondary sensory cortex (SII)
7. Receives afferents from:

- a. Spinothalamic projections that activate the ventral posterior inferior thalamic nuclei (VPI)
- b. Posterior VPM
8. The efferents from the anterior insular cortex include:
 - a. The anterior amygdaloid area
 - b. The medial, cortical, accessory basal magnocellular, the medial basal and lateral amygdaloid nuclei
 - c. Temporal and occipital lobes, the operculum and orbitofrontal cortex and the triangular and opercular parts of the inferior frontal gyrus. Asymmetrical connections have been noted between the hemispheres
 - d. The efferents from the posterior insula include:
 - i. The dorsal region of the lateral nuclei of the amygdala
 - ii. Central amygdaloid nuclei

Clinical Manifestations

1. Interoceptive awareness:
 - a. Both the right frontal insular cortex and the anterior cingulate cortex have von Economo (spindle) neurons that are thought to be involved with empathy and self-aware emotional feelings. It has been suggested that these feelings are a consequence of the role of the insula in the homeostatic aspects of consciousness. In particular, functional MRI studies suggest that the right insula is involved in the interoceptive awareness of body states
 - b. The insular cortex is a major component of the afferent pain matrix
 - i. It is the only area of the brain that when stimulated causes pain
 - ii. The insula is activated when a patient looks at painful events and when the patient anticipates forthcoming pain and its degree
 - iii. The right anterior insula is activated by the degree of non-painful warmth or coldness, gastric dilatation and a full bladder
 - iv. The unpleasantness of dyspnea may be processed by the right insula cortex
 - c. The insula may be activated by vestibular sensation. Lesions of the anterior insula cortex have been described that cause loss of balance and vertigo
 - d. Non-interoceptive perceptions processed or modulated by the insula include:
 - i. Laughter and crying
 - ii. Empathy and compassion
 - iii. Aspects of language
 - e. Motor control: The insular cortex has been ascribed to have a role in:
 - i. Hand and eye movement
 - ii. Swallowing
 - iii. Gastric motility
 - iv. Speech articulation:
 1. Involved in the capacity to maintain long and complex sentences

- v. Motor learning
- vi. Possible role in stroke recovery
- vii. Increases heart rate and blood pressure at the onset of exercise
- f. Homeostasis:
 - i. The insula cortex is a major component of the autonomic nervous system by its regulation of sympathetic and parasympathetic projections. It is important in homeostatic functions such as taste, visceral sensations and autonomic control
- g. Sense of self:
 - i. The IC has a role in the perception of self-awareness, sense of agency and body ownership
- h. Social emotional state:
 - i. Emotional experience that the anterior insular cortex processes includes:
 - 1. The sense of disgust to smells, and at the sight of mutilation or contamination which is a possible link between external and internal experience
 - 2. It is activated by norm violations; empathy and orgasm
- i. Affect:
 - i. The insula cortex is part of the limbic system. It has a major role in body representation and emotional experience, particularly visceral states that are associated with emotional experience

The anterior insula processes olfactory, gustatory, visceral, autonomic, and limbic functions. The posterior insular cortex is involved with auditory, somatosensory and motor functions. Both anterior and posterior insular cortices process convergent and primary inputs that induce an emotionally relevant context for sensory experience.

Functional MRI protocols have demonstrated activation of the anterior insular cortex by feelings of romantic and maternal love, anger, fear, sadness, happiness, sexual arousal, disgust, aversion, unfairness and inequity, indignation, uncertainty, disbelief and trust.

Importantly, the insular cortex as noted above is important in the affectual aspects of pain, food and drug craving as well as addiction.

The insular cortex is involved in the processes that link interoception with emotional salience which generates a subjective representation of the body. The distributed loops for this salience function include:

1. The anterior insular cortex, the pregenual anterior cingulate cortex (BA33)
2. The anterior and posterior mid-cingulate cortex
3. A general salience system that processes:
 - a. Monitoring of the environment
 - b. Response selection
 - c. Motor functions that engage all of the insular cortex as well as the mid-cingulate cortex
4. Additionally, it is proposed that the right anterior insular cortex regulates the dorsal attention system that controls the salience of selective attention required to complete a

task; the salience of arousal mediated by the ventral attention system needed to maintain focus on the behavioral task

Neuropathology

1. The insular cortex is most often involved in:
 - a. Neurodegenerative disease (FTLD)
 - b. Stroke (MCA branches)
 - c. Glioma
 - d. Rare inflammatory conditions
 - e. Autoimmune processes exemplified by paraneoplastic diseases
2. Progressive non-fluent aphasia:
 - a. Associated with hypometabolism and atrophy of the left insular cortex
 - b. Occurs in Pick's disease, frontotemporal dementia, some forms of motor neuron disease, corticobasal degeneration and rarely Alzheimer's disease
3. Addiction:
 - a. Functional MRI protocols have demonstrated that during drug craving in addicts the insular cortex is activated. This activation has been demonstrated for cocaine, alcohol, opiates and nicotine
 - b. It has been postulated that the insula stores representations of the pleasurable interoceptive sensations of drug use which are activated by exposure to environmental cues of post-drug use. Thus the insula may be involved in memory of pleasurable interoceptive drug effects
 - c. Subjective certainty:
 - i. The strong feeling of certainty may be caused by dysfunction of the anterior insular cortex. Mismatches between the predicted state and actual state are no longer perceived with anterior insular cortex malfunction. This produces a state of emotional confidence (with no anxiety)

Laboratory Evaluation

1. MRI:
 - a. Structural lesions from stroke and tumor
 - b. Gadolinium enhancement with pathologies that disrupt the blood-brain barrier
2. EEG
3. Laboratory evaluation for autoimmune, paraneoplastic and medical conditions
4. Neuropsychological evaluation in the early stages of dementia (FTLD and Pick's disease)

Arousal

General Characteristics

1. Arousal is the physiological and psychological state of being fully alert. It requires activation of the reticular activating system in the brainstem whose projections extend throughout the cortex. The transmitters involved are norepinephrine, dopamine, histamine, acetylcholine and serotonin

- a. The acetylcholinergic system is located in the pons and basal forebrain. Stimulation of the system increases cortical activity and alertness. The four other basic neurotransmitter systems activate acetylcholinergic neurons

The origin of the noradrenergic system is the locus coeruleus that projects to the neocortex, limbic system and basal forebrain. There is a heavy projection of noradrenergic innervations to the posterior cortex and the basal forebrain that synapse with acetylcholine neurons. Noradrenergic discharge increases wakefulness and increases vigilance.

The origin of the dopaminergic system is the ventral tegmental areas of the midbrain (A9 of the SNpc) and A10 primarily. Dopaminergic neurons project to the nucleus accumbens, the striatum, forebrain, limbic system and the prefrontal cortex. The limbic system is essential for the regulation of mood. The central nuclei of the amygdala signals fear, and the prefrontal cortex regulates movements associated with an emotional context.

The origin of the serotonergic system is the raphe nuclei of the reticular formation. Activation of this system causes cortical arousal, elevated mood and amplified movement.

The tuberomammillary system is the origin of the histaminergic system that projects widely to the frontal cortex, thalamus and basal forebrain. It stimulates the release of acetylcholine into the cortex.

The interplay between the ascending reticular activating system and posterior thalamic nuclei and their projections are major determinants of wakefulness. The ascending reticular activating system originates in the lateral medulla. It receives projections from the spinothalamic tract and all major special senses. The dorsal pons, periaqueductal gray and intralaminar nuclei of the thalamus are major subcortical components. The intralaminar nuclei project bilaterally to the cortex. Each cortical area is activated by a reticular activating system projection.

Arousal is compromised by lesions in:

1. Lateral > medial reticular formation
2. Dorsal pons
3. Periaqueductal gray matter of the midbrain
4. Intralaminar thalamic nuclei
5. Bilateral involvement of the cerebral cortex is required for a depression of consciousness
 - a. There is full alertness with one functioning hemisphere
6. The ventrolateral preoptic area is a descending GABAergic pathway that dampens wakefulness and arousal. Acetylcholine and norepinephrine inhibit projections from the ventrolateral preoptic nuclei

Clinical Manifestations

1. Akinetic mutism is a state of disordered arousal in which the patient neither initiates nor responds easily to verbal stimulation. Patients lack spontaneous movements, speech, facial expression or gestures. They may retain visual tracking movements that appear to be purposeful.

They appear to be alert. These characteristics are manifested by patients with bilateral frontal lobe damage

2. Mesencephalic akinetic mutism is distinguished by drowsiness, hypersomnolence, vertical gaze palsy, ophthalmoplegia and decreased spontaneous speech and movement

Neuropathology

1. Frontal lobe damage:
 - a. Lesions may be in the basal forebrain of the frontal lobe bilaterally
 - b. Trauma
 - c. Anterior cerebral artery rupture with vasospasm
2. Thalamic damage:
 - a. Most often hemorrhage or venous thrombosis (inferior or superior sagittal sinus thrombosis)
 - b. Trauma with disruption of the intralaminar nuclei
 - c. Midbrain:
 - i. Pressure from cerebral herniation (diencephalic)
 - ii. Stroke (interpeduncular artery) and hemorrhage
 - d. Ablation or damage of the cingulate gyrus

Laboratory Evaluation

1. MRI:
 - a. To evaluate structural lesions
2. EEG
3. Metabolic and toxic screen
4. CSF evaluation to r/o infectious etiologies

Differential Diagnosis

1. Respiratory and cardiac arrest that induces cerebral hypoxia
2. Rare encephalitis lethargica
3. Meningitis
4. Hydrocephalus
5. Trauma (frontal lobe, midbrain and cingulate gyrus)
6. Aneurysm (primarily anterior communicating and basilar) and their repair from vasospasm
7. Tumors (frontal lobe gliomas that cross the corpus callosum; thalamic tumors)
8. Olfactory groove meningioma (severe frontal lobe pressure)
9. Third ventricular cyst (head bobbing in children)
10. Toxins
11. Delayed post-hypoxic leukoencephalopathy (often occurs two weeks after a successful cardiac resuscitation)
12. End stage Creutzfeldt-Jakob disease (mesencephalic involvement)

Abulia

General Characteristics

1. Abulic patients resemble those suffering from akinetic mutism but differ in that, with intense verbal stimulation, they may be induced to respond or move

Clinical Manifestations

1. Lack of initiation and the ability to sustain purposeful movement
2. Decreased spontaneous movement
3. Decreased spontaneous speech with increased response time to questions
4. Reduced emotional responsiveness and social interaction
5. Inability to swallow (patients hold food in their mouths for hours)

Neuropathology

1. Disruption of frontal circuits
2. Lesions that involve:
 - a. The basal ganglia. Approximately 15% of patients with basal ganglia lesions have diminished motivation
 - b. Capsular genu:
 - i. Damage to the thalamocortical projections that originate in the ventral anterior and medial dorsal nuclei
 - c. Damage to the anterior cingulate circuit which is important for initiation of behavior, motivation and goal orientation
 - d. Caudate nucleus lesions; most often the left caudate is involved with extension into the putamen
 - e. Pathologies with prominent abulia include:
 - i. Depression
 - ii. Schizophrenia
 - iii. Parkinson's disease
 - iv. Huntington's disease
 - v. Pick's disease
 - vi. PSP
 - vii. Traumatic brain injury
 - viii. Stroke

Laboratory Evaluation

1. MRI:
 - a. To rule out structural lesions
2. EEG
3. Neuropsychological evaluation

Unresponsive Wakefulness (UWS)*General Characteristics*

1. The older terminology for unresponsive wakefulness was the chronic vegetative state

Clinical Manifestations

1. Residual cortical processing in the absence of behavioral signs of consciousness
2. Patients are in a state of partial arousal rather than awareness
3. Patients are unresponsive to external stimuli
4. Patients may be able to track moving objects, but often maintain a fixed position
5. The sleep-wake cycle may be retained or they may be in a state of chronic wakefulness

6. Brainstem reflexes may be evident and include:
 - a. Grinding of teeth
 - b. Swallowing
 - c. Smiling, shedding tears, moaning or screaming without external stimulation

Neuropathology

1. Hypoxic ischemic injuries
2. Stroke particularly of the vertebrobasilar system
3. Intracranial hemorrhage (most often basal ganglia or thalamic with midbrain compression)
4. Severe increased intracranial pressure from any structural lesion
5. Systemic infections and sepsis
6. Traumatic brain injury
7. Hepatic encephalopathy
8. Adrenal and thyroid failure
9. Electrolyte disorders
10. Seizures:
 - a. Non-convulsive status epilepticus
 - b. Post-ictal state
11. Meningitis (bacterial, viral, fungal)
12. Toxins (uremia, ethanol, opiates, lead)
13. Metabolic disease (urea cycle disorders, Reye's syndrome, mitochondrial disease)
14. Degenerative diseases
15. Acute disseminated encephalomyelitis

Laboratory Evaluation

1. MRI:
 - a. To rule out structural lesions
2. EEG
3. Toxic and metabolic screen
4. Functional MRI to evaluate brain functional connectivity and responsiveness

The Minimally Conscious State (MCS)*General Characteristics*

1. Following coma a majority of patients transition to unresponsive wakefulness syndrome or a minimally conscious state
2. MCS demonstrates the presence of inconsistent, but behavioral signs of awareness of self or the environment
3. The MCS has been subcategorized into MCS+ and MCS- conditions

Clinical Manifestations

1. MCS+ patients:
 - a. Are able to follow commands
 - b. Have intelligible verbalization
 - c. Can respond to gestural or verbal yes/no responses
2. MCS- patients:
 - a. Non-linguistic signs of conscious awareness that include:
 - i. Visual pursuit
 - ii. Localization of painful stimuli
 - iii. Appropriate behavioral response to some stimuli

Elicited Behaviors That Establish the Diagnosis of MCS

1. Following commands
2. Gestural or verbal yes/no responses
3. Intelligible verbalization
4. Purposeful behavior elicited from appropriate environmental stimuli
5. Reaching for objects with correct relationship between object location and direction of the reach
6. Manipulation of objects in accordance with their size and shape
7. Pursuit eye movements or sustained fixation in response to salient stimuli

Neuropathology

1. All of the pathologies noted to cause the unconscious awareness syndrome. Especially prominent are:
 - a. Recovery from hypoxic-ischemic injury (cardiac and respiratory arrest)
 - b. Severe post-traumatic brain injury
 - c. Cerebral vascular disease that includes large artery occlusions of both anterior and vertebrobasilar circulations
 - d. Basal ganglion thalamic hemorrhages

Laboratory Evaluation

1. MRI/MRA:
 - a. To evaluate structural lesions and blood vessel patency
2. Functional MRI:
 - a. Resting state functional magnetic imaging:
 - i. Group level functional connectivity of the following systems:
 1. Default mode network
 2. Frontoparietal
 3. Salience
 4. Auditory
 5. Sensory motor
 6. Visual networks were evaluated in patients with minimally conscious state, unconscious awareness syndrome and comas
 7. Coma recovery scale-revised correlates with nodes of each network that supports their involvement in consciousness
 8. All networks had >80% discriminative capacity to separate patients in a minimally conscious state from those with unresponsive wakefulness syndrome (UWS)
 9. The auditory network was more functionally connected in patients in the MCS compared to unresponsive wakefulness
 10. Multisensory integration and top-down processing supported by auditory and visual cross-modal connectivity of the auditory and visual cortices are essential for the MCS
3. Event-related potentials:
 - a. The P3 component is related to attention and may predict awakening from coma

- b. The salient value of the patient's own name has been chosen as the self-referential stimulus to elicit the P3 response

Differential Diagnosis of Disorders of Arousal

1. Cerebral herniation
 - a. Cingulate gyrus herniation under the falx cerebri:
 - i. Compromises venous outflow which increases intracranial pressure and is a major cause of central (diencephalic herniation)
 - ii. The usual lesions are structural and are located above the tentorium (intracranial hemorrhage, brain tumors, traumatic brain injury with edema, subdural and epidural hematoma)
 - b. Transtentorial diencephalic herniation:
 - i. Compresses the midbrain RAS at the level of the periaqueductal gray
 - ii. Causes rupture of pontine and midline mesencephalic arteries and veins (Duret hemorrhages)
 - iii. Unilateral uncal herniation:
 1. Unilateral temporal lobe swelling from tumor, trauma or a vascular event
 2. IIIrd nerve palsy is an early sign
 - iv. Upward herniation:
 1. Posterior fossa lesions
 2. Most often seen in children with posterior fossa tumors
 3. Extraocular movement paralysis occurs prior to pupillary involvement
 - a. Compression of the collicular plate by the vermis
2. Thalamic/subthalamic infarction:
 - a. Top of the basilar artery embolus
3. Various vertebrobasilar infarctions (most often the basilar artery)
 - a. Basal forebrain lesions
 - i. Abulia
4. Locked-in syndrome:
 - a. The patient is unable to move or speak due to paralysis of somatic muscles
 - b. The patient is completely alert and aware
 - c. Is able to follow commands utilizing vertical eye movements
 - d. In total locked-in syndrome, the eyes are completely paralyzed
 - e. Many patients retain all sensory modalities
 - f. A few patients may retain the ability to use some facial musculature
 - g. Most often caused by infarction of the ventral pons
 - h. Rare causes include:
 - i. Central pontine myelinolysis
 - ii. Traumatic brain injury
 - iii. Neurotoxic snake venom
 - iv. Autoimmune demyelinating disease

5. Acute agitated delirium
 - a. Caudate nucleus infarction (R > L)
 - b. Bilateral temporal lobe dysfunction
 - c. Right-sided temporo-parieto-occipital lesions
 - d. Orbitofrontal lesions
6. Hyperalertness or insomnia:
 - a. IIIrd cranial nerve ventricular lesions
 - b. Anterior thalamic structural lesions and prion disease of the same nuclei
7. Sleep disturbances
 - a. Sleep apnea
 - b. Locus coeruleus lesions
 - c. Pedunculopontine lesions
8. Delirium:
 - a. Drugs
 - b. Toxins
 - c. Metabolic disorders
9. MCS (minimal conscious state)
10. UWS (unresponsive wakefulness syndrome)

Memory and Amnesia

Overview

The three major processes involved in the very complicated mechanisms that underlie memory are:

1. Encoding or registration:
 - a. Processing and combining of specific information
2. Storage:
 - a. The record of the encoded information in short- or long-term memory
 - b. Retrieval of the stored information in response to a cue

At the molecular level, protein synthesis is required for long-term memory, but not for task acquisition and short-term memory formation. Pharmacological and genetic studies have demonstrated the critical role of *de novo* gene expression and protein synthesis in long-term memory. The fundamental process that underlies memory formation is synaptic plasticity, the ability of synapses to strengthen (long-term potentiation) or weaken (long-term depression) their connections between neurons from activity-dependent stimuli. The maintenance of these changes in synaptic efficacy is triggered by *de novo* protein synthesis.

Neuronal dendrites and spines contain polyribosomes, translation factors, and messenger RNA (mRNA). Protein synthesis is triggered at activated synapses. A complicated series of steps is involved in the process of mRNA translation, translational control primarily occurs as the rate-limiting initiation step rather than during elongation or termination. Gene-specific translational control occurs by phosphorylation of the protein initiating factor eIF2- α , which in turn is accomplished by eIF2- α kinases. EIF2- α phosphorylation is divergently activated during LTP or LTD which regulates the translation of specific sets of mRNA to strengthen or weaken synaptic efficacy.

Short-term memory is primarily referred to as working memory. It underlies recall for several seconds to a minute without recall. The store of short-term memory items is 4–5 items. Short-term memory uses an auditory more than a visual code.

Long-term memory is encoded semantically. A component of long-term memory is episodic memory, the encoding of specific events. Short-term memory is supported by neural circuits that include the dorsolateral prefrontal cortex, while long-term memory is more widely distributed throughout the brain. The hippocampus is required for learning new information and for the consolidation of information from short-term to long-term memory.

Declarative memory, also known as explicit memory, requires conscious recall. It is subdivided into semantic memory (principles and facts) and episodic memory (related to a particular context, the time and place of the event). Autobiographical memory, the personal events of one's life, is a subset of episodic memory.

Implicit or procedural memory is not conscious recall of information, but is based on implicit learning. It is primarily the memory of the process that underlies motor skills. It is dependent on the cerebellum and basal ganglia.

Isolated memory disorders in amnesia frequently occur following bilateral involvement of the medial temporal lobe and the CA1 region of the hippocampus, as well as the dorso-medial nucleus of the thalamus. Anterograde amnesia is the inability to learn new material, while retrograde amnesia is the inability to remember events prior to an injury. In some instances of retrograde amnesia, the memory loss can extend back for decades, while in other instances it may extend only for days or weeks. Both types of amnesia can manifest simultaneously. Patients may retain the ability to recall immediate information, and may still be able to form new memories. Most patients have difficulty learning new material, as well as with retrieval of stored information. They retain the ability to learn procedural knowledge. Many patients retain intellectual, linguistic, and social skills. In some patients, older memories are most resistant to amnesia.

In a core amnesic syndrome, patients suffer a global anterograde and retrograde memory deficit with occasional confabulation. Other cognitive functions, including attention and motivation, are intact.

Differential Diagnosis of Amnesia

Wernicke-Korsakoff's Syndrome

1. General characteristics:
 - a. Most often seen in a context of long-term alcohol abuse and malnutrition (stomach cancer, anorexia nervosa)
 - b. It is caused by vitamin B1 deficiency

Korsakoff's Syndrome

1. The acute onset of severe memory impairment without loss of other cognitive abilities

2. Clinical manifestations:
 - a. Anterograde amnesia
 - b. Variable retrograde amnesia
 - c. One of:
 - i. Aphasia
 - ii. Apraxia
 - iii. Agnosia
 - iv. Deficit in executive function
 3. Cognitive deficits:
 - a. Anxiety and difficulty with concentration
 - b. Confusion
 - c. Confabulation
 - d. Inability to focus
 - e. Deficits in cognitive estimation tasks
 - f. Confabulation
 - i. Spontaneous confabulation (incorrect memories that the patient may act on) is more common than provoked confabulation. It is posited that the patient cannot remember the spatial and contextual information of an event, and utilizes older or irrelevant memory traces to compensate for inaccessible information. Another hypothesis is that patients suffer executive dysfunction, in which they are unable to inhibit incorrect memories or to shift attention away from an incorrect response
 4. Neuropathology
 - a. Anatomically there are bilateral lesions of the mammillary bodies, the anterior column of the fornix, hypothalamic nuclei, the dorsal medial nuclei of the thalamus, the medial pulvinar, and lateral dorsal thalamic nuclei. The dorsal medial nuclei of the thalamus may be important for confabulation as well as memory
- iv. Hypothermia
 - v. Seizures
 - vi. Progressive hearing loss
 - vii. Photophobia
3. Neuropathology of WKS
 - a. Brain atrophy occurs in:
 - i. The mammillary bodies (they may also be enlarged in Leigh's myopathy); over time they atrophy
 - ii. Thalamus (mediodorsal nucleus)
 - iii. Hypothalamus
 - iv. Periaqueductal gray
 - v. The walls of the IIIrd ventricle and the floor of the IVth ventricle may be hemorrhagic
 - vi. The cerebellum and frontal lobe are involved
 4. Laboratory evaluation:
 - a. MRI: Evidence of cytotoxic edema in the mammillary bodies, mediodorsal thalamic nuclei, tectal plate and the periaqueductal region
 - b. Vitamin B1 assay

Post-Traumatic Amnesia

1. The amnesia may be retrograde, anterograde, or of mixed type
2. It is usually transient, but may be permanent, dependent on the degree of injury

Dissociative Amnesia

1. The inability to recall information following a stressful or traumatic event
2. Access to long-term memory is impaired due to psychological defense mechanisms
3. Patients retain the ability to learn new information, and with time there may be partial or complete recovery of memory

Transient Global Amnesia (TGA)

1. General characteristics
 - a. TGA's major defining elements are loss of short term memory and dysfunction in accessing older memories
2. Clinical characteristics:
 - a. Inability to encode new memories
 - b. The patient retains complete consciousness, has knowledge of self-identity, and maintains perceptual skills and a complex of learned behaviors
 - c. The degree of amnesia is severe, and the patient may be anxious during the attack. Memories for distant events may be affected to a degree
 - d. The attack is witnessed by a reliable observer who documents a clear loss of short-term memory (anterograde amnesia)
 - e. Consciousness is clear
 - f. There are no focal neurologic signs, such as seizure activity, during or after the episode
 - g. The attacks usually last between 2–8 hours, and resolve within 24 hours

Wernicke's Encephalopathy

1. General characteristics:
 - a. Most often there is an acute Wernicke's encephalopathy phase followed by chronic Korsakoff's syndrome
 - b. Wernicke's encephalopathy is caused by vitamin B1 deficiency
2. Clinical manifestations:
 - a. Confusion, apathy, inability to concentrate and decreased awareness of the environment
 - b. Mental status changes occur in approximately 80% of patients with Wernicke's encephalopathy
 - c. Approximately 30% of patients develop partial ophthalmoplegia. Caucasian patients are more frequently involved with ophthalmoplegia than black patients. Rarely there is disc swelling and abnormalities of the pupillary light reflex
 - d. Cerebellar and vestibular symptoms are seen as well as stance and gait abnormalities in 25% of patients
 - e. Variable features include:
 - i. Stupor
 - ii. Hypotension
 - iii. Severe tachycardia

- h. Perseveration, in which the patient repeats statements or questions, is common
- i. Patients may be disoriented in time and space
- j. Approximately 10% of patients appear emotional during an attack, with some expressing a fear of dying
- k. The majority of patients suffer no long-term effects, but there is a complete lack of recall for events during the attack; this is almost always anxiety provoking to the patient. Memory may be lost for events that occurred 1–2 hours prior to the attack
- l. Precipitating events can be documented in approximately 1/3 of patients. They include:
 - i. Vigorous exercise
 - ii. Sexual intercourse
 - iii. Swimming in cold water
 - iv. Emotionally traumatic or stressful events
 - v. Following medical procedures
- 3. Neuropathology
 - a. The hippocampus and amygdala are the primary sites of involvement
 - b. It has been posited that TGA may be caused by vascular insufficiency, a TIA (transient ischemic attack), a temporal lobe seizure, or migraine
- 4. Laboratory evaluation:
 - a. MRI:
 - i. Brain MRI with and without contrast, with 3 mm oblique axial hippocampal sections to rule out possible structural lesions
 - b. EEG:
 - i. Some patients have been posited to suffer transient epileptic amnesia
- 5. Differential diagnosis of transient global amnesia (TGA)
 - a. Vertebrobasilar TIA (ischemia of the hippocampus and amygdala)
 - b. Cardioembolic stroke (top of the basilar artery)
 - c. Complex partial seizures (temporal lobe origin) or focal frontal lobe seizure
 - d. Migraine variant
 - e. Posterior cerebral artery ischemia

Hypothalamic Tumors

- 1. Amnesic syndromes have been reported in cases of hypothalamic tumors, particularly in those surrounding the walls and floor of the IIIrd ventricle

Thalamic Lesions

- 1. Bilateral dorsomedial thalamotomies cause transient loss of the temporal organization and chronology of a patient's experience
- 2. Thalamic infarcts affecting the paramedian and dorsomedial nuclei are associated with severe anterograde and retrograde memory loss. Unilateral left thalamic lesions in the dorsomedial or anterior thalamic nuclei have been associated with anterograde amnesia, particularly for language

Basal Forebrain Lesions

- 1. Lesions affecting the septum, hypothalamus, and caudal orbitofrontal regions from tumor or anterior communicating aneurysmal rupture may cause severe amnesia. These pathologies damage the septal nuclei and the nucleus basalis of Meynert (NBM), which destroys the cholinergic innervation of the limbic and frontal cortex

Bilateral Fornix Lesions

- 1. Patients with tumors or bilateral injury may develop an amnesic syndrome

Cingulate Lesions

- 1. Bilateral cingulotomies are associated with transient memory disorders with confabulation similar to Korsakoff's syndrome. These patients may also suffer difficulty in ordering memories in a proper temporal sequence. Amnesic syndrome after callosal commissurotomy or posterior corpus callosum tumor may be due to posterior cingulate gyrus damage

Selective Amnesia from Unilateral Temporal Lobe Lesions

- 1. The recognition of recurring nonsense figures, faces, and maze learning may be difficult after right temporal lobe lesions. The recall of verbal material is disturbed after left temporal lobectomy. The right temporal lobe can recognize non-verbalizable tactile patterns better than the left after commissurotomy
- 2. These deficits clearly overlap with memory and learning deficits

Amnesia of Uncertain Anatomical Cause

- 1. Head trauma:
 - a. Long fiber bundles including the fornix are damaged by shearing forces
 - b. The temporal poles and the orbitofrontal cortex are often severely damaged
 - c. There is a correlation between the amount of damage in these areas with the severity of anterograde and retrograde amnesia

Electroconvulsive Therapy

- 1. Comparable to head injury
- 2. Unilateral ECT-material specific amnesic syndrome, much less severe memory deficits than bipolar techniques (often more effective)

Epilepsy

- 1. Some initial seizures may present as TGA
- 2. Transient epileptic amnesia:
 - a. Attacks are of short duration (<1 hour)
 - b. May recur

Drugs

- 1. Benzodiazepines cause a state similar to transient global amnesia (TGA)

2. Amytal induces “blackouts”
3. Scopolamine induces memory loss similar to amnesic syndromes (rarely used with deliveries)

Psychogenic Amnesia

1. This form of amnesia (dissociative) occurs after strong emotional or psychologic trauma
2. It may be associated with loss of personal identity: patients forget their names and their past, but memory for recent events is normal
3. Anxiety may not be apparent, although it may be accompanied by a fugue state that usually resolves in days to weeks

The Clinical Anatomy of Memory

Memory can be divided into three stages for clinical purposes:

1. Inscription:
 - a. This process takes place during the first 30 seconds, and occurs in the medial hippocampal structures. It has been posited to relate to reverberating circuits, and acetylcholine is the primary neurotransmitter
2. Consolidation:
 - a. The structures that are most important for this phase are:
 - i. The medial hippocampus (CA1 field)
 - ii. The mammillary bodies and the mammillothalamic tract
 - iii. The dorsomedial nucleus of the thalamus
 - b. Messenger RNA is synthesized in synaptic dendritic spines
 - c. The memory trace is vulnerable to intrusions
 - d. Long-term potentiation (LTP) with increased synaptic efficacy is accomplished; that may be the molecular base of the memory trace
 - e. Protein synthesis:
 - i. Long-term memory is related to protein synthesis
 - ii. Long-term potentiation and long-term depression (LTD) are basic mechanisms effected by gene activation
3. Retrieval:
 - a. The dorsolateral prefrontal cortex is important for activating and retrieving memory that has been consolidated
 - b. Cueing appears to affect the DLPFC

Forgetting may be due to LTD (long-term depression) of specific synapses, and due to the unfolding of the tertiary structure of specific synapses or proteins.

Benign Senescent Forgetfulness

1. The greatest difficulty is for names and details, although most events are easily recalled
2. Cueing improves performance
3. The deficit may be at the retrieval stage

Confusional States

1. Overview:
 - a. The definition of delirium or acute confusional state is an organically-caused decline from a previously attained baseline level of cognitive function. An acute confusional state is a change in mental status, the most important feature of which is failure of attention. Most often, there are no neurological signs other than a coarse tremor, myoclonus or asterixis. Vigilance is defective in intensity and selectivity. Attention either wanders aimlessly or is suddenly focused with inappropriate intensity, or an irrelevant stimulus becomes the source of distractibility. Thought and skilled movement are diminished by interference, impersistence, and perseveration. The stream of thought is interrupted by frequent intrusions of competing thoughts and sensations
 - b. The three cardinal features of a confusional state are:
 - i. Disturbance of vigilance and heightened distractibility
 - ii. Inability to maintain a coherent stream of thought
 - iii. Inability to carry out a sequence of goal-directed movements
 - c. Perceptual distortions lead to illusions and hallucinations. Patients are disoriented, have memory deficits, mild anomia, dysgraphia, dyscalculia, and constructional apraxia. Judgment is poor, insight is lacking, affect is labile with a curious tendency for facetious witticism. Some confusional states are apathetic while others cause extreme agitation. Confusional states fluctuate from hour to hour and are exacerbated at night
2. Clinical manifestations:
 - a. Inattention:
 - i. Distractibility and inability to shift and/or sustain attention
 - b. Disorientation:
 - i. Loss of awareness of the environment
 - ii. May occur in the sphere of time, place, or person
3. Deficits in memory occur and are associated with inattention. New long-term memories are not formed, but old memories may be retained
4. Higher cognitive deficits include deficits in:
 - a. Comprehension
 - b. Abstraction
 - c. Initiation/perseveration
 - d. Switching mental sets
 - e. Temporal sequencing and organization
 - f. Insight and judgment
5. Language dysfunction includes:
 - a. Anomic aphasia
 - b. Paraphasias
 - c. Decreased comprehension
 - d. Agraphia
 - e. Word finding
6. Disorganized thinking:
 - a. Tangentially, circumstantiality, and loose associations between elements of thought

7. Sleep abnormalities:
 - a. Disruption of the sleep-wake cycle, which may be seen prior to the episode
 - b. Sleep fragmentation
 - c. Reversal of the sleep-wake cycle, which is a reflection of abnormal circadian rhythm regulation
8. Motor activity:
 - a. Patients may be hypoactive, hyperactive, or show mixed symptomatology
 - b. Hypoactive patients are often misdiagnosed as suffering depression
 - c. Cognitive impairment and EEG slowing are seen with equal frequency in both hyperactive and hypoactive states
 - d. Psychiatric and psychotic symptomatology may be seen in both motor states
9. Psychiatric symptoms:
 - a. Psychotic symptoms occur in 50% of patients in delirium
 - b. Most patients who are in delirium do not have hallucinations or delusions
 - c. Thought content abnormalities include suspiciousness, overvalued ideation, and when severe, delusions which are often of impending danger or threat. Misperceptions include depersonalization and misidentification
 - d. Hallucinations and illusions are most often visual, although tactile and auditory ones have been reported
 - e. Affectual states fluctuate widely, so that a delirious patient may show fluctuations between terror and jocularity
 - f. The most common predisposing factors for delirium include:
 - i. Old age
 - ii. Cognitive impairment and dementia

Aphasia

Overview

Modern techniques of functional brain mapping with MRI and transcortical mapping during epilepsy and brain tumor surgery have demonstrated that the language-distributed networks are different than previously described.

Production of Speech

Prior to speech, the speaker must activate the knowledge of the sequence of consonants and vowel speech sounds (phonemes) of the word to be spoken. This function, prior to articulation, is phonologic retrieval and is accomplished by drawing upon a phonologic mental image of the sounds that make up the intended spoken words. Dysfunction of this retrieval function causes phonemic paraphasia in which there are errors in the phonemes of the intended words to be articulated or their sequence is incorrectly ordered. This type

of deficit is seen in both classic Wernicke's and conduction aphasia. This paraphasic dysfunction is a deficit of speech production rather than speech comprehension.

It has been demonstrated in healthy controls by fMRI, PET, and magnetoencephalography that Wernicke's area is important for phonologic retrieval. The anatomical substrates for this process are the posterior superior temporal gyrus, posterior middle temporal gyrus, and the supramarginal gyrus.

In studies of patients with conduction aphasia, it has been demonstrated that the left pSTG and left inferior parietal lobule are associated with phonemic paraphasia without loss of comprehension that is evidence that these areas are involved in prearticulatory phonologic retrieval which is an inability to retrieve an internal image of the phonemes. Similar clinical findings occur with logopenic primary progressive aphasia in which patients have inability to retrieve words, make phonemic paraphasias during speech but retain word comprehension. The major pathology of the condition is in the inferior parietal lobule and the posterior superior temporal gyrus. Clinical and experimental evidence supports the supposition that the pSTG and the supramarginal gyrus are essential for phonologic retrieval. Recent voxel-based pathologic lesion symptom mapping studies have demonstrated comprehension impairment from damage to the MTG, AG (angular gyrus), anterior STG and prefrontal cortex but not in the classic Wernicke's area of the pSTG or supramarginal gyrus (SMG). In addition, physiologic and mapping studies in patients with the semantic variant of primary progressive aphasia have pathology in the anterior areas of the temporal lobe. These patients have severe comprehension deficits with loss of the understanding of the meaning of words. This comprehension deficit can occur from damage to distributed speech networks that are not restricted to classic Wernicke's areas.

Present knowledge suggests that speech comprehension involves two specific stages. The first is a process in which auditory input is analyzed on a phonemic basis ("phonemic perception") in the STG, the superior temporal sulcus of both hemispheres. The STG region that is involved is anterior to that involved in speech production as well as being anterior to the classic Wernicke's area. The second stage of speech comprehension involves the retrieval of semantic information (the meaning of the words) of the auditory input. This function depends on a large distributed network that includes the AG, MTG, ventral temporal lobe, medial parietal cortex, medial prefrontal cortex, and the inferior lateral prefrontal areas. It is clear that many cortical areas are involved in speech comprehension but, surprisingly, the Wernicke's area is not.

Posterior Cortical Language Networks Derived from Lesion Analysis and Functional Mapping

1. Wernicke's area is essential for phonologic retrieval in which the phonemes and their temporal order of articulation are mentally represented. This process is necessary for:

- a. Repetition
 - b. Word retrieval
 - c. Naming
 - d. Reading aloud
2. Speech repetition requires input to the phonologic retrieval system from the auditory phonemic perception system (anterior temporal lobe). A similar mechanism underlies reading aloud. In this instance, the afference to the phonologic retrieval system is from a visual letter perception system located in the ventral occipital temporal area
 3. Spontaneous speech and naming is sequential:
 - a. A stage prior to phonologic retrieval in which a concept of the intended verbalization is formed
 - b. Word retrieval occurs by mapping of word meanings onto phonologic representations
 - c. The input to the phonologic retrieval system is from an internal word meaning (semantic) system
 - d. The distributed semantic processing network is located in the associative cortices of the temporal, parietal and frontal lobes
 4. Speech comprehension depends on mapping sequences of phonemes (auditory phonemic perception system) onto the semantic system

Lesion Analysis of Posterior Aphasic Syndromes

1. Damage of the phoneme perception system
 - a. Superior anterior temporal lobe
 - b. Pure word deafness
 - c. This syndrome occurs after bilateral lesions because both hemispheres are involved in phoneme perception
2. Lesions of the phonologic retrieval system
 - a. Midanterior temporal lobe
 - b. Causes phonemic paraphasia and anomia (impaired word retrieval)
 - c. In isolation this lesion causes:
 - i. Conduction aphasia
 - ii. Logopenic primary progressive aphasia
3. Lesions of the semantic network
 - a. Midtemporal gyrus
 - b. Posterior temporoparietal junction
 - c. Causes:
 - i. Transcortical sensory aphasia
 - ii. Semantic variant of primary progressive aphasia
 - iii. Comprehension deficits with intact automatic speech
 - iv. Anomia and empty speech that lacks meaningful content
4. Wernicke's aphasia is characterized by paraphasic speech and impaired comprehension due to damage to phonologic retrieval and to the semantic system

An alternate view of the anatomical basis of aphasia suggests that cortical areas can be roughly divided into dorsal and ventral pathways that mediate phonological and semantic processing respectively. The dorsal pathway extends from

the posterior superior temporal to the inferior frontal cortices. Semantic information is relayed in a ventral pathway that extends from the temporal pole to the basal occipito-temporal cortex that also includes anterior connections. Current theories support the hypothesis that the ventral stream processes acoustic-phonetic features of speech while the dorsal stream mediates interactions between auditory and articulatory-motor representations.

Classical Aphasia

Broca's Aphasia

General Characteristics

1. Diffusion tensor imaging has demonstrated an extended Broca's area that involves two new fascicles:
 - a. The operculo-premotor fascicle that connects the pars opercularis with the premotor area
 - b. The triangulo-orbicularis system that connects the pars triangularis with the pars orbitalis

Clinical Manifestations

1. The major components of Broca's aphasia are difficulty initiating and articulating speech
2. Non-fluency
3. An output of less than 20 words per minute
4. The phrases are short and have abnormal rhythm, inflection and timbre
5. The patient utilizes meaningful substantive words with a lack of syntactic language. This agrammatism is noted by a decreased use of prepositions, articles, grammatic modifiers and the use of endings which delineate plurals, possessives and tenses. Patients with anterior aphasia have a specific disturbance in use of syntactic aspects of language. Repetition is abnormal particularly for simple syntactic words and endings
6. Comprehension is abnormal particularly for syntactic function words such as the difference between in and on
7. Confrontation naming is abnormal but performance is improved with a phonetic or contextual cue
8. Reading comprehension is impaired due to failure to understand grammatically significant words
9. Writing is abnormal which is out of proportion to weakness and demonstrates omission of grammatical words and misspelling of substantive words
10. Persistent Broca's aphasia is frequently associated with an ideomotor apraxia of the left hand. A significant number of patients demonstrate apraxia in handling objects and for imitation of movement with the left arm and face

Neuropathology

1. The most common cause of expressive or Broca's aphasia is stroke. The prefrontal and frontal branches of the MCA are most commonly affected. Stem MCA occlusion causes both Broca's and Wernicke's aphasia due to decreased perfusion of both the inferior and superior divisions of the artery. Rarely vascular disease of the anterior

cerebral artery causes an anterior aphasia due to ischemia of the SMA

- Any structural lesion of the brain that damages BA44, BA45 and surrounding and connecting white matter pathways such as tumor, cerebral hemorrhage or trauma may cause an anterior aphasia

Laboratory Evaluation

- MRI/MRA:
 - To evaluate the structural integrity of Broca's area and surrounding white matter
 - The patency of MCA and ACA arteries and their origins
 - EEG
 - Neuropsychological language testing

Wernicke's Aphasia

General Characteristics

- Wernicke's aphasia renders a patient unable to understand spoken language due to damage of the classic left temporoparietal cortex (BA22). Auditory-verbal comprehension of written words and pictures may be partially spared
- Recent functional MRI studies have demonstrated a role for the anterior temporal lobes in multimodal semantic processing (phonemic and semantic systems)

Clinical Manifestations

- Patients demonstrate fluent verbal output and/or normal to increased rate of word production
- Normal prosody and phrase length
- Their primary difficulty is an inability to comprehend language which includes understanding their own spoken language
- Grammatical structure is nearly normal although there is a lack of substantive words
- There are characteristic verbal or semantic paraphasic errors (word substitutions), literal or phonemic paraphasias (consonant errors), and neologisms (non-existent) word errors
- In some patients comprehension of midline commands may be partially retained
- Naming ability is severely impaired
- Reading and writing are involved to varying degrees. Some patients are more "word deaf" than "word blind"
- Most patients lack insight into their deficit
- A hemiparesis is unusual; a superior quadrant defect may be present as well as an apraxia of imitation and object handling
- There is presence of speech and logorrhea (non-stop output of speech)
- Words that have affective associations may be retained (profanities)
- Non-dominant hemispheric Wernicke's area damage may be associated with errors in the perception of the pitch, rhythm and emotional tone of speech
- Patients that utilized sign language are affected similarly

Neuropathology

- The great majority of lesions that cause Wernicke's aphasia are from damage to Brodmann area BA22 in the posterior 1/3 of the superior temporal gyrus of the dominant hemisphere
- There is support for damage to the medial temporal lobe and underlying white matter as also important for receptive aphasia
- Damage to the posterior 1/3 of the superior gyrus of the temporal lobe also isolates this portion of the language core from the occipital, temporal and parietal cortex
- Vascular lesions are the primary cause of Wernicke's aphasia. These are primarily from involvement of the inferior division of the middle cerebral artery and particularly the temporal-occipital-parietal branch. If a Wernicke's aphasia is of sudden onset and appears in isolation it is most often associated with an embolus characteristically from atrial fibrillation. Disease of the ipsilesional carotid and middle cerebral artery may also be causative
- Any structural lesion of the posterior 1/3 of the superior temporal gyrus such as blunt trauma, tumor, arteriovenous malformation may cause this aphasia

Laboratory Evaluation

- MRI/MRA:
 - To evaluate the structural integrity of the temporal lobe and its vascular supply
- EKG and echocardiography to evaluate a cardiac source of embolus
- EEG

Conduction Aphasia

General Characteristics

- The classic concept of conduction aphasia was that of a disconnection between Wernicke's area for receptive speech and Broca's area for expressive speech
- Recent studies demonstrate that patients with conduction aphasia more often have lesions in the supramarginal gyrus or deep parietal cortex than the arcuate fasciculus
- Auditory-verbal short-term memory (AVSTM) and repetition appear to involve overlapping distributed networks

Clinical Manifestations

- Patients have intact auditory comprehension that is fluent (often with paraphasic errors)
- Speech repetition deficits that include:
 - Difficulty repeating phrases
 - The difficulty with repetition increases with phrase length and complexity
- Speech errors occur during spontaneous speech that include substituting or transposing sounds
- Patients are unaware of their errors of speech and have difficulties in correcting them
- Spontaneous speech is fluent and most often grammatically and syntactically correct

6. Error sequences are often incorrect approximations of known morphemes
7. Naming is impaired due to literal paraphasic substitutions
8. Reading aloud is performed poorly but comprehension is relatively well preserved
9. Writing demonstrates omissions, spelling errors and altered sequences of words and letters
10. Auditory-verbal short-term memory (AVSTM) may be impaired in conduction aphasia
 - a. AVSTM:
 - i. A memory store of verbal information that can be retrieved in a time period of seconds
 - ii. It requires phonological input processing with translation to speech output mechanisms but also requires a storage/rehearsal component
 - iii. Deficits of AVSTM are demonstrated by dysfunction in span tasks and the number of digits and words that can be repeated
 - iv. Impairment of delayed response tasks associated with dysfunction of the rehearsal component of AVSTM were found to have lesions of the pre-frontal cortex
 - v. Patients with lesion of the posterior temporoparietal areas had deficits in span tasks from disruption of the phonological store (also includes auditory rhyming and repetition)

Neuropathology

1. In most patients, anatomical correlation with detailed aphasia battery testing reveals that the lesion for conduction aphasia associated with left posterior temporoparietal cortical areas rather than the arcuate fasciculus
2. Repetition and the phonological store of information are associated with the left-mid-posterior STG and portions of the MTG and inferior parietal cortex
3. The phonological store component of AVSTM is also dependent on the left STG/IP (subserves digit and word span)
4. All pathologies, vascular, trauma, tumor or surgical that involve the posterior temporal and inferior parietal areas of the dominant hemisphere may cause conduction aphasia. There have been several patients described with intact arcuate fasciculi with conduction aphasia

Laboratory Evaluation

1. Functional MRI neuroimaging reveals:
 - a. Repetition/conduction aphasia is associated with lesions in the perisylvian cortex
2. Perfusion imaging and structural MRI demonstrate:
 - a. Impaired repetition is associated with:
 - i. Hypoperfusion in the left inferior supramarginal gyrus and temporoparietal areas
3. Summary of both structural and functional studies of conduction aphasia:

- a. Single word repetition is dependent on the left posterior STG and inferior parietal cortex
- b. Phonological store, measured by the word and digit span, is associated with the medial portion of the MTG/STG border that is adjacent to the underlying white matter and Heschl's gyrus

Transcortical Motor Aphasia

General Characteristics

1. Is usually caused by a stroke of the anterior superior frontal lobe

Clinical Manifestations

1. Difficulty in initiating speech
2. Patients stammer and may appear dysarthric
3. They may be able to repeat flawlessly but have difficulty with naming
4. They may have well preserved comprehension
5. They can read aloud and for comprehension, but writing is performed poorly
6. Patients may suffer a hemiparesis and may have an ideomotor apraxia of the left hand to verbal command
7. May have poor grammar (syntax) and narrative discourse that causes poor formation of complex sentences, the selection of appropriate words and the initiation of speech in conversation

Neuropathology

1. Most transcortical motor aphasias are caused by lesions in the superior frontal lobe convexity above Broca's area or in the supplementary motor area
2. Other pathologies include brain tumor, trauma and neurodegenerative diseases
3. Watershed area stroke between ACA/MCA territories

Laboratory Evaluation

1. MRI/MRA:
 - a. To evaluate for structural lesions and the vascular supply to the frontal lobe
 - b. Speech-language therapist for a comprehensive speech evaluation

Transcortical Sensory Aphasia

General Characteristics

1. This aphasia is similar to Wernicke's aphasia but patients can repeat

Clinical Manifestations

1. Patients demonstrate a normal or rapid rate of speech production, normal phrase length, rhythm of speech and prosody
2. Patients have a nominal aphasia and cannot read or write
3. Phonological processing is intact but lexical semantic processing is impaired
4. Patients can repeat complicated sentences but have impairments in comprehension of propositional speech

5. Paraphasias may be prominent
6. Patients may have an associated hemisensory and visual field deficit

Neuropathology

1. The usual brain area involved is the inferior left temporal lobe (left hemisphere speech dominant patient)
2. Transcortical sensory aphasia has also been described with damage to the angular gyrus, the second and third temporal gyrus or a MCA/PCA border zone infarction of the parietal-temporal junction
3. In addition to vascular disease, TCS aphasia may be caused by contusions and vascular malformations of the temporal lobe and tumors as well as neurodegenerative diseases

Laboratory Evaluation

1. MRI/MRA:
 - a. To evaluate the structural integrity of the left temporal lobe as well as the patency of the posterior cerebral artery
2. The Minnesota test for differential diagnosis which probes for weaknesses in auditory and visual components of aphasia as well as reading comprehension

Mixed Transcortical Aphasia and Isolation of the Speech Areas

General Characteristics

1. The majority of these patients suffer anterior and posterior vascular border zone ischemia or infarction

Clinical Manifestations

1. In border zone ischemia, patients often present with mixed transcortical motor and sensory aphasia that evolves to TCM, if anterior arteries, or TCS if posterior arteries, are predominately affected
2. If both MCA/ACA and MCA/PCA border zone infarctions are complete, patients have isolation of the speech areas. In this instance patients demonstrate:
 - a. Inability to initiate speech, name objects, follow commands, read or write
 - b. They can repeat a short phase

Neuropathology

1. Most patients have suffered a severe anoxic injury or prolonged cerebral hypotension
2. Carbon monoxide poisoning
3. A few patients have been reported with acute carotid occlusion, head trauma and severe cerebral edema

Laboratory Evaluation

1. MRI/MRA:
 - a. To evaluate for structural lesions in border zone distributions
 - b. Cardiac evaluation for ejection fraction and arrhythmia

Global Aphasia

General Characteristics

1. Global aphasia is non-fluent and severely affects both receptive and expressive components of speech

Clinical Manifestations

1. Most patients with global aphasia have suffered damage to the frontal and parietotemporal language areas from a carotid occlusion or stem middle cerebral artery embolism. They often appear mute at ictus (stunned)
2. These patients cannot initiate speech, follow commands, read, write, repeat or name
3. The impairment is present across all language modalities
4. The patient may be able to use one or two words that are a response to all questions
5. Patients are socially appropriate
6. Automatic speech has normal phonemia, phonetic and prosody
7. Patients may correctly utilize facial expression, gestures and intonation
8. Most patients suffer a concomitant right hemiparesis but some have been documented with minimal or no motor or sensory loss

Neuropathology

1. Most patients suffer severe left perisylvian lesions from occlusion of the stem of the middle cerebral artery that occludes both its superior and inferior divisions. Both thrombotic and embolic causes have been reported. Rarely, an anterior or superior trunk MCA occlusion can cause the syndrome acutely that rapidly evolves into a Broca's aphasia
2. Large hemispheric tumors (glioma) or severe head trauma as well as large hematomas from intracranial hemorrhage may cause the syndrome
3. Global aphasia without hemiparesis has been described with:
 - a. Single or multiple lesions
 - b. Subcortical lesions
 - c. Cardioembolic stroke
 - d. Internal carotid artery occlusion
 - e. Often there is rapid recovery

Laboratory Evaluation

1. MRI/MRA:
 - a. To detect embolic pattern of lesions and to evaluate the internal carotid and middle cerebral artery circulations
2. EKG and echocardiography to evaluate the heart as an embolic source
3. Medical evaluation to rule out systemic causes of arteritis that may also effect the cerebral arteries as exemplified by SLE and anti-nuclear antibody syndrome

Anomic Aphasia

General Characteristics

1. The most common aphasia

2. The three major types of anomia are:

- a. Word selection anomia
- b. Semantic anomia
- c. Disconnection anomia

Clinical Manifestations

1. Word selection anomia:

- a. The patient can explain how the object is used and can correctly identify the object within a group of other objects
- b. The patient is unable to name the object
- c. Some patients have selective anomia for particular types of objects
- d. In color anomia, the patient is able to distinguish among colors but is unable to identify them by name or the name of object's color. The patient is able to separate colors into categories

2. Semantic anomia:

- a. The meaning of words is lost
- b. The naming deficit is accompanied by a recognition deficit
- c. Patients are unable to select the target object from a group of objects even when given the object's name

3. Disconnection anomia:

- a. These patients may have modality-specific anomia in which the anomia is limited to a specific sensory modality
- b. There is disconnection between the sensory cortex and language areas
- c. Patients with disconnection anomia may also have associated callosal anomia. In this situation, corpus callosum disruption prevents the transfer of sensory information to language areas. The sensory information from the left hand is processed in the right somatosensory cortex which then cannot be transmitted to language areas of the left hemisphere. The patient is not able to identify objects in the left hand by touch

Neuropathology

1. A lesion of the left temporoparietal junction is most characteristic although anomic aphasia has been seen with dominant hemisphere frontal, temporal and parietal lesions. It has rarely been reported following right hemisphere and subcortical pathologies
2. Brain tumors may cause a slowly progressive anomic aphasia
3. Anomic aphasias may be seen in neurodegenerative diseases, traumatic brain injuries and with metabolic and toxic disorders. In the latter situation patients have evidence of an acute confusional state and writing may be more impaired than speaking
4. Pure anomic aphasia may occur with supramarginal gyrus lesions

Laboratory Evaluation

1. MRI/MRA:

- a. To evaluate lesion distribution or to delineate the patterns of cortical degeneration in neurodegenerative disorders

2. Speech evaluation

Subcortical Aphasia

General Characteristics

1. Three major subcortical areas have been associated with subcortical aphasia and include:

- a. Striatocapsular lesions
- b. White matter periventricular lesions
- c. Thalamic lesions

Clinical Manifestations

1. Striatocapsular and white matter periventricular lesions:

- a. Lack of speech fluency
- b. Paraphasias
- c. Minimal involvement of comprehension
- d. Naming is primarily intact
- e. Verbal output is slow and poorly articulated

2. Thalamic aphasia:

- a. Fluent speech
- b. Some have isolated naming deficits
- c. Comprehension deficits
- d. May have initial mutism or hypophonia

Neuropathology

1. Subcortical nuclei and areas that cause aphasia are the:

- a. Putamen
- b. Caudate
- c. External capsule
- d. Anterior internal capsule
- e. Thalamus

2. The language deficits following thalamic stroke have been postulated to occur from:

- a. Dysfunction of thalamocortical distributed networks directly which may secondarily cause mild diffuse hypoperfusion of the cortex
- b. Concurrent cortical hypoperfusion
- c. Diaschisis of cortical language areas
- d. The most prominent feature of striatocapsular aphasia is phonetic impairment of language, while in thalamic aphasia it is lexical semantic processing

3. The major pathology associated with subcortical aphasia is ischemia of the posterior cerebral artery particularly of the P1 segment that gives origin to the thalamogeniculate and interpeduncular arteries

4. Tumors, hemorrhage and traumatic brain injury that disrupt thalamic-cortical projections are also causative

Laboratory Evaluation

1. MRI/MRA:

- a. Delineation of the subcortical topography of the causative lesion
- b. DWI and PWI:
 - i. Aphasia is more correlated with PWI (perfusion weighted than diffusion weighted sequences)

Differential Diagnosis of Aphasia

1. Mutism:
 - a. A common entity misdiagnosed as aphasia is mutism which by definition is the total cessation of verbal output
 - b. The most common brain areas associated with mutism are frontal, supplementary motor, left thalamic, mesencephalic and the left posterior inferior portion of Broca's area
 - c. If a patient can write normal sentences when speech returns, speech will be normal with only a few aphasic errors
 - d. Stem occlusion of the MCA and SMA lesions often present with mutism prior to evolution into a specific aphasia
2. Dysarthria
 - a. Motor speech disturbances such as ataxia, hypo- or hyperkinetic speech, aphemia may be misinterpreted as an aphasia
 - b. Aphasia can only be diagnosed when a disturbance of language function is demonstrated by incorrect grammar usage or choice of words. Abnormal phonology, the learned rules for producing the sounds of specific language only occurs with aphasia
3. Aphemia
 - a. Aphemic patients have great difficulty with articulation:
 - i. They can express themselves in written language and fully comprehend written and spoken language
 - ii. Word choice and syntax are normal
 - b. Aphemia is a severe disorder of verbal output. Many patients are mute in the acute stage and demonstrate a transient right hemiparesis
 - c. As a patient recovers, speech is hypophonic and poorly articulated. The speech is grammatically correct but the prosodic quality is often altered
 - d. Neuropathology:
 - i. The usual lesions are small and affect the motor system for articulation: pars opercularis, inferior prerolandic gyrus and the white matter deep to these areas
 - ii. The usual pathology is ischemia of the articular speech areas supplied by the prefrontal branches of the MCA or A1 branches of the ACA
 - iii. Aphemia has been described with lesions of the medial frontal cortex, the supplementary motor area or the motor area of the cingulate gyrus
 - iv. Any structural lesions of these areas including tumor, traumatic brain injury or hemorrhage may cause aphemia
 - e. Laboratory evaluation:
 - i. MRI/MRA:
 1. Evaluations of the ACA and MCA territories
 2. Rule out any structural lesion of the appropriate areas
4. Pure word deafness
 - a. Patients with pure word deafness cannot comprehend spoken language but can identify non-verbal sounds
 - i. They are fluent, are able to read and write, but can neither comprehend spoken language or repeat it
 - b. Patients have been reported in which word deafness and Wernicke's syndrome occur concomitantly. These patients demonstrate a fluent aphasia in which there is a greater deficit in comprehension than in writing. The anatomic lesions that cause severe word deafness are damage to Heschl's gyrus and destruction of the radiations from the medial geniculate body as well as the callosal fibers from the contralateral superior temporal gyrus. This combination of lesions isolates the left hemisphere auditory association cortex from any auditory input
 - c. The second localization for this syndrome is bilateral damage to the anterior and midportion of the superior temporal gyrus
 - d. Non-verbal auditory agnosia, the inability to recognize non-verbal sounds, occurs with lesions of the right hemisphere. Cortical deafness occurs with bilateral damage to Heschl's gyrus and its connections. In this state, patients are aware of words and sounds but cannot interpret them
5. Auditory agnosia
6. Cortical deafness

Written Language Impairments***Agraphia****General Characteristics*

1. If patients suffer aphasia in spoken language writing is also affected
2. Agraphia by definition, is a loss of the ability to communicate through writing either due to motor dysfunction or an inability to spell
3. Central agraphia:
 - a. Involves language areas of the brain that causes difficulty with spelling or with spontaneous communication. It is accompanied by other language dysfunction
4. Peripheral agraphia:
 - a. There is dysfunction of motor and visuospatial modalities in addition to language dysfunction
5. Agraphia may be caused by dysfunction from:
 - a. Language processing
 - b. Spelling
 - c. Visual processing
 - d. Visuospatial orientation for graphic symbols
6. Motor planning
7. Motor control of handwriting

Clinical Manifestations of Central Agraphia

1. Central agraphia manifests with impairment in spoken language and with the motor and visualization abilities required for writing
2. Patients with agraphia in association with fluent aphasia:
 - a. Are able to write a normal quantity of well-formed letters
 - b. Lack the ability to write meaningful words
3. Patients with agraphia and non-fluent aphasia manifest:
 - a. An ability to write short sentences
 - b. Poorly executed handwriting that is produced with great difficulty
 - c. Syntax is poor and there are spelling mistakes
4. Alexia with agraphia patients manifest:
 - a. Difficulty with production and comprehension of written language
5. Deep agraphia:
 - a. Patients have difficulty with phonologic aspects of speech and with orthographic memory
 - b. Patients are unable to recognize words when spelled correctly or sound them out in preparation for spelling
 - c. Semantic errors are frequent
 - d. Patients have difficulty with abstract concepts and uncommon words (defect in orthographic memory)
 - e. There are reading and spoken language errors
6. Gerstmann's syndrome:
 - a. There is impairment with written language production in association with:
 - i. Finger agnosia
 - ii. Right-left confusion
 - iii. Acalculia
 - iv. Some patients have conduction aphasia
7. Global agraphia:
 - a. Impairs orthographic memory to a greater extent than occurs with deep agraphia
 - b. Severe spelling impairment. A patient may only be able to write a few meaningful words
 - c. Reading and spoken language are impaired
8. Lexical and structural agraphia:
 - a. This form of agraphia is caused by damage to orthographic memory
 - b. Patients are unable to visualize the spelling of a word but are capable of sounding them out
 - c. Patients have more difficulty spelling words without regular predictable spelling. Less impairment in the spelling of common words
 - d. Patients make mistakes with homophones (a word that is pronounced the same as another word but has a different meaning)
 - e. Grammar and sentence writing is maintained
9. Phonological agraphia:
 - a. The ability to sound out words is impaired but orthographical memory is not affected
 - b. Patients are better at spelling words than non-words

- c. More difficult for patients to spell prepositions than concrete nouns
10. Pure agraphia:
 - a. An impairment of written language without any other language or cognitive disorder

Peripheral Agraphia

1. Apraxia
 - a. Due to the disruption of the motor system
 - b. Patients manifest:
 - i. Slow, effortful and imprecise letter formation
 - ii. Retain the ability to spell aloud
 - iii. This form of agraphia is due to a loss of the engram (the motor plan) for the formation of letters
 - iv. It may or may not be associated with ideomotor apraxia
 - v. Motor disorders associated with agraphia are:
 1. Parkinson's disease:
 - a. Inability to sustain writing with gradual micrographia
 2. Cerebellar ataxias:
 - a. Large poorly formed letters
 3. Dystonia:
 - a. Writer's cramp
 4. Chorea:
 - a. Disjointed chaotic poorly formed letters
- c. Hysterical agraphia:
 - i. Caused by a conversion disorder
- d. Reiterative agraphia:
 - i. Letters, words or phrases are repeated in an abnormal fashion
 1. Examples are preservation, paragraphia and echographia
- e. Visuospatial agraphia:
 - i. Patients neglect the side of the written page
 - ii. Lines are slanted upward or downwards
 - iii. There is abnormal spacing between letters, syllables and words
 - iv. Deficits in the orientation and correct sequencing of writing
 - v. Visuospatial agraphia is often associated with left hemispatial neglect and constructional apraxia

Neuropathology

1. Clinical pathologic correlation as well as fMRI analysis of normal healthy controls and patients with agraphia reveals a primarily left-hemisphere network of 12 cortical and subcortical areas that are utilized with writing
2. Distinct functional areas have been delineated and include:
 - a. The middle frontal gyrus and the superior frontal sulcus
 - b. The left superior parietal cortex that includes the inferior parietal lobule, the superior parietal lobule and the intraparietal sulcus
 - c. The primary motor and sensory cortex

3. Primary writing-specific areas are:
 - a. Left superior frontal sulcus/middle frontal gyrus
 - b. Left intraparietal sulcus/superior parietal area
 - c. Right cerebellum
4. Areas that are activated with writing but are related to non-specific motor or linguistic processes include:
 - a. Primary motor and sensorimotor cortices
 - b. Supplementary motor area
 - c. Thalamus (posterior nucleus)
 - d. Putamen (left)
 - e. Linguistic processing:
 - i. Ventral premotor cortex
 - ii. Posterior/inferior temporal cortex
 - f. Left inferior frontal gyrus
 - g. Right posterior cerebellum
 - h. Right inferior parietal lobule
 - i. Left fusiform gyrus

Clinical Pathologic Correlations of Agraphia

1. Phonological agraphia:
 - a. Damage to perisylvian structure that include Broca's and Wernicke's area as well as the supramarginal gyrus
2. Lexical agraphia:
 - a. Damage to the left angular gyrus and/or posterior temporal cortex
3. Deep agraphia:
 - a. Damage to the left angular gyrus and posterior temporal cortex often posterior and inferior to perisylvian language areas
4. Gerstmann's syndrome:
 - a. Most often is caused by an angular gyrus lesion
5. Apraxic agraphia:
 - a. Most often is caused by lesions of the superior parietal or the premotor cortex (engram formation)
 - b. Cerebellar lesions have been reported as causative
 - c. Apraxic agraphia without an associated ideomotor apraxia has been reported from lesions:
 - i. Either parietal lobe
 - ii. The dominant frontal lobe
 - iii. The dominant thalamus
6. Visuospatial agraphia:
 - a. Most of the pathology is in the non-dominant hemisphere
 - b. Right frontal lobe damage causes motor deficits while damage to posterior parietal areas leads to spatial deficits
 - c. Vascular disease
 - d. Tumor
 - e. Head trauma

Laboratory Evaluation

1. MRI/MRA:
 - a. To evaluate the anatomic status of the areas defined for writing with their attendant blood supply
2. Functional magnetic resonance imaging:

- a. The left parietal (BA5) and premotor areas are activated when writing with the dominant hand
- b. The anterior aspect of the dorsal premotor cortex (BA6) may be the source of the engrams for writing

Alexia Without Agraphia

General Characteristics

1. Alexia without agraphia was the first disconnection syndrome described. It has also been designated as pure alexia or word blindness

Clinical Manifestations

1. Patients suffer an inability to comprehend written language
2. They are able to recognize words spelled aloud, graphesthetically produced words written on the palm or words constructed with blocks that are palpated
3. Most patients can recognize a few letters
4. There is often an associated right homonymous hemianopsia and impaired naming and understanding of color names in the face of normal color vision. A few patients have central achromatopsia
5. Associated anomia

Neuropathology

1. The usual lesion is occlusion of the left posterior cerebral artery with infarction of the left occipital lobe and the splenium of the corpus callosum which prevents transfer of visual information from the right occipital lobe to the left angular gyrus
 - a. Occlusion of the dominant middle cerebral artery or its distal branches may also lead to an acquired loss of the ability to read or write from infarction of the parietal lobe. These patients often have a concomitant mild hemiparesis, hemisensory loss, partial visual field deficit and anomia
2. Lesions of the posterior inferior frontal cortex of the dominant hemisphere may impair the ability to comprehend the syntactic structures such as function words and endings. These patients may understand substantive words but cannot recognize relational words. This defect is seen in both spoken and written language. Patients have difficulty in understanding sequences of semantically significant words
 - a. Some patients have a concomitant Broca's aphasia, right hemiparesis, and mild hemisensory loss. Paralexia refers to substitutions of words or syllables when reading aloud. Synonym substitutions of nouns for objects and an inability to read nonsense and function words. This type of dyslexia follows severe damage to the dominant hemisphere language areas and may be seen during recovery from complete alexia

Laboratory Evaluation

1. MRI/MRA:

- a. To evaluate these anatomically significant areas and their blood supply that may also be affected by tumor, cerebral trauma, hemorrhage as well as ischemia
2. Functional MRI demonstrates activation of the superior temporal gyrus, supramarginal gyrus, inferior frontal gyrus/operculum, precentral gyrus and insular cortex during reading
3. Diffusion tensor imaging reveals:
 - a. Lesions in the white matter tracts that connect these areas in patients with phonological alexia/agraphia

Syndromes of Calculating Impairment

Acalculia

General Characteristics

1. Acalculia is an acquired disability in which patients have difficulty performing simple mathematical functions
 - a. Dyscalculia is a developmental disorder during the acquisition of mathematical skills

Clinical Manifestations

1. The cognitive functions required for basic mathematical tasks include:
 - a. Every number represents a value
 - b. The recognition of a number's value with respect to other numbers
 - c. Understanding the number's location in a series of numbers
 - d. Association of a numerical symbol with its name
2. Aphasic acalculia:
 - a. The patient is not able to utilize numbers as a language entity
 - b. Patients are unable to comprehend or write numbers correctly or substitute one number for another
 - c. Aphasic acalculia is seen in most aphasic patients
3. Visual spatial acalculia:
 - a. The patient can compute, understands numbers and computational signs but is unable to place numbers in the correct position in space
 - b. Patients are unable to align numbers in columns or place decimal points which interferes with complex calculations although they can manipulate individual mathematical functions
 - c. The lesion affects the non-dominant hemisphere at the parieto-occipital junction
4. Anarithmia:
 - a. These patients are not able to manipulate numbers or compute
 - b. They can recognize and reproduce individual numbers, understand their value but cannot compute
 - c. The lesion most often is noted in the dominant posterior parietal cortex

Neuropathology

1. Lesions of the angular gyrus may cause greater impairment in memorized mathematical tasks such as multipli-

cation tables with relatively normal subtraction ability. Patients with lesions of the intraparietal sulcus have greater difficulty with subtraction than multiplication. It appears that specific regions of the parietal cortex are specialized for specific mathematical functions

Laboratory Evaluation

1. MRI/MRA:

- a. To evaluate for structural lesions particularly of the posterior parietal areas and the angular gyrus

Apraxia

General Characteristics

1. Apraxias are the inability to perform an individual or sequential function with intact motor, sensory and coordinative abilities
2. Different areas of the brain are specific for specific forms of apraxia
3. Apraxia is a disorder of motor planning (the development of an engram) for a specific movement

Clinical Manifestations

1. Ideomotor apraxia:

- a. Patients have an inability to plan or complete a single motor action that requires semantic memory
- b. They are able to explain how to perform the action but are unable to imagine it or carry it out
- c. The patient may retain the ability to perform the activity automatically

2. Ideational apraxia:

- a. Patients are unable to conceptualize and perform a multistep task
- b. There is loss of the ability to perform a learned task when given the appropriate tools
- c. Patients may not be able to initiate the sequence required to perform a task or abandon it in the middle
- d. Patients may have an inability to handle real objects even though they can mimic the use of the object

3. Constructional apraxia:

- a. Constructional apraxia is impairment in the ability to construct the copy of a visually presented object with blocks or by drawing. Patients must be able to perceive the elements of the object, their spatial relationships and possess the motor ability to perform the task
- b. Both left and right parietal lesions can cause a defect in constructional praxis, although right-sided lesions are more common. In right-sided lesions, the deficit is more severe as patients have left-sided neglect of the object to be copied
- c. Patients with left parietal lesions and constructional apraxia frequently have an associated fluent aphasia

4. Buccofacial or orofacial apraxia:

- a. The cardinal features of oral-buccal-lingual apraxia is the loss of the patient's voluntary ability to utilize muscles of mastication, swallowing and speech

- b. These muscles are innervated by the first four branchial arches
- c. Patients are unable or have difficulty with speech, swallowing, chewing and pursing their lips on command
- d. Coughing, sneezing and involuntary movements are preserved
- e. Oral motor apraxias may be seen with:
 - i. Landau-Kleffner syndrome
 - ii. Benign Rolandic epilepsy
 - iii. Anterior perisylvian lesions
 - iv. Foix-Chavany-Marie syndrome
 - a. Vascular bilateral insular infarctions
 - v. Frontotemporal dementia and other neurodegenerative diseases
- 5. Limb-kinetic apraxia:
 - a. Patients have difficulty making precise movements
- 6. Oculomotor apraxia:
 - a. Patients have difficulty in producing saccadic eye movements that direct gaze to specific targets on command. It is prominently seen in Bálint's syndrome
- 7. Dressing apraxia:
 - a. Patients are unable to dress themselves properly even when they are given the garment
 - b. The apraxia is rarely isolated and is often seen with neglect, Bálint's syndrome and in confused and demented patients
 - c. The responsible lesion is in the right occipitoparietal or bilateral occipitoparietal areas
- 8. Callosal apraxia:
 - a. Callosal apraxia is the inability to perform a simple command with the left hand although the right hand performs it easily
- 9. Gait apraxia:
 - a. Patients have trouble in initiating the swing component of gait, walk as if they are on eggs or have a foot grasp of the floor
 - b. Normal pressure hydrocephalus, lesions that affect the pedunculopontine nucleus or other components of locomotor centers as well as basal ganglia disease and lacunar stroke involvement of the corticospinal system are causative
- 10. Apraxia of speech:
 - a. Patients are unable to plan or program phonetic and prosodic speech
 - b. These patients suffer:
 - i. Inconsistent articulatory errors
 - ii. Unusual oral movements to prepare for articulation
 - iii. Produce errors with increased word and phrase length
 - iv. Difficulty with production of all of the sounds in a word
 - v. Vowels are easier to produce than consonants and single consonants are more easily produced than blends

- vi. Final components are easier to pronounce than those in the initial position
- c. Apraxia of speech is often seen with concomitant oral-buccal-lingual apraxia
- 11. Conceptual apraxia:
 - a. Patients lose the associative knowledge of tool action and may also not have an understanding of mechanical knowledge, which is the advantage tools offer
 - b. Frontal lobe degeneration is most often associated with conceptual praxis
- 12. Eyelid opening apraxia:
 - a. Patients are unable to open their eyelids on command
 - b. The apraxia may be seen in isolation or in conjunction with other neurologic features of neurodegenerative diseases
 - c. Most often seen with lesions of the superior frontal gyrus
 - d. Some demented patients think they are blind because they cannot open their eyes

Neuropathology

- 1. Specific apraxia by anatomical site:
 - a. Oral-buccal-lingual apraxia:
 - i. Insular cortex; if bilateral it may constitute the Foix-Chavany-Marie syndrome
 - b. Ideomotor apraxia:
 - i. Inferior parietal lobes; SMA; premotor cortex
L > R
 - c. Ideational apraxia:
 - i. Left posterior BA5 and BA7
 - d. Limb-kinetic apraxia:
 - i. BA6, inferior parietal lobe, SMA
 - e. Dressing apraxia:
 - i. Right parietal lobe
 - f. Constructional apraxia:
 - i. Right frontal and right parietal lobes
 - g. Eyelid opening apraxia:
 - i. Second frontal gyrus
 - h. Callosal or sympathetic apraxia:
 - i. Corpus callosum (usually anterior)
 - ii. Left and right prefrontal cortex
 - i. Gait apraxia:
 - i. Leg fibers surrounding the lateral ventricles; paracentral lobule
 - j. Conceptual apraxia:
 - i. Associative knowledge (tool action) the frontal lobe
 - ii. Mechanical knowledge of the tool (its advantage) the frontal lobe

The lesions causing apraxias are most often vascular, neurodegenerative disorders, normal pressure hydrocephalus, traumatic brain injuries and tumor

Laboratory Evaluation

- 1. Structural MRI studies reveal:

- a. Lesions in the left frontal, parietal and temporal lobes in patients with pantomime deficiency
2. Functional MRI:
 - a. Associates pantomimes with left parietal activation with or without concurrent frontal or temporal activations
 - b. Both lesion and functional studies demonstrate a left hemispheric frontal-temporal-parietal network that plays a key role in pantomiming object use

Distributed Brain Networks

Overview

Functional MRI (fMRI) imaging has been demonstrated to be exceptionally valuable in investigating human brain function. This functional neuroimaging procedure measures brain activity by detecting changes that are associated with cerebral blood flow in specific brain regions either at rest or during specific task related activities. fMRI utilizes blood-oxygen level dependent BOLD contrast that is based on the concept that local cerebral blood flow and neuronal activity are coupled. Thus if an area of the brain is activated its blood flow increases. The procedure utilizes the change in magnetization between oxygenated and deoxygenated blood. The change in MRI signal from neuronal activity is the hemodynamic response which lags the triggering neural event by 1 to 2 seconds. It has a peak rise in approximately 5 seconds after the activation. If there is continuous neuronal activity, the peak plateaus. Cessation of neuronal activity causes the BOLD signal to fall below the baseline level that is known as undershoot. The BOLD contrast signal primarily reflects neuronal input and integrative firing rather than the neuron's output discharge. The BOLD signal cannot distinguish between excitation or inhibitory activity in a network and thus the final signal is the summation of the network's activity. The BOLD signal may also be affected by sedation, anxiety, blood vessel physiology (ability to dilate) and medication that dilates blood vessels.

The Default Mode Network

The default mode network (DMN) consists of interacting brain regions (nodes) that are correlated with each other by white matter pathways (edges). It is active when the subject is not focused on a task-specific activity while the brain is at "wakeful rest". It is active during daydreaming, mind wandering, thinking of oneself or others, remembering the past, and planning for the future. In general, the network is deactivated during goal-oriented tasks but can be activated for social work, memory or autobiographical goals. It is negatively correlated with attention networks

Anatomy of the DMN

The DMN can be defined by placing the seed in the posterior cingulate cortex and analyzing which brain areas correlate

with it during the resting state. It has also been structurally defined by the nuclear areas that are deactivated during externally directed goal-directed tasks as compared to rest.

The major hubs of the DMN include:

1. The posterior cingulate cortex (PCC):
 - a. The ventral PCC activates with reflections of self, remembering the past, thinking about the future and spatial navigation
 - b. The dorsal PCC is activated during involuntary awareness and arousal
 - c. The precuneus may be activated by visual, sensorimotor and attentional input
2. Medial prefrontal cortex is activated by self-processing information, autobiographical memories and future goals and events. Its lower component is activated by emotional content and internally valued reward
3. Angular gyrus activation occurs with:
 - a. Episodic memory
 - b. Attention
 - c. Spatial cognition
4. Dorsal medial subsystem:
 - a. Activates when thinking about others
5. Dorsal medial prefrontal cortex activates with:
 - a. Inferring the purpose of others' actions
6. Temporoparietal junction:
 - a. Activates when reflecting on the beliefs of others
7. Lateral temporal cortex activates with the retrieval of social semantic and conceptual knowledge
8. Anterior temporal pole:
 - a. Activates when reflecting on abstract conceptual information
9. Medial temporal subsystem:
 - a. Activates with autobiographical memory and future goals
10. Hippocampus:
 - a. Activates with the formation of new memories and reflections of the past and imagining the future
11. Parahippocampus activation occurs with spatial scene recognition and its stimulation
12. Retrosplenial activation:
 - a. Spatial navigation
13. Posterior inferior parietal lobe activation occurs with:
 - a. Integration of auditory, visual and somatosensory afferences
 - b. Attention

Modulation of the DMN

1. Acupuncture:
 - a. Deactivation of limbic areas
2. Meditation:
 - a. Structural changes have been defined in posterior cingulate cortex and precuneus in intense practitioners
3. Sleeping and resting wakefulness:
 - a. Strong functional connectivity between nodes of the DMN

- b. Onset of sleep:
 - i. There is a decrease in connectivity between the DMN and task-positive networks
- c. REM sleep:
 - i. Questionable increase of nodal connectivity in the DMN
- d. Stages of N2 and N3 of NREM sleep
 - i. Decreases of connectivity between the posterior cingulate and medial prefrontal cortices
- e. Sleep deprivation;
 - i. Decrease of connectivity within the DMN
 - ii. Sleep loss may induce a decrease between the DMN and task-positive networks

Neuropathologies in Which There May Be Involvement of the DMN

- 1. Autism:
 - a. Failure to deactivate the DMN during cognitively demanding tasks
- 2. Schizophrenia:
 - a. Overactive DMN
- 3. Alzheimer's disease:
 - a. Preferential accumulation of amyloid-beta in the DMN
- 4. Severe long-term trauma and abuse:
 - a. Lower connectivity across the network
- 5. Post-Traumatic Stress Disorder:
 - a. Lower activation in the posterior cingulate gyrus
- 6. Depression and chronic pain:
 - a. Hyperconnectivity across the DMN

Task-Related Functional Networks

Cognitively demanding tasks consistently recruit the dorsal anterior cingulate cortex (dACC), the orbitofrontal insula (FI), the lateral prefrontal cortex and the lateral parietal cortex that has been termed the task-activation ensemble (others have termed it the task-activation network).

The lateral prefrontal cortex (PFC) and parietal areas coactivate with the dACC and FI during attention, working memory and response selection. They also activate during pain, uncertainty and threats to homeostasis. Thus, it has been questioned whether these areas are activated in a task-specific manner or to cognitive, homeostasis or emotional salience which are inherent in these tasks and require change in sympathetic tone. The salience network, primarily the dACC and the orbitofrontal insula (FI) are intimately involved in interoceptive-autonomic processing which coactivate during the affective aspects of pain, empathy for pain, metabolic stress, hunger, pleasurable touch and specific social situations. The dorsal medial thalamic nucleus may be an essential integrative node for the system. The ACC has been hypothesized to play a cognitive role by processing errors and conflict. It, along with the FI, has also been postulated to be specialized nodes for sympathetic control and interoception.

The executive control network is fundamental for operations that require:

- 1. Directed attention to pertinent stimuli
- 2. Behavioral choices
- 3. Contextual cues
- 4. Homeostatic demands

This network contains sites for:

- 1. Sustained attention and working memory (the DLPFC and lateral parietal cortex)
- 2. Response selection (dorsomedial frontal/preSMA cortex)
- 3. Response suppression (ventrolateral prefrontal cortex)

Neural Orientation

Neural oscillation in the CNS refers to repetitive or rhythmic neural activity driven by mechanisms within individual neurons or by interactions between neurons. Oscillations in individual neurons are produced by changes in membrane potential which then cause oscillatory activation of postsynaptic neurons. Macroscopic oscillations, those are at the level of the nuclei, represent synchronized activity of large numbers of neurons, and can be seen on the electroencephalogram. Oscillations between groups of neurons are often produced by feedback loops that cause synchronization of the firing patterns. Synchronization between neuronal aggregates may have oscillations at a different firing frequency than that of their component individual neurons.

The function of neural oscillations includes:

- 1. Feature binding
- 2. Information transfer
- 3. The generation of rhythmic motor patterns

Oscillations are seen at all levels of the neuraxis and include:

- 1. Spike trains
- 2. Local field potentials
- 3. EEG (large scale oscillations)

They are characterized by their frequency, amplitude, and phase. Amplitude changes in large-scale oscillations are due to changes in synchronization within a neuronal aggregate (local synchronization). Neural oscillations and their synchronization across distributed loops (often concordant with areas of activation delineated by fMRI) are essential for many cognitive functions that include:

- 1. Information transfer
- 2. Perception
- 3. Memory
- 4. Motor control

EEG signals (measure of large oscillations) reveal oscillatory activity in specific frequency bands that include:

- 1. Alpha activity:
 - a. 8–13 HZ
 - b. Detected from the occipital lobe
 - c. During periods of relaxed wakefulness
 - d. Increased when the eyes are closed
- 2. Delta band:
 - a. 1–4 Hz
- 3. Theta band:
 - a. 4–8 Hz

4. Beta band
 - a. 13–30 Hz
5. Gamma band:
 - a. 30–70 Hz

b. Gamma activity has been linked to cognitive processing. Neural oscillations are linked to cognitive states that include sleep, awareness and levels of consciousness. Single cell readings in patients, primarily in those undergoing surgery for epilepsy or brain tumors, have demonstrated that neurons fire at particular frequencies and are termed resonators. Spike firing patterns have been associated with information coding. Neuronal aggregates that fire synchronously produce oscillations in local field potentials.

Multiple action potentials in neurons in sequence produce spike trains that have been posited to be the basis of neural coding and information transfer in the CNS. Spike train patterns are varied and include rhythmic spiking and bursting as well as oscillatory activity. Activity patterns of neuronal spiking are classified as class I or class II.

1. Class I neurons:
 - a. Generate action potentials with low frequency band that depends on input strength
2. Class II neurons:
 - a. Generate action potentials in a frequency band relatively independently of input strength
 - b. They demonstrate subthreshold oscillations in membrane potential

Neuronal aggregates (a nucleus or group of nuclei) generate oscillatory activity by synaptic interactions that synchronize different neuronal firing patterns. The rhythmic change in electrical potential produced by summated action potentials further summates. These synchronized firing patterns produce a synchronized afference into other distributed nuclei that cause large amplitude oscillations of local field potential. They are evaluated (large oscillations by EEG or magnetoencephalography activity) and are the reflection of the synchronized activity of millions of neurons that have similar spatial orientation. Inhibitory neurons generate a narrow window for excitation and rhythmic modulation of the firing rate of excitatory neurons and are essential for generating synchrony in neuronal aggregates.

Neuronal oscillation is fundamental to the function of distributed neural circuitry. Brain areas are bidirectionally coupled that form feedback loops. Positive feedback loops cause oscillatory activity whose frequency is related to delay time between neuronal aggregate interactions.

The mechanisms that determine oscillatory activity are determined by:

1. Neuronal properties that determine membrane potential oscillations
 - a. Voltage-gated ion channels
2. Network properties that affect the timing of spike trains, coupling strength, time delay, and sign (excitation or inhibition) determine if the spike trains of interacting neurons will be synchronized. The coherent activity of multiple modality brain activity connected by dynamic links between brain areas is essential for cognitive function

3. Neuromodulation of oscillatory activity is accomplished by neurotransmitters. The concentration of specific neurotransmitters regulates the amount of oscillatory activity in a distributed network. This is primarily affected by the diffuse brain projections for norepinephrine, acetylcholine, and serotonin. These transmitter systems effect wakefulness and arousal and influence the amplitude of different brain waves

Task-specific functional MRI and analysis of the oscillations and coherence of distributed networks are rapidly changing many concepts of the physiologic organization and function of the cerebral cortex.

Further Reading

Further Reading on Cerebral Cortex

M1

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Chapter 13

Dementia

Overview

Most dementing illnesses have specific clinical patterns of deterioration, destroy particular areas of the brain in a sequential pattern and are associated with seminal clinical features that permit a clinical classification. They are now being categorized on a molecular, biological, genetic and neuropathological basis.

The prevailing theories of brain function emphasize modularity and connectivity that processes information flow across large-scale distributed networks. Modularity is specialized processing within specific brain regions while connectivity describes the correlation of the major hubs of networks. It is clear that long term potentiation (LTP) and long term depression (LTD) are major mechanisms that determine synaptic efficacy for learning and memory. In the former (LTP), specific integrated loops and neurons are strengthened whereas in the latter these neurons are suppressed and their neurons cannot fire. Neurotransmitter systems that include acetylcholine are essential for memory and many other aspects of cortical function. The interplay of GABA-ergic and acetylcholinergic systems at the thalamic level is important for maintaining consciousness and directed attention. Dopamine has a major role in basal ganglia function at all levels and most probably with affect and subcortical dementia. Serotonin has been shown to be pivotal in many aspects of emotional expression and pain. Thus, dementing processes that destroy neurotransmitter systems in the brainstem have far-reaching neurological manifestations.

A fundamental aspect of all dementing processes appears to be the loss of synapses as well as neurons. Synaptic loss may be the best correlate of the severity of dementia and may be an early manifestation. Synaptogenesis and maintenance of formed synapses may depend on activity dependent neuroplasticity, neurotrophic factors and connectivity. Synaptic "pruning" (loss of dendrites) is prominent in many of the childhood and early adult storage diseases that eventuate in severe dementia.

The intense interest in the formation of nuclear and cytoplasmic inclusions points to the role of protein metabolism in dementing illnesses. The exact mechanism of cellular death when inclusions accumulate is not known but is hypothesized to include failure of axonal transport, apoptosis, the malformed protein response, and damage from free radicals.

The electrical correlates of normal brain function and that which occurs with dementing illness is now being unraveled. The EEG is often slow in dementing disorders. The ability to make cortical negative variants (readiness potentials) gives some insight into the brain's functional activity. The recent discovery of specific brain oscillations for attentiveness (beta

oscillations) and gamma oscillations (active during perception) suggest a mechanism for information transfer between different distributed loops. Magnetoencephalography allows for precise localization of a brain electrical event in real time. Its major use at present is to localize epileptic foci. It appears to take 0.5 msec to process a stimulus to a perception. This figure has been derived from an analysis of cortical negative variant potentials and thalamically generated gamma waves.

Functional MRI, PET and SPECT all localize an area of activity during a specific event, but do not identify its sign (inhibitory or excitatory) or localize its precise origin, the synapse or neuron. Most metabolic activity occurs at the synapse (estimated to be 85%).

The fundamental characteristics of a dementing illness are:

1. The cognitive impairment is acquired
2. The impairment involves multiple domains of cognitive function
3. There is no impairment of arousal
4. There is deterioration of previously acquired intellectual abilities of sufficient severity to interfere with social or occupational function
5. There is memory impairment with at least one other aspect of cognitive behavior
6. The disturbances of higher cognitive functions include:
 - a. Aphasia
 - b. Apraxia
 - c. Agnosia
7. Often personality change
8. There is no intoxication or delirium

Core Clinical Features of Cortical Dementias

1. Neuropsychological deficits:
 - a. Memory impairment:
 - i. Recall is not aided by cues
 - ii. Decreased retention
2. Cognitive domain deterioration:
 - a. Aphasia
 - b. Apraxia
 - c. Agnosia
 - d. Poor visuospatial abilities
 - e. Decreased executive function
3. Speed of cognitive function:
 - a. Normal
4. Psychiatric manifestations:
 - a. Depression (all)
 - b. Hallucinations (synucleinopathies)
 - c. Day to day variability (LBD); Lewy body dementia
 - d. Delusions (all)
 - e. Apathy (all)
5. Motor abnormalities:
 - a. Depends on the specific dementing illness; often specific:
 - i. Asymmetry (CBG); Cortical basal ganglia

- ii. Parkinsonism (akinetic rigidity > tremor)
 - 1. PDD (Parkinson's disease dementia)
 - 2. CBG
- iii. Loss of vertical gaze:
 - 1. PSP (Progressive supranuclear palsy)
- 6. Severity and progression:
 - a. Dependent on the specific dementing illness
 - b. Significant inter- and intrafamilial variance in genetic disorders
 - c. Variability is the rule in sporadic disease

Core Clinical Manifestations of Subcortical Dementia

- 1. Neuropsychological deficits:
 - a. Frontal memory impairment:
 - i. Recall aided by cues
 - ii. Decreased verbal fluency and recall
- 2. Speed of cognitive function:
 - a. Slow
- 3. Psychiatric manifestations:
 - a. Apathy
 - b. Depression
- 4. Motor abnormalities:
 - a. Dysarthria
 - b. Extrapyrmidal signs
- 5. Severity and progression:
 - a. Mild to moderate
 - b. May be intermittent if the disorder is due to specific structural lesions

Primary Dementing Illness

- 1. Definition:
 - a. The primary characteristics of dementia will be a feature of the clinical presentation of the dementing illness
- 2. Differential diagnosis of primary degenerative dementing disease:
 - a. Alzheimer's disease
 - b. Frontotemporal dementia and variants
 - c. Dementia with Lewy bodies (LBD)
 - d. Multiple system atrophies (MSA)
 - e. Progressive supranuclear palsy (PSP)
 - f. Corticobasal ganglia degeneration (CBG)
 - g. Wilson's disease
 - h. Huntington's disease
 - i. Pantothenate kinase deficiency
 - j. Familial Creutzfeldt-Jakob disease
 - k. Pick's disease
 - l. Posterior dementia with medial temporal sclerosis

Alzheimer's Disease

General Characteristics

- 1. Epidemiology:
 - a. Incidence of 5–8/thousand person years

- b. Approximately every five years after the age of 65 the risk doubles
- c. Women have a higher risk of developing the disease than men particularly in the age group of older than 85
- d. It is estimated that the prevalence rate will triple and the absolute number of patients will quadruple by the year 2050

Genetic Factors Associated with Alzheimer's Disease

- 1. Approximately 1–5% of patients:
 - a. Most of autosomal dominant familial AD is caused by mutations in 3 genes:
 - i. Amyloid precursor protein
 - ii. Presenilin-1 and presenilin-2
 - b. Most of the mutations in these genes increase the production of AB42 (amyloid-beta 1–42), (the major component of senile plaques)
 - c. Some mutations alter the ratio between AB42 and AB40 without increasing AB42 concentrations
- 2. Most patients with AD are sporadic with some genetic risk factors
 - a. The most studied genetic risk factor is inheritance of the E4 allele of the apolipoprotein E (ApoE). Approximately 40–80% of patients with AD have at least one ApoE E4 allele which increases risk 3 times in heterozygotes and 15 times in homozygotes
 - b. Mutations in genes that may affect risk are:
 - i. CASS4
 - ii. CELF1
 - iii. FERMT2
 - iv. HLA-DRB5
 - v. INPP5D
 - vi. MEF2C
 - vii. NME8
 - viii. PTK2B
 - ix. SORL1
 - x. ZCWPW1
 - xi. SIC24A4
 - xii. CLU
 - xiii. PICALM
 - xiv. BIN1
 - xv. MS4A
 - xvi. ABCA7
 - xvii. EPHA1
 - xviii. CR1
 - xix. CD2AP
 - c. Mutations in the TREM2 gene are associated with 3 to 5 times higher risk of developing the disease

ApoE4 Gene: Major Genetic Risk Factor for Late Onset AD General Characteristics

- 1. Located on the proximal long arm of chromosome 19:
 - a. Risk factor for late onset AD
- 2. ApoE is important for
 - a. Lipid transport

- b. Metabolism
- c. Targeting and clearance of amyloid-beta peptide
- 3. ApoE allele frequency:
 - a. E2/E2 – 1%
 - b. E3/E3 – 60%
 - c. E4/E4 – 3%
 - d. E2/E3 – 12%
 - e. E2/E4 – 2%
 - f. E3/E4 – 20%
- 4. E4 allele:
 - a. Noted in 40% of patients with late onset AD
 - b. If patient is homozygous for the E4 allele, he has a 90% chance of AD by age 80
 - c. The E4 allele bestows an earlier onset of sporadic AD
 - d. The E4 allele is found at its normal frequency in early onset familial AD
 - e. 50% of ALZ patients do not have an E4 allele
 - f. Pathology associated with ApoE:
 - i. Senile plaques (found within the plaques)
 - ii. Amyloid angiopathy
 - iii. Neurofibrillary tangles
 - iv. Binds to amyloid-beta fibrils which increases AB (amyloid-beta) aggregation

Clinical Manifestations

- 1. Minimal cognitive impairment:
 - a. May appear up to a decade prior to the onset of dementia and manifests as:
 - i. Short term memory loss
 - ii. Difficulty learning new information
 - iii. Deficits in executive function that are featured by loss of attentiveness, decreased mental flexibility, loss of abstraction, impairment of semantic memory (the memory of meaning and concept relationships in language)
 - iv. Apathy, depression, irritability and loss of awareness of memory deficits. If memory deficits are predominant, this form of minimal cognitive impairment is termed amnesic MCI
- 2. Early AD:
 - a. Most often, there is increasing impairment of short term memory and learning
 - b. Variable features:
 - i. Language deficits
 - ii. Apraxia, agnosia, and loss of executive function
 - iii. Episodic memory, semantic memory (facts learned) and implicit memory (motor engrams) may be less affected than that for new information
 - c. Language deficits:
 - i. Decreased vocabulary and fluency both in oral and written language

Moderately Advanced AD

- 1. Continued mental deterioration that starts to hinder the patient's ability to perform the usual activities of daily living

- 2. Language deficits accelerate:
 - a. The patient is unable to recall vocabulary that causes word substitutions (paraphasia)
 - b. Progressive loss of the ability to read and write
- 3. Deterioration of complex motor sequences
- 4. Behavioral and neuropsychiatric changes become evident; approximately 30% of patients develop illusionary misidentifications, and delusional symptoms, anosognosia develops

Advanced Alzheimer's Disease

- 1. Language deteriorates to single phrases or words: some patients develop a complete loss of speech
- 2. Apathy and exhaustion are common
- 3. Sarcopenia (loss of muscle mass) and a bedridden state with complete dependency on caregivers

Cognitive Defects in Alzheimer's Disease

- 1. Attention:
 - a. Definition:
 - i. The ability to select specific information to process
 - ii. Limitation of selective attention:
 - 1. Divided attention:
 - a. Inability to process multiple sources of information as efficiently as one source
 - b. Focused attention:
 - i. Difficulty in blocking irrelevant information
 - iii. AD Patients:
 - 1. Difficulty in dividing attention
 - 2. Better at focusing attention
 - 3. Difficulty in disengaging from an attended stimulus
 - iv. Alertness in AD patients:
 - 1. Phasic changes:
 - a. The time to process an expected input increases
 - 2. Tonic changes:
 - a. Slow decline in performance during a long and repetitive task
 - v. Language deficits:
 - 1. Failure of semantic speech (the production and comprehension of the meaning of words):
 - a. Inability to find the appropriate word
 - b. Comprehension of complex sentences
 - c. Inability to search semantic categories
 - d. Poor production of a semantic association to a given stimulus
 - e. Minimal difficulty with syntax; speech is grammatically correct
 - vi. Memory:
 - 1. Severe disruption of memory
 - 2. Deficiencies in encoding new information
 - 3. Memory for distant events (remote) memory:

- a. Less disrupted
- b. Demonstrates a temporal gradient (recall of distant information better than more information that is recent)
- 4. Implicit memory is relatively preserved in some studies but has been found to be deficient in others

Neuropsychiatric Manifestations of Alzheimer's Disease

1. Behavioral changes in Alzheimer's disease:
 - a. Psychoses
 - b. Agitation
 - c. Depression
 - d. Anxiety
 - e. Personality changes
 - f. Neurovegetative changes
2. Distribution of behavior changes:
 - a. Apathy – 72%
 - b. Agitation – 60%
 - c. Delusion – 22%
 - d. Hallucinations – 10%
 - e. Anxiety – 48%
3. Neuropsychological detection of preclinical Alzheimer's disease:
 - a. Deficits on confrontation naming
 - b. Deficits in abstract reasoning and executive function
 - c. Decreased memory encoding
 - d. Delayed recall (list learning task)

Alzheimer's Disease Variants

1. Alzheimer's with extrapyramidal features:
 - a. Faster rate of decline
 - b. Earlier neuropsychiatric manifestations
2. Alzheimer's disease variant with visual complaints:
 - a. Present with Bálint's syndrome
 - b. Complex visual complaints
 - c. Decreased occipital cortex and visual association area hypometabolism (PET scanning)

Amyloid Precursor Protein Mutation (APP)

General Characteristics

1. APP is an integral membrane protein expressed in many tissues and enriched in neuronal synapses
2. It has been postulated to play a role in the regulation of synapse formation, neural plasticity, and ion export
3. It is the precursor molecule that when proteolyzed generates amyloid-beta (AB) a 37–49 amino acid peptide. The amyloid fibrillar form of the protein is a major component of the amyloid plaques of AD
4. Mutation of the gene for APP maps to chromosome 21. Mutations in the critical regions of the protein, that which generates amyloid-beta, causes susceptibility to AD. Several mutations outside of the AB region increase the production of AB and are associated with familial AD

5. The APP gene encodes a 695–770 aa precursor protein:
 - a. The gene has 19 exons
 - b. Exon 16/17 codes AB (amyloid-beta)
 - c. Amyloid-beta (39–43 aa) is processed to pathologic amyloid fibrils
 - d. Specific mutations:
 - i. Exon 17 (3 mutations); codon 717
 - ii. The most common mutation is APP 717 (Val 717-Leu) > Val/Phe > Val 717/Gly
 - iii. There is a double mutation of exon 16 at codon 670–671
 - iv. In early onset AD:
 1. Mutations flank the amyloid
 2. Beta sequence
 3. Mutations within the sequence cause hemorrhage
 - v. APP's post-translational modifications include: glycosylation, phosphorylation, sialylation, tyrosine sulfation and proteolytic cleavage that generate peptide fragments:
 1. Alpha-secretase and beta-secretase cleave the protein that releases membrane-anchored carboxy-terminal fragments that may induce apoptosis
 2. Gamma-secretase cleaves the protein within the membrane-spanning domain after beta-secretase generates the amyloid-beta fragment

Clinical Manifestations

1. Early onset AD
2. Clinical features of the 717 codon mutations (Val/Glycine):
 - a. Myoclonus
 - b. Hypertensive cardiovascular disease
 - c. Heart disease
3. 717 Val/Ile mutation:
 - a. Klüver-Bucy-like syndrome (without the hypermetamorphopsia or hypersexuality)
 - b. NPH (normal pressure hydrocephalus)
 - c. Auditory hallucinations
4. Some mutations in APP gene are protective for AD by decreasing the production of AB, reducing amyloidogenic processing of APP or decreasing AB aggregation. A recent example is the A673T mutation in the APP gene

Presenilin-1

General Characteristics

1. Mutations in the presenilin-1 gene (PSEN1) that maps to chromosome 14 is one of the core proteins in the presenilin complex that causes autosomal dominant early onset AD
2. The protein may regulate proteolytic processes intracellularly one of which involves gamma-secretase that cleaves APP
3. Neuronal cultures derived from presenilin-1 deficient mouse embryos demonstrate that:

- a. Cleavage by alpha- and beta-secretase is normal
- b. Cleavage by gamma-secretase of the transmembrane domain of APP is absent
4. The presenilins may be involved in the cleavage of the Notch receptor that may also regulate gamma-secretase activity
5. The protein is located within nerve cells, the Golgi apparatus, and the endoplasmic reticulum

Clinical Manifestations

1. Age at onset of AD is between (35–55 years)
2. Progressive aphasia
3. Myoclonus
4. Generalized seizures
5. Penetrance is complete by age 60
6. Extrapyrimal signs
7. The range of onset varies within families
8. Duration of the disease is short 5.8–6.8 years

Variant of AD with Spastic Paraparesis

General Characteristics

1. Deletion of exon 1 of PSEN1

Clinical Manifestations

1. Described in a Finnish kindred
2. Spastic paraparesis
3. Onset 40–60 years of age; mean of 51 years of age
4. Memory impairment
5. Decreased hand coordination
6. Dysarthria

Neuropathology

1. “Cotton wool” plaques
2. The plaques are immunoreactive for amyloid-beta
3. No congophilic cores

Neuroimaging

1. MRI:
 - a. Temporal and hippocampal formation atrophy
2. PET:
 - a. Bilateral temporoparietal hypometabolism

Presenilin-2

General Characteristics

1. Mutations of the presenilin-2 gene (PSEN2) map to chromosome 1
2. As with presenilin-1, PSEN2 is postulated to regulate APP processing through its effect on gamma-secretase or by cleavage of the Notch receptor
3. The PSEN2 gene has 67% homology to PSEN1; the most common mutation is on chromosome 1:227073304 A > T

Clinical Manifestations

1. Early onset AD

2. Volga German population
3. Age of onset is 54.9 ± 8 years
4. Variation of age of onset is between 40–75 years
5. Two patients >80 years of age have been described with no clinical signs
6. Penetrance is usually >95%
7. Duration of illness is approximately 7.6 years: mean age of death is 64 years of age
8. Disease onset is characterized by memory deficits and other cortical cognitive dysfunction
9. Disease course is slower than other familial AD mutations particularly PSENs
10. Rare pyramidal or parkinsonian features
11. Approximately 30% of patients had seizures and 33% suffered hallucinations, delusions or other psychiatric manifestations

Neuropathology

1. Gross atrophy of the medial temporal and parietal lobes with lesser atrophy of the frontal cortex and cingulate gyrus
2. Early loss of synapses and neurons in the cerebral cortex and subcortical nuclei
3. As the disease progresses there is degeneration of the locus coeruleus
4. Loss of cholinergic neurons in the nucleus basalis of Meynert of the substantia innominata
5. Intraneuronal neurofibrillary tangles (NFTs) associated with neuritic plaques and dystrophic neurites:
 - a. Filamentous insoluble inclusions
 - b. Located in the cell body
 - c. Extend into the dendrites but not the distal axons
6. NFT tangles:
 - a. The major component is the hyperphosphorylated microtubule associated protein tau:
 - i. Tau normally binds to tubulin to stabilize microtubules
 - ii. When hyperphosphorylated it aggregates and interferes with cellular function
 - iii. Ghost tangles represent insoluble residues in dead neurons
 - iv. Evolution of NFT spread:
 1. The earliest area of involvement is the entorhinal cortex; it next spreads to the limbic cortex and lastly the cortex
 - v. The amyloid plaques:
 1. The amyloid plaques are extracellular and diffuse initially
 2. At later stages, they are cored
 3. The cores are 50–200 nm in diameter
 4. Cored plaques:
 - a. Are surrounded by dystrophic neurites
 - b. Reactive glial inflammatory response
 - c. Plaque core:

- i. 70% of the proteinaceous material is amyloid-beta (derived from the enzymatic cleavage of APP)
 - ii. Abnormal organelles
 - iii. Tau protein
 - iv. Apolipoprotein E (ApoE)
- d. Synaptic alterations:
 - i. Decreased presynaptic terminal density
 - ii. Disconnected neurons
 - iii. Synaptic pruning
- e. Cerebral amyloid angiopathy (CAA):
 - i. A feature of AD
 - ii. Can occur separately
 - iii. Associated with hemorrhagic stroke:
 - 1. AD Dutch disease
 - iv. ApoE allele may predispose to angiopathy in contradistinction to ApoE4 that is associated with AD
- f. Granulovacuolar degeneration:
 - i. Mainly confined to the hippocampus
 - ii. Vacuoles are found in pyramidal cells that contain a single granule:
 - 1. Reactive with antineurofilament antibodies
- g. Plaques and tangles are noted in normal aging:
 - i. They are less widely distributed and much fewer in numbers; amyloid can be abundant

Risk Factors for Alzheimer's Disease

1. Genetic forms of early onset disease with autosomal dominant inheritance (APP, PSEN1 and 2):
 - a. Associated genetic mutations (19 genes)
 - b. E4 allele
2. Age is the major risk factor
3. Geographic distribution:
 - a. Similar incidence worldwide
4. Women are more affected than men
5. Prevalence putatively related to educational background
6. Weak associations:
 - a. Head injury (repeated)
 - b. Parental age at birth
7. Age-associated cognitive decline:
 - a. Brain atrophy:
 - i. In normal controls, it is 0.4% per year
 - ii. In Alzheimer's disease, it is 2.4% per year
 - b. The deficits in age-associated cognitive decline are only in one cognitive domain
 - c. The deficit is greater than six months in duration
 - d. The deficits are greater than one standard deviation below values for age-matched controls
 - e. ApoE4 has no relation with cognitive decline of aging

Distribution of Pathologic Amyloid Plaques

1. Amygdala

2. Hippocampus:
 - a. Dentate gyrus (molecular layer)
 - b. Ca1 and Ca3 subregions
 - c. Subiculum
3. Layer III and V of the entorhinal cortex
4. Layer II contains NFTs
5. Temporoparietal neocortex > frontal lobe
6. Laminar degeneration of the posterior cingulate cortex
7. Histologic diagnosis of AD requires both neuritic amyloid plaques and NFTs in the neocortex
8. Lewy bodies may be seen

Possible Mechanism of Alzheimer's Disease

1. The amyloid hypothesis:
 - a. The accumulation of amyloid-beta peptides is the pathologic trigger that destroys neurons. Amyloid fibrils possibly are the toxic form of the protein that accumulates and causes:
 - i. Abnormally folded amyloid-beta protein (proteopathy)
 - ii. Disrupted calcium homeostasis
 - iii. Induction of apoptosis
 - iv. Accumulates in mitochondria (mitopathy)
 - v. Decreases glucose utilization
 - vi. Increased inflammatory response with abnormal proinflammatory cytokines and chemokines
 - vii. Alterations in neurotrophic factor physiology
2. Abnormal aggregation of tau protein:
 - a. Hyperphosphorylation of tau that aggregates and creates neurofibrillary tangles that disrupt the neuron's cytoarchitecture and internal transport processes

Laboratory Evaluation

1. Neuropsychological testing
2. Comprehensive medical evaluation to rule out B12 and folate deficiency, endocrine disorders, syphilis, liver and renal failure, electrolyte disorders

Neuroimaging

1. Characterizes the pattern of cerebral atrophy and its progression in Alzheimer's disease
2. Alzheimer's disease disrupts functional connectivity of intrinsic brain networks most prominently in the default mode network
3. MRI:
 - a. Medial temporal lobe atrophy is more important than small vessel disease in predicting minimal cognitive impairment
 - b. MRI tractography confirms that structural connectivity across almost all nodes of intrinsic brain networks are disrupted in AD
4. PiB PET is being utilized along with Florbetapir to demonstrate the distribution of amyloid deposition in the brain
5. The cingulum-angular bundle is disrupted
6. Thinning of the precuneus
7. Alterations in the uncinate fasciculus

Dementia with Lewy Bodies*General Characteristics*

1. Lewy body dementia is a progressive degenerative dementia characterized by an accumulation of alpha-synuclein and ubiquitin protein in the brain
2. There are alpha-synuclein plaques in greater numbers throughout the cortex than expected for age

Clinical Manifestations

1. Initial deficits:
 - a. Deficits of frontal subcortical abilities
 - b. Decreased visuospatial skills
2. Later in the course of the illness
 - a. Memory deficits
3. Core components of the disorder:
 - a. Fluctuating cognitive function with pronounced variation in attention
 - b. Recurrent visual hallucinations
 - i. Formed; detached
 - c. Parkinsonism
 - i. Bradykinesia and rigidity
 - ii. Rare tremor
 - iii. Poor response to L-dopa
 - d. Associated features
 - i. Repeated falls
 - ii. Syncope and transient loss of consciousness
 - iii. Neuroleptic hypersensitivity
 - iv. Delusions (other than visual) that are often paranoid
 - v. Urinary incontinence occurs later than cognitive decline
 - vi. REM sleep disorder
 - vii. Depression
 - viii. Sleep-disordered breathing
 - ix. Difficulty swallowing
 - x. Visual hallucinations include:
 1. Perceptions of non-existent people or animals
 - xi. Delusions:
 1. Reduplicative paramnesia
 2. Elaborate misperceptions
 3. Patients may have insight into the illness
 - xii. Double vision
 - xiii. Stroke-like episodes

Neuropathology

1. The major antigenic components of Lewy bodies include:
 - a. Presynaptic protein alpha-synuclein
 - b. Neurofilament proteins
 - c. Ubiquitin
2. Cortical Lewy bodies:
 - a. Lack a clearly definable central core and distinct peripheral corona

- b. The inclusions are formed from aggregated masses of intermediate neurofilaments
3. The number of cortical LB is variably correlated with the severity of the dementia:
 - a. Temporal lobe Lewy bodies correlate with visual hallucinations
4. Cortical Lewy bodies occur:
 - a. Cingulate gyrus
 - b. Entorhinal cortex
 - c. Insular cortex
 - d. Frontal cortex
 - e. Amygdala
5. The pathology of Lewy body disease is often concomitant with Alzheimer's disease
6. Neurofibrillary tangles are not common in DLB
7. There is loss of dopaminergic neurons in the substantia nigra as well as loss of acetylcholine producing neurons of the nucleus basalis of Meynert in the substantia innominata

Laboratory Evaluation

1. Structural tensor and diffusion tensor imaging of DLB disease reveals:
 - a. Anterior thalamic radiation (ATR) and the cingulum-cingulate gyrus are altered in DLB disease
 - b. Secondary axonal degeneration within the anterior thalamic radiations are due to microstructural damage within the medial dorsal thalamic nucleus
 - c. White matter alterations are seen in the uncinate fasciculus
 - d. It is posited that the structural connectivity disruptions in DLB disease is linked to gray matter neuronal loss rather than direct white matter injury
 - e. The ATR is altered in DLB disease and not in AD
 - i. The tract connects the dorsomedial thalamic nucleus to the prefrontal cortex
 - f. Degeneration is noted in the inferior longitudinal fasciculus (a ventral associative connection that transmits visual afferences to the temporal lobe; possible relationship to the hallucinations seen in DLB disease)
 - g. There is disruption of the supracallosal white matter bundle in DLB but not in AD
 - i. These white matter tracts wrap around the corpus callosum from the medial frontal cortex and anterior cingulate cortex to the dorsal posterior cingulate cortex. They are posited to regulate attentional focus. The loss of these white matter bundles may be linked to neuronal loss in posterior cortical regions

Frontotemporal Dementia*General Characteristics*

1. Frontotemporal lobar degeneration (FTLD) is heterogeneous and includes tauopathies

2. FTD may account for 20% of early onset dementia; the process affects men and women equally
3. The FTDs are heterogeneous clinically, pathologically and genetically
4. They are characterized by:
 - a. Behavioral variants (bvFTD)
 - b. Language impairment:
 - i. Semantic dementia
 - ii. Progressive non-fluent aphasia

Clinical Manifestations

1. In general patients with FTD have normal:
 - a. Perception
 - b. Visuospatial skills
 - c. Memory
 - d. Praxis
2. In the later stages of FTD clinical phenotypes may overlap. Patients have variable binge eating and compulsive behaviors
 - a. The neural substrates for the abnormal eating behavior are posited to include:
 - i. Right ventral insula
 - ii. Striatum
 - iii. Orbitofrontal cortex
 - b. Executive functions of planning, and organization and sequencing deteriorate
 - c. Clinical phenotypes may overlap

Neuropathology

1. The three major subtypes of FTD are:
 - a. FTD-tau
 - b. FTD-TDP
 - c. FTD-FUS
2. Behavioral variant FTD has the most severe atrophy and is associated with corticobasal ganglia degeneration, Pick's disease and TDP pathology

Laboratory Evaluation

1. MRI:
 - a. Frontal lobe and/or temporal lobe atrophy
 - b. Atrophy can be bilateral and asymmetric
2. FDG-PET:
 - a. Frontal and/or anterior temporal hypometabolism (differentiates it from Alzheimer's disease). AD demonstrates biparietal hypometabolism
3. A ventromedial prefrontal cortex distributed loop is primarily affected
 - a. The degeneration initially involves the orbitofrontal cortex and ventromedial cortex and spreads to the dorsolateral cortex and temporal lobe

Neuropsychological Testing

1. The Iowa gambling task:
 - a. Evaluates decision making; the assessment of the values of available choices

- b. Evoked emotion (somatic marker) is associated with outcomes that form experience which biases future decision making during specific behaviors
- c. This behavior is posited to be a function of the orbitofrontal cortex
2. Faux Pas Recognition Test:
 - a. Deficits in self-monitoring (an inability to evaluate one's behavior in specific situations)

Behavioral Variant Frontotemporal Dementia (bvFTD)

1. The deficits of behavior and social interaction include:
 - a. Early onset
 - b. They are out of proportion to the memory deficit
 - c. Loss of personal hygiene and deficient grooming
 - d. Loss of social graces
 - e. Disinhibition
 - f. Impulsivity
 - g. Hyperorality and hyperphagia
 - h. Depression, psychosis and stereotyped behavior
2. Criteria for behavioral variant frontotemporal dementia (bvFTD):
 - a. Disinhibition
 - b. Apathy/inertia
 - c. Loss of sympathy/empathy
 - d. Perseverative/compulsive behavior
 - e. Hyperorality
 - f. Dysexecutive neuropsychological profile
 - g. For a possible diagnosis of bvFTD the patient must present with at least three of the designated features

Semantic Dementia (SD) Variant of FTD

General Characteristics

1. Semantic dementia is associated with loss of semantic memory in both verbal and non-verbal domains
2. Primarily associated with temporal lobe atrophy (L > R)

Clinical Manifestations

1. Presents often with word finding difficulty
2. Fluent aphasia
3. Anomia
4. Inability to comprehend the meaning of words
5. Inability to match semantically related pictures or objects (an associative visual agnosia)
6. Rarely, a selective deficit in reading unusual words that has atypical spelling-to-sound correlations (surface dyslexia)

Neuropathology

1. Most patients have ubiquitin-positive, TDP-43-positive and tau-negative inclusions
2. Rare pathologies seen in SD are AD pathology and tau-positive Pick's disease

Laboratory Evaluation

1. MRI:
 - a. Atrophy of the L > R temporal lobes that includes:

- i. Anterior > posterior topology
 - ii. Inferior > superior involvement
- 2. FDG-PET:
 - a. Alterations (hypometabolism) of the temporal poles and amygdalate
 - i. Decreased metabolism in areas that have been associated with semantic information processing and social cognition
- 3. Neuropsychological testing:
 - a. Patients have severe deficits with semantic knowledge (the meaning of words) as demonstrated by:
 - i. The Warrington Concrete and Abstract Word Synonym Test
 - ii. The Pyramids and Palm Trees task in which patients demonstrate picture naming deficits (semantic errors) and category fluency

Progressive Non-Fluent Aphasia (PNFA) Variant of FTD

General Characteristics

1. Initial language deficit is in the absence of other cognitive abnormalities

Clinical Manifestations

1. The left hemisphere is primarily affected
2. The primary characteristics of the disorder are with speech production that is manifested by:
 - a. Hesitant, stuttering, effortful speech output
 - b. Speech apraxia
 - c. Stuttering
 - d. Anomia
 - e. Sound errors in speech that produce a phonemic paraphasia
 - f. Agrammatism (deficits of syntax, sequence and wrong tense)
3. Over time, speech output progressively decreases to mutism (some patients)
4. Later in the disease:
 - a. Deficits in reading, writing and speech comprehension occur
 - b. Behavioral abnormalities are seen

Neuropathology

1. Presence of misfolded, insoluble and hyperphosphorylated tau proteins in neurons and glia in the frontotemporal distributed network for phonological and syntactical speech processing

Laboratory Evaluation

1. MRI:
 - a. Severe left perisylvian atrophy
2. FDG-PET:
 - a. Decreased metabolism in the frontotemporal distributed networks for speech
3. Neuropsychology:
 - a. Speech evaluation

Major Tau Mutations

Overview

Tau is the major microtubule-associated protein (MAP) of neurons. Its major functions are the assembly and stabilization of microtubules (MTs) that are essential for morphogenesis and axonal transport. Neuronal and glial inclusions of abnormal tau fibrils cause neuronal death, brain atrophy and dementia. The genetic tauopathies with mutations of the tau gene impair the ability of tau to bind microtubules and alter the normal ratio of tau isoforms that causes fibril formation. Tau may also have a role in DNA protection and genome stability. Some mutations cause oligomeric rather than fibrillar aggregates. The primary neuropathological signatures of tauopathies are the deposition of misfolded, insoluble hyperphosphorylated tau proteins.

The primary tauopathies are:

1. FTD (behavioral, SD and PNFA)
2. Progressive supranuclear palsy
3. Corticobasal syndrome (CBS)

The major Mendelian genes linked to FTD are those coding for microtubule-associated protein tau (MAPT), progranulin (GRN) and chromosome 9 open reading frame 72 (C9orf72).

Other uncommon mutations that have been associated with FTD include:

1. Inclusion body myopathy with Paget's disease of bone (UCP gene)
2. Charged multivesicular body protein 2B (CHMP2B gene)
3. Fused in sarcoma (FUS gene)
4. Dynactin (DCTN1)
5. Sequestosome 1 (SQSTM1)
6. Colony-stimulating factor 1 receptor (CSF1R)
7. Triggering receptor expressed in myeloid cells (TREM2)
8. Ubiquilin-2 (UBQLN2)
9. Heterogeneous nuclear ribonucleoprotein (A2B1)

FTD-tau represents approximately 30–40% of FTD patients that are found in MAPT gene mutations as well as in Pick's disease, PSP and corticobasal degeneration. TAR DNA-binding protein 43 (TDP-43) are the inclusions originally identified as ubiquitin-positive and are now identified as FTD-TDP. The majority of FTD with ALS also have TDP-43 inclusions. Approximately 10% of FTD patients that are negative for tau or TDP-43 inclusions have FUS inclusions. Some patients with FUS have immunostaining for TATA-binding protein-associated factor 15 (TAF-15) and Ewing sarcoma protein (EWS).

MAPT Mutations

General Characteristics

1. The MAPT gene maps to chromosome 17; approximately 44 mutations have been identified in the gene to date
2. Alternate splicing of mRNA in exons 2,3 and 10 of the MAPT gene produces 6 isoforms of the protein

3. The exclusion or inclusion of exon 10 produces 3 isoforms with four repeats (4R) or three isoforms with three repeats each (3R). The repeats are in the microtubule-binding domains of the tau protein
4. The 4R repeat produces more microtubule assembly
5. Mutations are missense in exons 9–13 which determines tau effectiveness in microtubule stabilization
6. Intronic and coding mutations modify the splicing of exon 10 at the mRNA level that changes the 3R/4R tau isoform ratio
7. The frequency of MAPT mutations is 0–3% in sporadic patients to 5–20% in familial FTD patients

Clinical Manifestations

1. Mutations produce a heterogeneous clinical phenotype with high penetrance
2. Disease onset is variable between 45–65 years of age with a mean of 55; rarely it may present at age 20–30; its presentation is approximately 10 years earlier than in patients with the progranulin mutation (GRN)
3. The mean disease duration is 9 years (range 5–20 years)
4. Primarily there is a dementia or Parkinsonian phenotype
5. The most common type is bvFTD with loss of inhibition, social behavioral deficits and obsessive-compulsive disorder
6. Patients may later develop Parkinsonism that usually develops concomitantly with the behavioral disorder; a few patients have a primarily Parkinsonian disorder which can be seen with PSP or CBG
7. Parkinsonism is characterized by bradykinesia, postural instability and axial and appendicular rigidity; there is no resting tremor
8. Variable features include:
 - a. Supranuclear gaze palsy
 - b. Upper and lower motor neuron signs
 - c. Dystonia
 - d. Myoclonus
 - e. Postural and action tremor
 - f. Apraxia of eyelid opening and closing
 - g. Dysarthria and dysphagia
9. Patients with the N279K mutation may present with an asymmetric resting tremor and Parkinsonism
10. Language impairment may occur but is not seen at presentation
11. There is no clear correlation between type of mutation and clinical phenotype
12. Rarely there may be memory impairment

Neuropathology

1. Temporal lobe atrophy is the most frequent loss of neural tissue, but may be associated with basal ganglia and brainstem tissue loss
2. MAPT mutations involving exon 10 are associated with medial temporal lobe atrophy while those in the coding region cause lateral temporal lobe atrophy

Laboratory Evaluation

1. MRI:
 - a. Heterogeneous pattern of cortical atrophy with predominant frontal and temporal lobe atrophy
 - b. Atrophy is most prominent in the anterior medial temporal lobes
 - c. Cortical atrophy is most often symmetrical
 - d. Atrophy of the basal ganglia and brainstem is seen particularly in patients with parkinsonism
2. F¹⁸ fluorodeoxyglucose (FDG-PET):
 - a. Hypometabolism of the frontal and temporal lobes
3. Functional connectivity studies reveal:
 - a. Alterations in connectivity of the DMN between the precuneus and the lateral temporal lobe and the medial prefrontal cortex
 - b. Decreased fractional anisotropy (FA) and increased radial diffusivity bilaterally in the uncinate fasciculus
 - c. Decreased FA in the forceps minor

Progranulin (GRN) Mutations

General Characteristics

1. GRN mutations (approximately 70 delineated to date) account for approximately 20% of familial and 5% of sporadic FTD patients
2. Progranulin:
 - a. Is a secreted growth factor expressed in neurons and glial cells
 - b. It has a role in biological processes that include:
 - i. Cellular and tissue development
 - ii. Inflammation
 - iii. Wound healing
 - iv. Cancer
 - v. Neurotrophic properties
 - vi. It is proteolytically processed into peptides (granulins) whose function is largely unknown
 - vii. Mutations cause disease by haploinsufficiency
 - viii. Its expression is modulated by variants in the TMEM106B and by SORT1 gene as well as by microRNAs

Clinical Manifestations

1. Phenotypic expression is highly variable even in families with the same mutation
2. Age at onset varies from 35 to 89 years with an average of 65 years of age. Penetrance is 90% by the age of 70 years
3. The initial presentation is often with the behavioral variant FTD symptomatology primarily apathy and social withdrawal
4. Aphasic disorder similar to PNFA (progressive non-fluent aphasia)
5. 40% of patients have extrapyramidal features
 - a. Limb apraxia
 - b. Asymmetrical parkinsonism
 - c. Dystonia

6. In approximately 25% of patients there are hallucinations
7. In 10–30% of patients there can be a significant memory deficit
8. A subgroup of patients demonstrates dyscalculia, visuospatial deficits and limb apraxia
9. A few patients have had ALS and complete GRN deficiency has been shown to cause neuronal ceroid lipofuscinosis

Neuropathology

1. GRN mutations are associated with FTD-TDP pathology and is also seen in a subgroup of ALS patients and those with FTD-MND (motor neuron disease)

Laboratory Evaluation

1. MRI:
 - a. Asymmetrical atrophy of the hemispheres
 - b. Involvement of the inferior frontal, temporal and inferior parietal lobes
 - c. Involvement of the parietal lobes that is unusual in other FTD
 - d. Long intrahemispheric association white matter pathways are involved
 - e. Carriers may demonstrate deep subcortical gray matter atrophy in the:
 - i. Caudate nucleus
 - ii. Bilateral thalami
 - iii. Rare cerebellar atrophy
2. Annualized rates of whole brain atrophy and ventricular enlargement are greatest in GRN > sporadic FTD > C9orf72 > MAPT
3. SPECT evaluation:
 - a. Hypoperfusion of the hippocampus and the cingulate gyrus

C9orf72 Mutations

General Characteristics

1. The GGGGCC hexanucleotide repeat is located in a non-coding region of the C9orf72 gene that maps to chromosome 9p21
2. The mutation has been posited to cause haploinsufficiency due to loss of gene expression
3. A gain of function mechanism due to secondary RNA toxicity caused by sequestration of RNA-binding proteins has been proposed
4. The number of repeat expansions varies from several hundreds to thousands of copies whereas control subjects have 2–24 repeats. There is no clear evidence of anticipation

Clinical Manifestations

1. The pathogenic hexanucleotide expansion has been described in:
 - a. 37% of familial ALS
 - b. 6% of sporadic ALS
 - c. 21% of familial FTD

- d. 6% of sporadic FTD
2. Age at onset is variable and ranges from 27–83 years (mean of 50 years of age); penetrance is 90% at age 70
3. Disease duration ranges from 1–22 years
4. The most common presentation is FTD then ALS or both
5. Most common subtype of FTD is the behavioral variant with rarer NFPA
6. As has been seen in GRN and MAPT patients, deficits of episodic memory at onset of the illness have been reported as have extrapyramidal and cerebellar dysfunction
7. During the course of the illness the majority of patients develop behavioral, language and motor deficits

Neuropathology

1. TDP-43 immunoreactive inclusions are found in the cerebral cortex, hippocampus, basal ganglia, substantia nigra, and the lower motor neurons of the brainstem and spinal cord
2. There are TDP-43-negative, p62-positive inclusions with characteristic star-like morphology in the cerebellum, hippocampus and frontal cortex
3. The inclusions with p62 have been posited to consist of dipeptide repeat (DPR) proteins that are the result of bidirectional translation of the non-coding GGGGCC expansion repeat by non-ATG-initiated translation (RAN translation). The DPR proteins have been detected in the neocortex, hippocampus, cerebellum and to a lesser degree in motor neurons
4. It has been posited that DPR aggregation due to RAN translation is the pathologic trigger for TDP-43 accumulation

Laboratory Evaluation

1. MRI:
 - a. Symmetrical, bilateral, cortical and subcortical atrophy; the frontotemporal areas are most severely affected
 - b. VBM analysis:
 - i. Atrophy of frontal, insular, temporal, parietal cortex
 - ii. Thalamus and cerebellar atrophy
2. FDG-PET and SPECT imaging:
 - a. Frontal, temporal, parietal and subcortical deficits
 - b. White matter atrophy of long intrahemispheric commissural and corticospinal tracts have been demonstrated with diffusion tractography
 - c. Seed-based intrinsic connectivity demonstrates deficits in the salience and sensorimotor networks; the behavioral symptoms have been shown to correlate with salience and DMN deficits
 - d. Presymptomatic imaging signature may be seen in carriers

VCP Mutations

General Characteristics

1. Missense mutations in the VCP gene that maps to chromosome 19p13.3 cause autosomal dominant inclusion body

- myopathy with Paget's disease of bone and FTD (IBMPD)
- The Valosin-containing protein (also referred to as p97) is an ATPase and is associated with:
 - Protein degradation
 - Membrane fusion
 - Transcriptional activation
 - Apoptosis
 - Molecular chaperoning
 - The frequency of VCP mutations in FTD is approximately 1.6%; approximately 80% of VCP mutation carriers have a positive family history

Clinical Manifestations

- The disorder's onset is approximately age 40
- The presentation is muscle weakness (proximal) in approximately 80% of patients
- Approximately 60% of patients develop adult-onset Paget's disease of bone
- FTD develops later in the course of the disease (55–60 years of age) and affects about 30% of patients
- Rarely there are:
 - Psychiatric disorders
 - Dementia-only phenotype
 - Early language deficits
 - Semantic impairment
 - MND with FTD

Laboratory Evaluation

- MRI:
 - Prominent frontal lobe atrophy
 - Some patients have demonstrated:
 - Asymmetric focal atrophy in the anterior and temporal lobes
- FDG-PET:
 - Glucose hypometabolism of the bilateral frontotemporoparietal regions

TARDBP Mutations

General Characteristics

- TDP-43 is a ribonucleoprotein encoded by the TARDBP gene that maps to chromosome 1
- Putative functions include:
 - Regulation of transcription
 - Messenger RNA splicing
 - Exon skipping
 - MicroRNA biogenesis
- A possible mechanism for its involvement in neurodegenerative disorders is:
 - Its redistribution from the nucleus to the cytoplasm
 - Sequestrations into inclusions that are composed of abnormally phosphorylated and c-terminally truncated TDP-43 fragments
- Mutations in the TARDBP gene occur in 2–3% of ALS patients in both familial and sporadic forms of the disease

Clinical Manifestations

- FTD with MND:
 - Significant motor neuron involvement
 - FTD-MND with extrapyramidal signs
 - FTD with supranuclear palsy
- 16 patients with pure FTD without motor neuron involvement have been reported to date:
 - bvFTD > PNFA with age of onset from 29–77 years

Neuropathology

- TDP-43 inclusions may be seen in GRN, VCP and C9orf72 mutation patients
- Pathologic TDP-43:
 - Is hyperphosphorylated and cleaved and is the major pathogenic protein in ubiquitin-positive, tau and alpha-synuclein-negative FTD (previously called FTL-D-U)
 - It has also been reported (in addition to above described genetic forms of the disease) in:
 - Chronic traumatic encephalopathy
 - Subset of Alzheimer's disease

Neuroimaging

- MRI: Temporal lobe atrophy

CHMP2B Mutations

General Characteristics

- A heterozygous mutation in the CHMPB2 gene (chromatin-modifying protein/charged multivesicular body proteins) that maps to chromosome 8p11.2 was identified in causing FTD in a large Danish kindred. Gene transversions and truncating mutations have also been reported as causative. The Danish kindred had autosomal dominant inheritance
- The encoded proteins are components of ESCRT-III (endosomal sorting complex required for transport III)
- The complex of which CHMP is a component is involved in degradation of surface receptor proteins and the formation of endocytic multivesicular bodies

Clinical Manifestations

- Onset in the Danish kindred is 55 years of age (range of 46–65 years)
- Primarily bvFTD symptomatology
- Associated with:
 - Late onset Parkinsonism
 - Dystonia
 - Myoclonus
 - Pyramidal signs
- Missense mutations have been associated with FTD-ALS

Neuropathology

- Ubiquitin p62-positive, TDP-43/FUS-negative neuronal inclusions (FTLD-U)
- Endosomal pathology has been reported in mutation-positive patient brains

3. Endosomal pathology has been detailed in patient fibroblasts; experimental studies suggest disruption of endosome-lysosome fusion in which the mutant CHMP2B protein constitutively binds to MVB and prevents recruitment of Rab7 that disrupts fusion
4. Specific lower motor neuron variant of ALS with CHMP2B mutation microarray analysis reveals:
 - a. Downregulation of genes involved in axonal transport
 - b. Autophagy induction
 - c. Protein translation
5. One patient with ALS had:
 - a. Intraneuronal inclusions immunopositive for ubiquitin and p62/sequestosome 1 (SQSTM1)-reactive inclusions in oligodendroglia of the motor cortex

Laboratory Evaluation

1. MRI:
 - a. In presymptomatic carriers of the CHMP2B mutation:
 - i. Cortical thinning of the frontal and occipital lobe and the L temporal lobes
 - ii. Increased atrophy rates bilaterally in the inferior temporal cortex, the superior frontal cortex, and the insular cortex
 - b. Structural neuroimaging with CT and MRI:
 - i. Generalized cortical and central atrophy
 - ii. Enlargement of lateral ventricles
 - iii. No white matter changes
2. H₂ O₁₅-PET evaluation of regional cerebral blood flow in symptomatic patients revealed:
 - a. Decreased flow in frontal, parietal and temporal lobes

FUS Mutations

General Characteristics

1. Mutations in the FUS gene that maps to chromosome 16 gives rise to familial ALS and FTD
2. FUS belongs to the FET family of DNA/RNA-binding proteins that bind to overlapping RNA targets
3. It has been posited that the protein is involved with:
 - a. Cell proliferation
 - b. Transcription regulation
 - c. DNA repair
 - d. RNA and microRNA processing

Clinical Manifestations

1. ALS:
 - a. Average age at onset is approximately 44 years of age
 - b. Rarely onset is reported in adolescence
 - c. Approximately 90% of patients die within 3½ years (more rapid demise than with SOD1 or TARDBP)
 - d. Approximately 1/3 of patients have a bulbar onset
 - e. Four mutations in FUS have been associated with FTD. Most mutations are sporadic

Neuropathology

1. In ALS-FUS there is concordant accumulation of other FET proteins into FUS-positive inclusions
2. TAF-15 and EWS proteins are identified in FUS-positive cytoplasmic inclusions in patients with FTD
3. Cell line experiments demonstrate that:
 - a. Wild type FUS is cleaved post-translationally which produces various sized fragments that are localized to the nucleus
 - b. Mutant FUS forms inclusion bodies in the cytoplasm in 5–13% of cells. The proposed pathologic inclusions were similar to stress granules (enclose mRNA and RNA-binding proteins) during various forms of cellular stress. The stress granules have been posited to cause cellular toxicity

Neuroimaging

1. MRI:
 - a. Loss of volume in the anterior temporal lobes, amygdala, anterior hippocampus, anterior insular cortex and anterior cingulate cortex
 - b. Bilateral anterior striatal atrophy severe in the head of the caudate that may differentiate FUS-FTD from FTD-tau and FTD-TDP

TREM2 Mutations

General Characteristics

1. Homozygous loss of function mutations in the TREM2 gene (triggering receptor expressed on myeloid cells 2) that maps to chromosome 6p21 has been associated with an autosomal recessive form of early onset dementia

Clinical Manifestations

1. Bone cysts and fractures (polycystic lipomembranous osteoplasia)
2. Onset in the third decade with pain and swelling of the ankles and wrists; fractures caused by minor trauma
3. By the fourth decade patients develop:
 - a. Memory deficits
 - b. Euphoria
 - c. Loss of social inhibitions
 - d. Impotence
 - e. Increased deep tendon reflexes
 - f. Dysphasia
 - g. Death occurs between ages 35–45
 - h. The late manifestation of the disease resembles Alzheimer's disease
 - i. Variable features in other described kindreds include:
 - i. Myoclonic twitches
 - ii. Seizures
 - iii. Disorder of intestinal motility
 - iv. Leukemia
 - j. Homozygous and compound heterozygous TREM2 (exon 2) mutations have been identified in families that demonstrate:

- i. No bone involvement
- ii. Early age at onset (20–50 years of age)
- iii. Behavioral change
- iv. Extrapyrarnidal features
- v. Hippocampal deficits
- vi. Seizures
- k. TYROBP (also known as DAP12) that maps to chromosome 19q13.12 causes polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOS):
 - i. Most patients have been seen in Finland and Japan
 - ii. These patients have earlier bone fractures than those with TREM2 mutations

Neuropathology

1. Cystic rarefactions in the epiphyses of bones
2. The cysts are noted in phalanges, metacarpals, carpals, metatarsals, patella and the ends of long bones
3. Sclerosis and demyelination of white matter
4. Abnormalities of blood vessels in the brains and bone characterized by thickened and reduplicated basement membranes and abnormal endothelial cells
5. TREM2 interacts with DAP12 in microglia:
 - a. The interaction triggers phagocytosis of amyloid-beta peptide and apoptotic neurons without inflammation
 - b. The mutations in TREM2 interfere with phagocytosis and have been posited to increase the risk of Alzheimer's disease because of failure to clear amyloid-beta peptide

Laboratory Evaluation

1. X-rays that demonstrate cystic rarefaction of the epiphyseal regions of bones
2. Neuroencephalography in the early described patients demonstrated cortical atrophy and dilated ventricles
3. MRI:
 - a. Extensive white matter lesions; frontotemporal atrophy
 - b. An American family of Czechoslovakian ancestry had basal ganglia calcifications
4. Genetic analysis:
 - a. The CQ33X, R47H and the T66M mutations in TREM2 are associated with the disease

Dynactin Mutations

General Characteristics

1. Mutations in the DCTN1 gene that maps to chromosome 2p13.1 have been associated with FTD, motor neuron disease/ALS as well as distal hereditary motor neuropathy type VIIB and Perry syndrome
2. The gene encodes p150 (glued) a large dynactin complex polypeptide that:
 - a. Binds directly to microtubules and cytoplasmic dynein, a motor protein
 - b. Dynactin is required for cytoplasmic-driven movement of organelles along microtubules
 - c. The binding of dynactin to dynein is essential for vesicle motility along microtubules

Clinical Manifestations

1. A few families have demonstrated FTD and MND/ALS
2. Distal hereditary motor neuropathy with vocal cord paralysis
3. Perry syndrome:
 - a. Parkinsonism (occurs early in the course)
 - b. Hypoventilation (occurs late in the course)
 - c. Depression (and apathy)
 - d. Weight loss (late in the course)
 - e. The mean age of onset is 48 years of age and disease duration is approximately 5 years
 - f. Defined DCTN mutations in some families with PSP

Neuropathology

1. Neuronal loss in the substantia nigra (without Lewy bodies)
2. Some neuronal loss is seen in the locus coeruleus, caudate/putamen, hypothalamus, periaqueductal area, dorsal raphe nuclei and the brain stem reticular formation
3. Loss of respiratory neurons in the ventrolateral medullary and dorsal raphe areas
4. Immunohistochemistry:
 - a. Ubiquitin and transactive response DNA-binding protein 43 (TDP-43)-positive neuronal inclusions, dystrophic neurites, glial cytoplasmic inclusions and axonal spheroids. TDP-43 inclusions are predominant in the extrapyramidal system and are similar to those in FTD-4 and ALS

Laboratory Evaluation

1. Structural MRI:
 - a. Most often normal
2. FDG-PET:
 - a. Reduced metabolic rate in lateral prefrontal temporal areas
3. Dopaminergic pathway functional imaging (18-fluodopa (FDG-PET))
 - a. Reduced striatal uptake
4. 4 patients in one Japanese family:
 - a. Decreased cardiac uptake of I-metaiodobenzylguanidine scintigram

Frontotemporal Lobe Variants

Logopenic Progressive Aphasia (LPA)

General Characteristics

1. A language variant of Alzheimer's disease overlaps with LPA
2. There is controversy in regard to the entity as some clinicians feel that LPA and posterior cortical atrophy are clinical presentation of sporadic early onset Alzheimer's disease

Clinical Manifestations

1. A progressive non-fluent aphasia that is characterized by:

- a. Slow rate of speech
- b. Difficulty with word retrieval
- c. Impaired repetition
- d. Poor auditory short-term memory
- e. Maintained single word comprehension and semantic associations
- f. Differential points that distinguish the disorder:
 - i. Slow output of words; much faster in semantic dementia
 - ii. No agrammatism and articulation difficulties that are seen in PNFA
- g. ApoE4 is not a risk factor for LPA or posterior cortical atrophy that distinguish them from Alzheimer's disease

Neuropathology

1. Brain atrophy is more posterior than that of semantic dementia and Alzheimer's disease
2. White matter abnormalities are most severe in the tempoparietal areas of the dorsal language network

Laboratory Evaluation

1. MRI:
 - a. Atrophy of the left posterior, superior and temporal regions
 - b. Atrophy of the inferior parietal lobe
 - c. Hypoperfusion of the structurally affected areas

Corticobasal Ganglia Degeneration

General Characteristics

1. The prevalence of CBGD is 4.9 to 7.3 patients per 100,000 people
2. Slight predominance of women

Clinical Manifestations

1. Onset is usually between 50–70 years of age; may be sudden
2. Average disease duration is 6 years
3. Symptoms and signs are typically asymmetric
4. Parkinsonism:
 - a. Usually present in one extremity and is always asymmetric; the non-dominant arm may be more frequently affected
5. Rigidity, bradykinesia, shuffling gait
6. Alien hand syndrome:
 - a. Affects approximately 60% of patients
 - b. The alien hand is most often of the posterior variety in which the arm and hand move sinuously. The arm may be elevated and appears to act on its own. It may follow the physician's hand (seen in other dementia as well). Rarely patients complain of sensory symptoms in the hand
7. Apraxia:
 - a. The inability to repeat or mimic a particular movement with or without objects. If the apraxia occurs in the lower extremity, it may impair walking

- b. Limb kinetic apraxia may impair fine movements of the hand and fingers
8. Aphasia:
 - a. The aphasia is of the non-fluent, progressive type
 9. Psychiatric disorders may have bvFTD characteristics along with depression and instability
 10. Cortical parietal sensory loss (almost always asymmetric)
 11. Rare myoclonus and dystonia

Neuropathology

1. Astroglial inclusions that may appear as astrocytic plaques (blurred margins from the astrocyte) primarily
2. Encountered in the anterior frontal and premotor areas
3. Abnormal accumulation in astrocytes and glial cells of tau protein (a tauopathy)
4. Ballooning of neurons
5. Diagnosis can only be secured at post-mortem

Laboratory Evaluation

1. MRI:
 - a. Posterior parietal and frontal cortical atrophy that is asymmetrical
 - b. Corpus callosum atrophy
2. fMRI:
 - a. Reduced connectivity of the parietal cortex, sensorimotor and supplementary motor cortex
3. SPECT evaluation:
 - a. Hypoperfusion of the posterior frontal and parietal lobes
 - b. Variable perfusion deficits have been noted in the thalamus, temporal cortex, basal ganglia and frontocerebellar connections
4. Imaging of the dopamine system with PET:
 - a. Diminished dopamine uptake in the caudate and putamen

Differential Diagnosis

1. PSP
2. Parkinson's disease
3. Alzheimer's disease
4. Lewy body dementia
5. FTD

Frontotemporal Dementia with PSP

General Characteristics

1. The prevalence of PSP is approximately 4–6 per 100,000 people; it is the second most common form of parkinsonism after PD
2. Men and women are affected equally
3. The progression is insidious with a mean survival time of 5.6 years

Clinical Manifestations

1. Onset is most often in the seventh decade of life

2. The early symptom in approximately 2/3 of patients is loss of balance with frequent falls
3. Supranuclear gaze palsy:
 - a. Patients often complain early of inability to read because they can't look down
 - b. Downward saccades may be worse than upward saccades
 - c. The supranuclear palsy can be easily overcome by vestibular input (oculocephalic maneuvers)
 - d. "Square wave jerks" are seen when a patient fixes at a distance (saccadic in appearance with no smooth phase)
 - e. Difficulty with convergence that may cause diplopia with down gaze
4. Bradykinesia
5. Axial dystonia and rigidity
6. Pseudobulbar palsy
7. Postural instability with characteristic falling backwards
8. Apathy and emotional blunting
9. Slow mental processing
10. Reduced verbal fluency
11. Neck dystonia (the head is held in extension; in other akinetic rigid parkinsonian syndromes the head is flexed)
12. Deep nasolabial folds
13. PSP has been categorized into 3 subtypes:
 - a. Richardson syndrome
 - b. PSP-parkinsonism
 - c. PSP-pure akinesia with gait freezing
14. Cognitive deficits and cortical atrophy are most severe in the Richardson subtype (clinical PSP)

Neuropathology

1. Most PSP is sporadic; less than 1% of PSP patients have an affected family member
2. A variant of the gene for tau, the H1 haplotype located on chromosome 17 has been delineated in several families
3. PSP patients have:
 - a. Abnormal neuronal and glial neurofibrillary tangles and neuropil threads that are:
 - i. Composed of hyperphosphorylated microtubule-associated protein tau primarily in the 4 repeat isoforms
 - ii. Tufted astrocytes
 - iii. Oligodendroglial coiled bodies
 - iv. Swollen "ballooned" neurons primarily in paralimbic areas but not as dense in number as seen in CBG degeneration
 - v. Neurotransmitter deficits occur in the dopaminergic, cholinergic, GABA-ergic and serotonergic systems
 - vi. Mitochondrial dysfunction may occur, leading to oxidative stress that promotes the formation of tau filaments

Laboratory Evaluation

1. MRI:
 - a. Atrophy of premotor and supplementary motor areas
 - b. Sparing of the inferior frontal lobe
2. PET imaging:
 - a. Several new selective in-vivo PET imaging ligands have been developed which include
 - i. [18F]THK523, [18F]Thk5117, [18F]THK5105, and [18F]THK5351
 - ii. [18F]AV1451(T807) and [11C]PBB3 are being intensely evaluated in regard to the rate of tau formation in neurodegenerative diseases

Frontotemporal Dementia and Parkinsonism Linked to Chromosome 17 (FTDP-17)

General Characteristics

1. Over the last several decades dominant forms of FTD were delineated whose major features are:
 - a. CBG-like
 - b. PSP-like
 - c. Associated with amyotrophy in some patients
2. The different delineations of these disorders were defined as:
 - a. Familial Pick's disease
 - b. Disinhibition dementia parkinsonian complex
 - c. Familial progressive subcortical gliosis
 - d. Familial presenile dementia with tangles
 - e. Autosomal dominant parkinsonism
 - f. Dementia with pallidopontonigral degeneration
 - g. Multiple system tauopathy with presenile dementia
 - h. FTD-17 is divided into:
 - i. Dementia-dominant
 - ii. Parkinsonian type
3. The majority of FTD-17 patients have mutations in the tau gene that occur within the microtubule binding domain. Most known mutations in non-coding regions affect the splicing of exon10 which alters the proportion of tau isoforms (ratio of 3 to 4 repeats) or to the ability of tau to bind to microtubules
4. There are FTDP-17 kindreds in which there are no tau mutations or pathology. Their phenotype is similar to that of patients with tau mutations. The genetic linkage is to the same region of chromosome 17q21 that contains the tau gene. This suggests that there are mutations in intronic sequences, regulatory regions of tau or other causative genes that have not been delineated

Clinical Manifestations

1. Onset is usually insidious
2. Behavioral and personality disorders that include:
 - a. Disinhibition
 - b. Apathy
 - c. Compulsive behavior
 - d. Drug addiction
 - e. Aggressiveness

3. Cognitive deficits:
 - a. Progressive speech difficulty primarily manifest as non-fluent or aphasia
 - b. Disorder of executive function
 - c. Over time patients develop loss of memory, orientation and visuospatial abilities as well as echolalia, palilalia and vocal and verbal perseveration
 - d. Dementia and mutism are apparent in end stage disease
4. Motor signs and symptoms:
 - a. Parkinsonism can be the first manifestation of the disease, although in some kindreds it occurs late in the disease. It is manifested by:
 - i. Symmetry
 - ii. Bradykinesia
 - iii. Postural instability
 - iv. Rigidity of axial and appendicular musculature
 - v. Usually no resting tremor
5. Poor or no response to levodopa
6. Variable features include:
 - a. Dystonia
 - b. Supranuclear gaze palsy
 - c. Myoclonus
 - d. Postural and action tremor
 - e. Eyelid opening and closing apraxia (frontal lobe involvement)
 - f. Dysphagia and dysarthria
 - g. Upper and lower motor neuron signs
7. Dementia predominant phenotype:
 - a. Is the more common phenotype
 - b. Seen in families with mutations in exon 1, 9, 11, 12, 13 and 10
8. The Parkinson-Plus predominant phenotype:
 - a. Manifests in families with intronic and exonic mutations in exon 10 that causes overproduction of 4R tau isoform

Neuropathology

1. Aggregation of recombinant tau in the presence of polyanions from the pool that is unbound to microtubules
2. The disruption of alternative splicing of exon 10 biases the tau ratio in the form of 4R:3R repeat sequences
3. In families without tau mutations:
 - a. Ubiquitin-positive, tau-negative intranuclear neuronal inclusions are seen in layer II of the cerebral cortex and the dentate gyrus of the hippocampus

Laboratory Evaluation

1. CT and MRI:
 - a. Dilation of the ventricular system
 - b. Frontal, temporal and parietal cortical atrophy
 - c. MRI T2-weighted sequences may demonstrate iron in mesencephalic nuclei
 - d. Some kindreds have asymmetrical cortical atrophy
2. SPECT:
 - a. Perfusion abnormalities in affected areas

3. I¹⁸ FDG-PET:
 - a. Reduced frontal-parietal-temporal uptake patterns
4. [¹⁸F]-fluoro-L-dopa (6FD) and [¹¹C]-raclopride tracer demonstrate greater caudate involvement than in the putamen which distinguishes it from idiopathic PD
5. EEG:
 - a. Diffuse slowing as the disease progresses
 - i. Patients with the P3015 mutation have sharp waves, spikes and epileptic discharges
6. EMG:
 - a. Electromyography may demonstrate neurogenic changes; nerve conduction velocities are normal

Differential Diagnosis of FTDP-17

1. Pick's disease
2. PSP
3. Corticobasal syndrome
4. Parkinson-plus syndrome
5. Dementia with Lewy bodies (DLB)
6. Parkinson's disease
7. MSA-P

Disinhibition-Dementia-Parkinsonian Amyotrophy Complex (DDPAC)

General Characteristics

1. AD; chromosome 17q21

Clinical Manifestations

1. Mean age at onset is 45 years
2. Disinhibition
3. Features of Klüver-Bucy syndrome
4. Schizophrenic behavior
5. Social withdrawal
6. Initial preservation of orientation, processing speed and ability to calculate
7. Hyperphagia
8. Later in the course of the disorder:
 - a. Perseveration
 - b. Constructional apraxia
 - c. Decreased speech output
 - d. Inability to calculate
 - e. Parkinsonism
 - f. Fasciculations and muscle wasting

Neuropathology

1. Anatomic areas of involvement:
 - a. Anterior temporal lobes
 - b. Entorhinal and cingulate cortex
 - c. Amygdala
 - d. Piriform cortex
2. Histopathology:
 - a. Circumscribed laminar spongiosis:
 - i. Limbic areas
 - ii. Association cortices
 - b. Neural intracytoplasmic inclusions

- i. Phosphorylated neurofilament lattice-like formations with ubiquitin
- ii. Located in the brainstem nuclei, hypothalamus, and basal ganglia
- iii. Negative for amyloid
- iv. Oligodendroglial cytoplasmic inclusions similar to those seen with multiple system atrophy

Neuroimaging

1. MRI:
 - a. Ventricular enlargement
 - b. Atrophy of the anterior temporal lobes, cingulate gyrus, and amygdala

Pallidopontonigral Degeneration (PPND)

General Characteristics

1. Missense mutations in exon 10 of the tau gene that maps to chromosome 17
2. Encodes a tau isoform with 4R repeats

Clinical Manifestations

1. Stage I (begins >30 years):
 - a. Mild dementia and parkinsonism
2. Stage II:
 - a. Moderate parkinsonism
 - b. Dementia
 - c. Dysarthria
 - d. Pyramidal tract signs
 - e. Extraocular muscle involvement
 - f. Sensory defects
3. Stage III:
 - a. Severe parkinsonism
 - b. Dementia
 - c. Dysphagia
4. Stage IV:
 - a. Terminal manifestations
 - b. Perseverative vocalizations
 - c. Frontal lobe release signs
 - d. Exceptionally progressive course
 - e. Symptom onset and death occur in the fifth decade

Neuropathology

1. Neuronal and glial tau inclusions
2. Hyperphosphorylated tau
3. Severe neuronal loss with gliosis in the substantia nigra, pontine tegmentum, and globus pallidus with less involvement of the caudate and putamen nuclei
4. Absent plaques, tangles and Lewy bodies

Laboratory Evaluation

1. [¹⁸F] 6-fluoro-L-dopa (6FD) positron emission tomographic studies reveal:
 - a. Markedly decreased striatal uptake of 6FD
 - b. Severe presynaptic dopaminergic dysfunction with intact striatal D2 receptors (RAC and 6FD scans)

Familial Progressive Subcortical Gliosis (FPSG)

General Characteristics

1. Autosomal dominant Parkinsonism that maps to chromosome 17

Clinical Manifestations

1. Onset in the presenium
2. Slowly progressive course
3. Early clinical features:
 - a. Personality change
 - b. Depression
 - c. Disinhibition
 - d. Degeneration of social graces
 - e. Memory impairment
 - f. Psychotic symptoms
4. Late clinical manifestations:
 - a. Progressive dementia
 - b. Verbal stereotypies
 - c. Decreased speech production
 - d. Features of Klüver–Bucy syndrome
5. Terminal clinical manifestations:
 - a. Profound dementia
 - b. Mutism
 - c. Dysphagia
 - d. Extrapyramidal signs

Neuropathology

1. Tau mutations:
 - a. Overexpression of the soluble form repeat tau isoform
 - b. Neuronal and glial tau accumulation
2. Generalized cerebral atrophy:
 - a. The frontal and temporal lobes are the most severely affected
 - b. Fibrillary astrocytosis of the subcortical white matter
 - c. Subpial and deep layers of the frontal and temporal lobes are affected most prominently
 - d. Laminar spongiosis in lamina II and III
 - e. Axonal spheroids with the 5q32 mutations

Laboratory Evaluation

1. There is a radiologic phenotypic spectrum as many patients reported do not have mutations in the MAPT gene
2. MRI:
 - a. Ventriculomegaly
 - b. Frontotemporal cortical atrophy
3. Patients with hereditary diffuse leukoencephalopathy with spheroids (HDLS) is caused by heterozygous mutation in the CSF1R gene on chromosome 5q32:
 - a. Localized white matter involvement of deep, subcortical and periventricular areas
 - b. Bilateral asymmetric lesions
 - c. Most prominent in frontal and parietal areas
 - d. Cortical atrophy
 - e. Involvement of the corpus callosum
 - f. Corticospinal tracts are involved late in the course of the illness
 - g. Minimal gray matter involvement

Hereditary Dysphasic Disinhibition Dementia (HDDD)**General Characteristics**

1. Autosomal dominant inheritance
2. Maps to chromosome 17q21-22

Clinical Manifestations

1. Global dementia
2. Disproportionate dysphasia
3. Behavioral frontotemporal symptoms

Neuropathology

1. Neuronal loss in layer II of the cortex
2. Cortical astrocytosis
3. Status spongiosus
4. Asymmetric atrophy of frontotemporal areas (left side)

Neuroimaging

1. MRI:
 - a. Left-sided > than right atrophy of frontotemporal areas

Progressive Language Disorder Due to Lobar Atrophy of FTD

The language variant of FTD becomes apparent when there is a gradual deterioration of speech and semantic abilities while other cognitive domains are relatively intact. FTD-related primary progressive aphasia (PPA) is divided into a non-fluent and agrammatic form (nfvPPA) and a semantic variant (svPPA). In nfvPPA there is progressive atrophy of the left inferior frontal regions and opercular and insular cortex. In svPPA there is bilateral atrophy of the anterior temporal lobes that is more severe on the left side.

The logopenic variant of PPA demonstrates atrophy that extends from frontotemporal areas into the parietal lobe and has Alzheimer's disease pathology. However, approximately 1/3 of patients with lvPPA have both clinical and pathologic characteristics of FTD.

There are many complicating features in determining phenotype and pathology in FTD patients with language disturbance.

These include:

1. The clinical phenotype changes as the disorder evolves
2. There are mixed clinical features at presentation; a common example being patients with PPA and bvFTD symptomatology
3. FTD syndromes overlap with:
 - a. Motor neuron disease
 - b. Corticobasal ganglia degeneration
 - c. PSP
4. Patients with nfvPPA demonstrate the extrapyramidal features of CBD and PSP within the first two years of language impairment
5. In general, lobar PPA is most often associated with FTD-tau, while nfvPPA is related to FTD-ubiquitinated (FTD-U) as is bvFTD

Non-Fluent/Agrammatic Variant of PPA**Clinical Manifestations**

1. The earliest disability is anomia and word finding
2. Early fluent speech evolves to effortful speech production due to articulatory deficits
3. Early difficulty with sentence construction and syntax
4. Agrammatic speech due to a shortage of verbs associated with phonological mistakes
5. Failure of subject-verb concordance
6. Apraxia of speech with motor planning and sequencing deficits that lead to:
 - a. Stuttering
 - b. Inability to repeat strings of syllables
 - c. Abnormal prosody, slow rate of speech production and decreased complexity of speech
 - d. As the disease progresses:
 - i. Difficulty with writing is greater than reading deficits that are primarily phonetic
 - ii. Patients have maintained comprehension but agrammatism interferes with comprehension of complex syntactic sentences and sequential commands

The Semantic Variant of PPA

1. The most homogeneous of the PPAs
2. There is progressive loss of semantic knowledge, the meaning of words, particularly in the comprehension of single words and naming
3. Patients utilize circumlocutions, overuse pronouns, verbs and high frequency nouns
4. Patients are able to repeat multisyllabic words
5. As the disease progresses patients demonstrate:
 - a. Disinhibited speech output
 - b. Stereotypic thematic perseverations
 - c. Inability to listen
 - d. Due to severe lexical-semantic impairment, patients become mute
 - e. As opposed to Alzheimer's disease, in svPPA patients do not benefit from cuing because there is no knowledge of the word's meaning rather than an inability to access it

Logopenic Variant of PPA**Clinical Manifestations**

1. Initially it is characterized by slow speech, difficulty with word finding and phonemic paraphasias
2. There is no agrammatism, articulatory difficulty or expressive aprosodia
3. Patients do not utilize telegraphic speech with missing function words and morphemes
4. Confrontation naming is only moderately affected
5. Single word comprehension is preserved but patients are impaired in repeating or comprehending sentences and long phrases

6. A phonological short-term memory deficit has been posited as the underlying deficit of lvPPA
7. Patients with lvPPA may have concomitant episodic memory deficit and acalculia

Pick's Disease

General Characteristics

1. Autosomal dominant inheritance in some patients
2. Mutations in the tau gene (MAPT) that maps to chromosome 17q21-22

Clinical Manifestations

1. Early personality changes
2. Deterioration of social skills
3. Early non-fluent aphasia:
 - a. Echolalia
 - b. Isolated word-finding difficulty
 - c. Relative sparing of auditory comprehension
4. Disinhibition, euphoria, and apathy at onset
5. Klüver-Bucy symptomatology in some patients
6. Variable signs of cortical dementia:
 - a. Aphasia (non-fluent)
 - b. Apraxia of speech:
 - i. Articulatory difficulty without language breakdown
 - ii. Lesion of the left pars operculum rather than pars triangularis
 - iii. Buccofacial apraxia and dysarthria
7. Absence of ideomotor apraxia
8. Absence of gait abnormalities at onset
9. Memory is usually preserved

Neuropathology

1. Pick bodies and Pick cells stain with anti-tau and anti-ubiquitin antibodies
2. In atypical Pick's disease these cells are absent
3. Pick bodies are located in the dentate gyrus, the pyramidal cells of the CA1 area and the subiculum of the hippocampus
4. The neocortex in layers II and IV; layers III and V demonstrate severe neuronal loss but have few Pick bodies
5. The caudate, putamen, globus pallidus and locus coeruleus and the lateral tuberal nucleus of the hypothalamus may be severely involved
6. The dentate nucleus is often involved but the substantia nigra is usually spared
7. Pick bodies usually demonstrate the 3R isoform of tau that are shaped with a round body that includes an indentation in the region that faces the nucleus
8. Pick bodies have a variety of other proteins that include the N-terminal of amyloid precursor protein, ubiquitin, Alz-50, neurofilament proteins, clathrin, synaptophysin and neuronal surface glycoside (A2B5)
9. Ballooned neurons

Neuroimaging

1. MRI:

- a. Frontal and temporal lobe atrophy often more severe on the left side
- b. Decreased volume of the caudate head

Frontal Lobe Dementia with Motor Neuron Disease

General Characteristics

1. Approximately 5% of patients with ALS inherit the illness
2. Some kindreds have members with ALS, FTD, and ALS-FTD
3. Genetic mutations causing FTD-ALS include:
 - a. The GGGGCC hexanucleotide repeat in C9orf72:
 - i. <23 repeats correspond with the wild-type allele; >30 repeats express the disease
 - ii. This expansion is seen in 12% of familial FTD and 22.5% of FALS
 - iii. European populations demonstrate a prevalence rate of 46% in familial ALS, 21% in sporadic ALS and 29% in familial FTD
 - b. Mutations in the TARDBP gene that maps to chromosome 1p36.22
 - c. Mutations in UBQLN2 have recently been shown to cause X-linked dominantly inherited ALS/FTD
 - d. DDPAC is linked to a tau gene mutation (MAPT) on chromosome 17q21

Clinical Manifestations

1. C9orf72:
 - a. Patients differ from typical FTD patients due to psychiatric symptoms that include:
 - i. Delusions, paranoia and irrational thoughts

Neuropathology (C9orf72)

1. TDP-43 inclusions
2. p62 positive cytoplasmic inclusions are found in the hippocampus and cerebellum
3. TDP-43 inclusions vary depending upon clinical phenotype:
 - a. Patients with pure ALS have TDP-43 inclusions primarily in the spinal cord
 - b. In those with pure FTD the pathology is in the cortex
 - c. Those with FTD/ALS have pathology in both the cortex and the spinal cord
 - d. TDP pathology may also be found in the cerebellum, parietal and occipital lobes
 - e. TDP-43 levels are higher in the CSF in patients with ALS or FTD than in controls
4. MND and parkinsonism the DDPAC variant:
 - a. Tau inclusions
5. UBQLN2 gene mutation (X-linked dominant ALS/FTD):
 - a. The pathology is ubiquitin-2 protein inclusions in the brain and spinal cord due to impaired degradation of ubiquitinated proteins
6. SOD-1 mutations cause approximately 20% of familial ALS:
 - a. Ubiquitin positive inclusions are found in the brain and spinal cord that are not TDP-43 positive

Clinical Manifestations

1. Characteristic upper and lower motor neuron manifestations
2. Onset of symptoms is between 50–60 years of age
3. Slightly more common in men than women
4. The motor neuron signs and symptoms may precede, occur concomitantly or follow the cortical features of FTD. Most often, cognitive deficits precede motor manifestations
5. The interval between cognitive changes and motor signs may be months to several years (mean of 2 years)
6. Bulbar onset may be more frequent than in ALS
7. A subset of patients has greater upper extremity involvement than lower
8. Behavioral changes are primarily in personality that is manifested by euphoria, indifference or apathy
9. Language deficits have components of non-fluent and semantic aphasia
10. Disease progression and death occur earlier than with ALS or FTD alone

Laboratory Evaluation

1. EEG may be normal or demonstrate background or focal slowing
2. Voxel-based MRI morphometry:
 - a. Atrophy in frontotemporal regions
3. SPECT:
 - a. Reduced uptake in the frontal lobes

Differential Diagnosis of the Tauopathies

1. FTD-17 Parkinsonism
2. Variants of FTD-17:
 - a. DDPAC (dementia depression disinhibition amyotrophy complex)
 - b. PPND (pedunculopallidal pontine nigral degeneration)
 - c. FSCG (familial subcortical gliosis)
 - d. HDDD (hereditary dysphasic disinhibition dementia)
 - e. FTDP-17 (missense mutations):
 - i. Splicing variants in exon 9, 10, 12
 - ii. 3 intronic mutations (regulate the alternative splicing of exon 10)
 - f. Primary progressive aphasia:
 - i. Semantic variant
 - ii. Non-fluent variant
 - iii. Logopenic variant
3. CBGD (corticobasal ganglionic variant)
4. PSP
5. Parkinson's disease ALS dementia complex of Guam
6. Head trauma

Post-Encephalitic Parkinsonism*General Characteristics*

1. Post-encephalitic parkinsonism or encephalitis lethargica appeared suddenly in 1916–1917 and continued to 1926.

Approximately one half a million patients were infected throughout the world. Approximately 1/3 patients died, 1/3 developed post-encephalitic disease and 1/3 completely recovered

2. Sporadic patients continue to be seen but it is not clear if these patients share the same etiology as those of the original pandemic
3. Recent studies support the hypothesis that encephalitis lethargica (EL) is an autoimmune disorder based on:
 - a. The clinical presentation
 - b. Intrathecal oligoclonal bands
 - c. Antibodies against basal ganglia antigens
 - d. There is indirect evidence that the disorder may be due to a specific enterovirus

Clinical Manifestations

1. The acute stage:
 - a. Somnolent or manic behavior
 - b. Mask-like facies
 - c. Rigidity
 - d. Tremor (not the pill-rolling type of classic Parkinson's disease)
 - e. Rarely, post-encephalitic Parkinsonism (PEP) developed without the acute stage
2. Chronic stage:
 - a. Akinetic rigidity
 - b. Oculogyric crisis
 - c. Ophthalmoplegia
 - d. Autonomic crises:
 - i. Blood pressure fluctuations
 - ii. Hyperhydrosis
 - iii. Pupillary dilatation
 - e. Central respiratory irregularities
 - f. Prolonged somnolence

Neuropathology

1. Possible enterovirus etiology; the autoimmune features described being secondary
2. Small virus particles have been identified in the cytoplasm and nucleus of neurons from classical and modern cases of EL. They have also been described in one patient with PEP
3. Severe neuronal loss and gliosis in brainstem nuclei, particularly the substantia nigra
4. Tau-positive neurofibrillary tangles: absent alpha-synuclein and TDP-43 inclusions

Laboratory Evaluation

1. CSF leukocytosis
2. Anti-BG antibodies
3. MRI:
 - a. Structural abnormalities of the cortex and basal ganglia
 - b. ¹⁸F-FDG PET:
 - i. Basal ganglia hypermetabolism

FTD*Clinical Manifestations*

1. bvFTD (behavior variant)
2. avPPA (the agrammatic variant)
3. svPPA (the semantic variant)
4. Genetic causes of FTD:
 - a. MAPT mutations:
 - i. GRN (progranulin)
 - ii. C9orf72
 - iii. VCP (valosin-containing protein)
 - iv. TARDBP (transactive response DNA-binding protein-43)
 - v. CHMP2B (charged, multivesicular body protein 2B)
 - vi. FUS
 - vii. DCTN1
 - viii. TREM2
5. Variant FTD:
 - a. DDPAC
 - b. PPND
 - c. FSCG
 - d. HDDD

Niemann-Pick Disease Type C*General Characteristics*

1. Niemann-Pick type C is caused by mutations in the NPC1 gene (95% of patients) and mutations in the NPC2 genes. The former is type C1 and the latter C2. The NPC1 gene maps to chromosome 18q11-q12
2. Niemann-Pick types C1 and C2 have a similar phenotype whose functions encompass the egress of lipids primarily cholesterol from late endosomes or lysosomes
3. The protein encoded by NPC1 is found in membranes within cells and moves cholesterol and lipids intracellularly. The protein functions as a transporter; the protein encoded by NPC2 concomitantly functions with NPC1 in cellular transport of unesterified cholesterol and glycosphingolipids

Clinical Manifestations

1. The clinical phenotype has a wide spectrum that includes:
 - a. Juvenile or adult patients who primarily present with neurologic or psychiatric signs and symptoms
 - b. Cerebellar ataxia (76%)
 - c. Vertical supranuclear ophthalmoplegia (75%)
 - d. Movement disorder (58%)
 - e. Cognitive deficits (61%)
 - f. Affective and psychiatric disorder (45%)
 - g. Splenomegaly occurs in 45% of adult patients
 - h. Variable symptoms and signs include:
 - i. Sleep inversion
 - ii. Partial or generalized seizures
 - iii. Gelastic epilepsy
 - iv. Progressive dementia

- v. Psychosis
- vi. Dystonia
- vii. Spasticity

Neuropathology

1. Accumulation of free or unesterified cholesterol in lysosomes that leads to deficiencies of cholesterol in neuronal membranes and for steroid synthesis
2. Tau-positive tangles and neuropil threads are detected in the midbrain and cerebral cortex

Laboratory Evaluation

1. Filipin test:
 - a. The demonstration of lysosomal cholesterol storage in cultured fibroblasts
2. Genetic analysis
3. MRI:
 - a. Periventricular white matter signal hyperintensities
 - b. Cortical atrophy
 - c. Mild cerebellar atrophy

Parkinson Dementia Complex of Guam (PDC)*General Characteristics*

1. The highest prevalence is in Guam, New Guinea and the Kii Peninsula of Japan:
 - a. Recently the incidence and prevalence rates have dramatically declined
2. There is evidence that mutation in the TRPM7 gene that maps to chromosome 15q21/2 may be causative:
 - a. It encodes a member of the transient receptor potential cation channel family:
 - i. PARK7 – a similar phenotype is caused by a double homozygous mutation in the DJI gene

Clinical Manifestations

1. A linear retinal pigment epitheliopathy is present in 50% of patients with ALS/PDC but in only 15% of asymptomatic Chamorro individuals. The retinopathy is also described in patients from the Kii peninsula of Japan
2. The Muro district of the southern coast of Japan is endemic for Kii ALS/PDC, also known as Muro disease
3. Parkinsonism-dementia complex:
 - a. Progressive parkinsonism
 - b. Dementia
 - c. Levodopa-unresponsive
4. The core neuropsychological features of patients with ALS/PDC from the Kii peninsula include:
 - a. Abulia
 - b. Apathy
 - c. Bradyphrenia
 - d. Hallucinations
 - e. Amnesia
5. Lytico (ALS) in patients from Guam and the Western Pacific Islands:

- a. Patient to patient variability
- b. Severe muscle atrophy
- c. Bulbar involvement
- d. Diaphragm and respiratory muscle involvement
- 6. Dementia (Chamorro patients) is progressive:
 - a. Severe emotional lability:
 - i. Mania
 - ii. Aggressive outbursts
 - b. A few patients are not cognitively compromised throughout their illness
- 7. Late in the course of the illness, they develop an akinetic-rigid state. Some patients have tremor; some patients are unable to close their mouths

Neuropathology

- 1. It is a complex and genetically heterogeneous disorder:
 - a. Muro disease (Kii peninsula) has four subtypes that include:
 - i. Sporadic ALS
 - ii. ALS/PDC with tauopathy
 - iii. ALS with C9 or 67y gene mutations
 - iv. ALS with optineurin genetic mutations
 - b. Neurofibrillary tangles (NFT) in the brain and loss of anterior horn neurons and corticospinal tract destruction in the spinal cord
 - c. NFTs in the temporal, frontal lobe and brainstem
 - d. Tau protein consisted of 3R and 4R isoforms

Laboratory Evaluation

- 1. Kii ALS/PDC patients:
 - a. SPECT:
 - i. Decreased blood flow of the frontal and temporal lobes
 - b. CT/MRI:
 - i. Atrophy of the frontal and temporal lobes

The Differential Diagnosis of Tauopathies with Parkinsonism

- 1. PSP
- 2. Corticobasal degeneration
- 3. Frontotemporal dementia and variants
- 4. Pick's disease
- 5. Niemann-Pick disease type C
- 6. Post-encephalitic Parkinsonism
- 7. ALS/PDC of Guam
- 8. FTD-17 (variants):
 - a. DDPAC
 - b. PPND
 - c. FSCG
 - d. HDDD
- 9. Generic MAPT (tau) mutations:
 - a. GRN
 - b. C9orf72
 - c. TARDP
 - d. UCP
 - e. FUS

- f. DCTN1
- g. CHMPB2
- h. TREM2
- 10. Mutations in the LRRK2 gene
- 11. Chronic traumatic encephalopathy

Prion Disease

Overview

A prion is an infectious protein that is the cause of the transmissible spongiform encephalopathies. It is a protein that is able to fold in structurally distinct forms and one of which is transmissible to other prion proteins. Thus, prions are able to self-propagate and transmit their conformation to other prions. Prions are misfolded protein molecules that induce normally folded proteins into a misfolded prion form. They contain no DNA or RNA. All prion diseases in humans affect the brain and neural structures. In its most general form, a prion protein is a template that shapes the misfolding of proteins into a prion form. Prions cause amyloid to fold in which its target protein polymerizes into aggregates of tightly packed beta-sheets. These amyloid aggregates are composed of fibrils that extend at their ends that replicate by breakage, the newly formed ends initiating growth.

The incubation of a prion disease depends on the exponential growth rate associated with its replication that is dependent on its linear growth and the breakage of aggregates. Prion propagation requires normally folded proteins for misfolding and propagation. Prion aggregates are very stable and are resistant to denaturation by chemical and physical agents. The normal form of prion protein is denoted as PrP^c. The "c" refers to cellular PrP. The infectious form is termed PrP^{sc}, the "Sc" denotes "scrapie" that is the prototypic prion disease discovered in sheep. PrP^c is a normal protein found on cell membranes. Its structure includes:

- 1. 209 amino acids
 - 2. One disulfide bond
 - 3. An alpha-helical structure
 - 4. There are several topological forms
 - 5. The protein cannot be separated by centrifugation
- Prion function is complex and not completely defined. It has been found to:
- 1. Bind copper (11) ions
 - 2. It is digested by proteinase K
 - 3. Possible role in long term memory
 - 4. Hippocampal LTP
 - 5. Can be cleaned from the cell surface by phosphoinositide phospholipase (PI-PLC) that disrupts the glycol phosphatidyl inositol (GPI) anchor
 - 6. Posited to be a component of cell-cell adhesion and intracellular signaling

Infectious PrP^{sc} that converts normal PrP^c into the infectious form by changing its conformation always causes disease. This isoform has a higher amount of β -sheet structure rather

than the α -helix conformation. The aggregation of the abnormal isoforms forms the structured amyloid fibers of the prion plaque. Free protein attaches to the end of each fiber that forms the template for growth. In general, PrP molecules with the identical amino acid sequence to the infectious PrP^{Sc} isoform are incorporated into the lengthening fiber.

The conformational change of PrP^C may occur spontaneously, from dominant mutations in the prion protein (PRNP) gene that encodes PrP^C or from infection by PrP^{Sc}. The exponential growth rate results from the combination of fibril growth and breakage that is dependent on the square root of the PrP^C concentration.

The exact mechanism underlying prion diseases has not been identified. A prion can be formed by the combination of PrP^C, polyadenylic acid and lipids in a protein misfolding cyclic amplification (PMCA) reaction. The pathology is vacuole formation in neurons that leads to spongiform degeneration in the affected parts of the CNS. All inherited cases of prion diseases are caused by mutations in the PRNP gene that causes their encoded proteins to fold into pathogenic prion.

The cause of prion disease to date may be sporadic, genetic, infectious and in some instances a combination of these mechanisms. The human prion disorders are:

1. Creutzfeldt-Jakob disease (CJD)
2. Gerstmann-Sträussler-Scheinker syndrome (GSS)
3. Kuru
4. Fatal familial insomnia (FFI)
5. Variable protease-sensitive prionopathy (VPSPr)

All of the disorders involve the conformational change of normal cellular prion protein (PrP^C) into the misfolded scrapie prion protein (PrP^{Sc}).

Creutzfeldt-Jakob Disease

General Characteristics

1. The classification of CJD includes:
 - a. Sporadic CJD (sCJD):
 - i. In approximately 85% of patients
 - b. Familial CJD (fCJD):
 - i. Accounts for most of the remaining 15% of patients
 - c. Variant CJD (vCJD):
 - i. Caused by the consumption of contaminated beef (now rare)
 - d. Iatrogenic:
 - i. Contamination from an infected patient primarily acquired during a medical procedure that have included:
 1. Blood transfusion
 2. The use of human-derived pituitary growth hormone
 3. Corneal transplants
 4. Gonadotropin hormone therapy
 5. Contaminated EEG needles

Clinical Manifestations

1. The first symptom is usually a rapidly progressive dementia characterized by:

- a. Anxiety, depression, paranoia
- b. Obsessive-compulsive behavior
- c. Psychosis
2. As the disease progresses:
 - a. Speech impairment (dysarthria)
 - b. Ataxia
 - c. Gait deterioration
 - d. Rigidity
 - e. Seizures
 - f. Myoclonus
3. Sporadic disease may be extremely rapid with death within weeks; most patients succumbing six months following the onset of symptoms
4. Approximately 15% of patients may survive for 2 or more years

Neuropathology

1. Spongiform degeneration in gray matter
2. The presence of vacuoles of one to 50 micrometers in the neuropil of all six cortical layers of the cerebral cortex
3. Some patients have diffuse involvement of the cerebellar molecular layer
4. Vacuoles may appear glassy or eosinophilic
5. Severe neuronal loss and gliosis in affected areas
6. In approximately 1/3 of patients with sporadic CJD, PrP^{Sc} can be detected in skeletal muscle and/or the spleen

Laboratory Evaluation

1. CSF analysis for 14-3-3 protein
2. Neuron-specific enolase (NSE) may be elevated and reaches more significance if associated with high 14-3-3 protein
3. Surround optical fiber immunoassay (SOFIA) is being validated
4. Nasal bushing method that detects PrP in olfactory epithelial cells is being validated
5. EEG:
 - a. Periodic sharp waves

Neuroimaging

1. MRI:
 - a. DWI images are most sensitive:
 - i. Approximately 25% of patients demonstrate cortical hyperintensity only
 - ii. In 68% of patients, there are cortical and subcortical lesions (hyperintensity)
 - iii. High signal intensity in the caudate and putamen bilaterally on T2-weighted sequences
 - iv. Posterior thalamic involvement on sagittal T2 sequences

Variant CJD

General Characteristics

1. VCJD is associated with the ingestion of beef contaminated with bovine spongiform encephalopathy (BSE)

- Most patients have been diagnosed in the United Kingdom; the risk of contracting the disorder is low. No cases of vCJD ("mad cow disease") have been reported in the USA

Clinical Manifestations

- Age of onset primarily young adults (mean 28 years)
- Median duration of the disorder is 13–14 months
- Psychiatric and behavioral symptomatology
- Painful dysesthesia
- Delayed neurological signs

Neuropathology

- Marked accumulation of protease-resistant prion protein
- Abnormal prion is found in lymphoid tissue
- Presence of amyloid plaques in the brain

Laboratory Evaluation

- EEG:
 - Periodic sharp waves may be absent

Neuroimaging

- MRI:
 - Pulvinar sign (bilateral high signal intensity) on Flair sequences is seen in >75% of patients
 - DWI high signal in the caudate and putamen may be absent

Mutations in the PrP Gene

General Characteristics

- PRPN gene maps to chromosome 20
- The mutations cause conformational changes in the PrP^c protein:
 - A shift from the normal alpha-helix to a beta-sheet
 - Affects the degree of glycosylation of the PrP^c protein
- The secondary and tertiary structure of PrP^{sc} determines:
 - The size of the protein
 - Differences (clinical)
 - Different mutations cause different pathologic changes:
 - Spongiosis
 - Amyloidosis
 - Neurofibrillary degeneration
 - Congophilic angiopathy
 - Gliosis
 - Neuronal loss
 - The tertiary structure of the PrP^{sc} newly formed conformational structure causes the different pathologies
 - Prion proteins PrP^{sc} are:
 - Neurotoxic
 - Fibrillogenic
 - In a beta-sheet secondary structure
 - Protease resistant

Classification of the Classic Form of Prion Disorders by the Underlying PrP Polymorphism at Codon 129

General Characteristics

- PrP^{sc} type I:
 - Methionine at codon 129:
 - The usual CJD presentation of rapidly progressive dementia associated with myoclonus (CJD – m/m1)
- PrP^{sc} type II:
 - The size of the protease-resistant core is 21kD
 - CJD m/m2:
 - A longer disease duration and lack of myoclonus
 - Met/Val at codon 129:
 - Related to the variant with Kuru plagues (CJD – m/v)
 - Val/Val at codon 129
 - Ataxia and late dementia (CJD – V/V)
 - CJD with M/V and V/V polymorphism at 129:
 - Less pathology on the neocortex
 - Involve primarily the deep nuclei and the cerebellum

Neuropathology

- Cortical atrophy
- Spongiosis:
 - Vacuoles within the neuropil that contain membrane fragments
 - Gliosis
 - Neuronal loss
 - Abnormal amyloid fibrils
 - Pathologic changes are due to a different degree and combination of:
 - PrP^{sc} fragment size
 - Tertiary structure of the protein
 - Type I/II PrP^{sc} coexist 33% of the time

Pathologic Distribution of Involvement by Polymorphism at Codon 129

- Met/Met at codon 129:
 - Mild accumulation of aggregates
 - Occipital lobe
 - Low PrP^{sc} load
 - Few focal PrP^{sc} amyloid deposits
 - No amyloid plaques
- Met/Val at codon 129:
 - Multiple lesions throughout the brain
 - The parahippocampal gyrus is particularly involved
 - Numerous amyloid plaques
- Val/Val at codon 129:
 - Younger at onset (<55 years of age)
 - Longer disease duration (mean of 11.5 years)
 - The hippocampal formation and basal ganglia are severely involved
 - Focal non-amyloid deposits

- e. Rare amyloid plaques
- 4. Unusual mutations:
 - a. E 200k or V 210I mutations are associated with familial CJD
 - b. 178 ASP to ASN mutations are associated with fatal familial insomnia (FFI) and familial CJD
 - c. Missense mutations at codon 102 (P 102 L):
 - i. Clinical manifestations:
 - 1. Cerebellar ataxia and dementia
 - d. Polymorphism at codon 129 and 219:
 - i. Clinical manifestations:
 - 1. Babinski signs are noted early
 - 2. Leg pain and dysesthesia:
 - a. Loss of ankle reflexes
 - 3. Some patients:
 - a. Axonal neuropathy
 - b. Motor neuron disease
 - ii. Neuropathology:
 - 1. PrP^{sc} amyloid plaque deposition:
 - a. Cerebral and cerebellar cortex
 - b. Involvement of anterior and posterior spinal horns
 - c. Deep basal ganglia nuclear involvement
 - d. Involvement of the dentate gyrus
 - e. Missense mutation of codon 105 (P 105 L):
 - i. Clinical features:
 - 1. Spastic paraparesis
 - 2. Dementia
 - 3. Age at onset 38–50 years
 - 4. Severe gait disturbance
 - 5. Involuntary movements

Gerstmann-Sträussler-Scheinker Syndrome

General Characteristics

1. The incidence is not known but is estimated to be 1–10 individuals per 100 million of the population
2. Familial patients show autosomal dominant inheritance
3. A mutation in the PRNP gene that maps to chromosome 20 causes a change in codon 102 (proline to leucine) that causes the disorder in most patients

Clinical Manifestations

1. Onset is from age 20–60 with dysarthria and ataxia
2. Over time dementia is evident
3. Memory loss may be the presenting symptom
4. Variable features include:
 - a. Extrapyrimal and pyramidal signs
 - b. May mimic a spinocerebellar degeneration early in its course
 - c. Myoclonus (less common than in classic CJD disease)
 - d. Nystagmus
 - e. Blindness and deafness (rare)

Neuropathology

1. Widespread deposition of amyloid plaques (multicentric)

Laboratory Evaluation

1. Genetic evaluation to detect the mutated gene

Neuroimaging

1. MRI:
 - a. High signal in the basal ganglia on T2-weighted sequences

Fatal Familial Insomnia (FFI)

General Characteristics

1. FFI is linked to a GAC to AAC point mutation at codon 178 of the PRNP gene that causes a substitution of asparagine for aspartic acid
2. This mutation is associated with the methionine polymorphism at codon 129 in the mutant allele
3. The mutation is at codon 178 but the phenotype is CJD unless there is a methionine at codon 129

Clinical Manifestations

1. The age at onset is highly variable between 18 to 60 years with an average age of 50
2. Patients succumb usually between 7 and 36 months after the onset of symptoms
3. Phenotypic expression is variable in families
4. The disease has been divided into 4 stages:
 - a. Stage I:
 - i. Increasing insomnia that causes or is associated with panic attacks, paranoia and phobias. This period lasts for approximately four months
 - b. Stage II:
 - i. Hallucinations occur with the panic attacks that last for approximately 5 months
 - c. Stage III:
 - i. Complete insomnia associated with weight loss that lasts for approximately 3 months
 - d. Stage IV:
 - i. Dementia with muteness. This stage lasts for 6 months
 - e. Associated signs and symptoms:
 - i. Hyperhidrosis
 - ii. Pinpoint pupils (miosis)
 - iii. Impotence
 - iv. Sudden menopause
 - v. Increased blood pressure and heart rate
 - vi. Constipation
 - vii. Extremity movement as if the patient is dreaming
 - viii. Myoclonus
 - ix. Dysarthria
 - x. Ataxia
 - xi. Severe memory impairment

Neuropathology

1. Neuronal loss and gliosis in:
 - a. Anterior ventral nuclei of the thalamus
 - b. Mediodorsal thalamic nuclei
 - c. Pulvinar

2. Morphometric analysis reveals a 60% loss of neurons in limbic-paralimbic, intralaminar and reticular nuclei
3. Atrophy of the inferior olive with neuronal loss and gliosis
4. Some spongiform change in cortical areas

Laboratory Evaluation

1. Tonsillar biopsy demonstrates PrP^{sc}
2. Increased levels of protein 14-3-3 in the CSF
3. EEG:
 - a. Patients do not advance past stage I sleep
4. FDG-PET:
 - a. Thalamic hypometabolism is usual even in presymptomatic stages
 - b. In a Korean kindred:
 - i. Decreased glucose metabolism of the midbrain and the hypothalamus
 - c. Other studies have reported hypometabolism in the thalamus, caudate and some cortical areas
 - d. Structured MRI was negative in this Korean kindred

Kuru

General Characteristics

1. Primarily a disorder of the Fore people of Papua New Guinea transmitted by ritual cannibalism
2. The incubation period is from 5–20 years

Clinical Manifestations

1. The disorder has been divided into 3 clinical stages:
 - a. Stage I (ambulant stage):
 - i. Unsteady gait and stance
 - ii. Incoordination
 - iii. Dysarthria
 - iv. Hypotonia
 - b. Stage II:
 - i. Inability to walk without support
 - ii. Severe ataxia with action tremor
 - iii. Emotional lability with associated depression
 - iv. Uncontrolled spontaneous laughter
 - v. Retained deep tendon reflexes
 - c. Stage III:
 - i. The patient is unable to sit
 - ii. Increased ataxia
 - iii. Mute
 - iv. Incontinent of bowel and bladder
 - v. Dysphagia
 - vi. Infection is often the cause of death

Neuropathology

1. Susceptibility to the disorder is associated with homozygosity for methionine at codon 129 of the PRPN gene. Heterozygosity is protective
2. The G127V polymorphism was found to be a resistance factor during the Kuru epidemic
3. Spongiform encephalopathy

Neuroimaging

1. MRI: Not defined

Focal Cortical Degenerations with Dementia

Frontal Lobe

1. Predominantly left hemisphere:
 - a. nfFTD (non-fluent)
 - b. IFTD (logopenic)
 - c. Hereditary disinhibition dysphasic dementia
2. Frontal and temporal lobe atrophy:
 - a. FTD:
 - i. bvFTD (behavioral variant)
 - ii. svFTD (semantic variant; primarily temporal lobe involvement)
 - iii. IFTD (logopenic variant)
 - b. FTD-17:
 - i. DDPAC
 - ii. PPND
 - iii. FSCG
 - iv. HDDD
 - c. Genetic MAPT gene (tau) mutations:
 - i. GRN
 - ii. C9orf72
 - iii. TARDP
 - iv. UCP
 - v. CHMPB2
 - vi. FUS
 - vii. TREM2
 - viii. DCTN1
 - d. Frontal lobe degenerations with ALS:
 - i. C9orf72
 - ii. TARDP43
 - iii. UBQLN2
 - iv. DDPAC – chromosome 17q21
 - e. Frontal lobe degeneration with primary lateral sclerosis
 - i. Corticobasal ganglionic degeneration (SI degeneration)
 - ii. Parietal Pick's disease
 - iii. Posterior cortical atrophy:
 1. Alzheimer's disease
 2. Hereditary subcortical gliosis
 3. Heidenhain variant of CJD
 4. Posterior lobar atrophy

Thalamic Dementia

1. Associated with MND
2. Familial multisystem atrophy (MSA)
3. Familial fatal insomnia (FFI)
4. Thalamic degeneration of Shulman

Hereditary Dementias

1. Alzheimer's disease:
 - a. Amyloid precursor protein (codon mutations); chromosome 21

- i. 717
 - ii. 670
 - iii. 691
 - iv. Val 717
 - v. Val 717 (phe)
- b. Presenilin-1 (chromosome 14)
- c. Presenilin-2 (chromosome 1)
- d. Trisomy 21
- e. APOE ϵ 4 (chromosome 19)
- f. Congophilic angiopathy with hemorrhage
 - i. Mutations of codon 693 and 692
2. Tauopathies:
 - a. FTD and variants
 - b. MAPT (tau) mutations
 - c. CBG degeneration
 - d. PSP
 - e. FTD-17 and variants
3. Prion diseases:
 - a. Creutzfeldt-Jakob disease (chromosome 20) Variant
 - b. CJD subtypes:
 - i. Heidenhain (occipital lobe)
 - ii. Gerstmann-Sträussler-Scheinker (cerebellum)
 - iii. Kuru
 - iv. Fatal familial insomnia
 - v. Variant CJD
4. FTD and variants:
 - a. bvFTD
 - b. mFTD
 - c. l FTD
 - d. FTD-17 and variants:
 - i. DDPAC
 - ii. PPND
 - iii. HSCG
 - iv. HDDD
 - e. MAPT gene mutations
 - f. FTD mutations on chromosome 9 and 13
5. Pick's complex
6. Diffuse NF tangles with calcification:
 - a. Chromosome 21
 - b. Codon 717 (val to gly mutation)
7. Huntington's disease (chromosome 4)
8. Wilson's disease (chromosome 13q 4.3)
9. Pantothenate kinase deficiency (chromosome 20p12.3-p13)
10. Multiple system atrophy:
 - a. Olivopontocerebellar atrophy
 - b. SCA3 (Machado-Joseph disease) chromosome 14q32.12
 - c. DRPLA-ATN1 gene on chromosome 12p13.31
11. Parkinsonism ALS dementia complex of Guam (X-linked)

Familial British Dementia

General Characteristics

1. FBD is caused by heterozygous mutation in the ITM2B gene that maps to chromosome 13q14.2

Clinical Manifestations

1. Onset is between 40–60 years of age
2. Early signs of spasticity
3. As the disease progresses there is severe leg rigidity
4. Progressive tetraparesis
5. No cerebellar dysfunction
6. Cognitive deterioration is progressive with impaired memory and ability
7. Survival may be up to 13 years from disease onset
8. Familial Danish dementia is similar clinically and also maps to chromosome 13q14.2 with mutation of the ITM2 β gene

Neuropathology (Autopsy of One Patient)

1. Widespread demyelination in the brain around hyalinized blood vessels
2. Distinct densely woven tangles of fibers and microglia
3. Minimal neuronal loss most marked in Purkinje cells
4. The corpus callosum, brainstem and cerebellar white matter tracts are involved and U-fibers are spared
5. Hyalinization of small blood vessels in the white matter
6. Amyloid deposition in both FBD and familial Danish Dementia
7. Complement system and proinflammatory activation products are detected
8. Activation of both the classic and alternative complement system from amyloid peptides occurs in both disorders

Neuroimaging

1. MRI:
 - a. Periventricular, white matter pathways of the brainstem and cerebellum demonstrate hyperintense signals on T2-weighted MRI sequences
 - b. U-fibers are intact

Dementias in Association with Basal Ganglia Degeneration

1. Huntington's disease
2. Wilson's disease
3. Pantothenate Kinase deficiency
4. Parkinson's disease
5. Multiple system atrophy-P
6. FTDP-17:
 - a. DDPAC
 - b. PPND
7. CBG degeneration
8. PSP
9. Pick's disease

Dementia in Association with Inherited Cerebellar Degeneration

Cerebrotendinous Xanthomatosis (CTX)

General Characteristics

1. CTX is a rare AR lipid storage disorder caused by mutations in the CYP27A1 gene that maps to chromosome 2q35

2. The gene encodes the mitochondrial enzyme sterol 27-hydroxylase that is involved in bile acid synthesis
3. The mutation causes a decreased synthesis of bile acid, an increased production of cholesterol with the accumulation of cholesterol in tissues
4. The prevalence of CTX is approximately 1/50,000 in Caucasians

Clinical Manifestations

1. The age of onset is 19 years (mean)
2. The initial manifestations are seizures and Parkinsonism
3. The manifestations have been divided into
 - a. Classic form:
 - i. Cerebellar dysfunction and supratentorial symptoms
 - ii. Chronic myelopathy
 - iii. Variable features include:
 1. Cognitive impairment
 2. Dementia
 3. Psychiatric and behavioral disorders
 4. Pyramidal signs
 5. Progressive ataxia
 6. Dystonia
 7. Palatal myoclonus
 8. Peripheral neuropathy
 9. Mild myopathic change by biopsy
 - iv. Ocular system:
 1. Childhood onset of cataracts
 2. Paleness of the optic disc
 - v. Systemic manifestations:
 1. Premature atherosclerosis
 2. Cardiovascular disease
 3. Osteoporosis
 4. 50% of patients have severe diarrhea

Neuropathology

1. Histopathology of the tendon xanthomas reveal multiple dispersed lipid crystal clefts
2. Cholesterol deposits in the white matter of the cerebellum and cerebral peduncles
3. Cerebral and cerebellar atrophy

Laboratory Evaluation

1. High serum cholestanol and low serum cholesterol (some patients)
2. MRI:
 - a. Bilateral symmetrical increased signals on T2-weighted sequences in the white matter of:
 - i. The cerebellum
 - ii. Periventricular areas
 - iii. Basal ganglia
 - iv. Dentate nuclei
 - v. Brainstem nuclei
 - b. Cerebral and cerebellar atrophy

Dentatorubral Pallidoluysian Atrophy (DRPLA)

General Characteristics

1. DRPLA is caused by an expanded trinucleotide repeat in the AN1 gene that maps to chromosome 12p13.31. Inheritance is autosomal dominant
2. Haw River syndrome and DRPLA are caused by the same expanded repeat of the ATN1 gene although they have slightly different clinical manifestations

Clinical Manifestations

1. Onset is between 5 and 55 years of age
2. Myoclonus
3. Epilepsy
4. Cerebellar ataxia
5. Choreaethetosis
6. Dementia
7. Patients usually succumb in their forties
8. Rare in Western countries and more common in Japan
9. Haw River syndrome clinical manifestations:
 - a. Onset is between 15–30 years of age (5 generation kindred studied in the Haw River region of NC USA)
 - b. Ataxia
 - c. Seizures
 - d. Choreiform movements
 - e. Progressive dementia
 - f. Death is often after 15–25 years of illness
 - g. Phenotype differences between Haw River syndrome and DRPLA are:
 - i. No myoclonic seizures in the Haw River syndrome

Neuropathology of DRPLA

1. Combined degeneration of the dentatorubral and pallidoluysian systems
2. Neuronal intranuclear inclusions; intracytoplasmic inclusions are found in the dentate nucleus
3. Neuropathology of Haw River patients:
 - a. Demyelination of the subcortical white matter
 - b. Basal ganglia calcifications
 - c. Neuroaxonal dystrophy

Neuroimaging

1. MRI:
 - a. Cortical, brainstem and cerebellar atrophy
 - b. Atrophy of the globus pallidus and dentate nuclei
 - c. Delayed myelination in some patients
 - d. Microcalcification of the globus pallidus in some Haw River patients

Olivopontocerebellar Atrophy

General Characteristics

1. OPCA occurs in several neurodegenerative syndromes that are inherited and non-inherited ataxias that include SCA3, MSA-C and in some patients with prion disease (Gerstmann-Sträussler-Scheinker variant)

Clinical Manifestations

1. Cerebellar ataxia predominates
2. Autonomic dysfunction
3. Mild Parkinsonism
4. Cranial nerve involvement (Fick-Winkler variant)
5. Inspiratory stridor
6. Dorsal column involvement (Menzel variant)
7. Some patients develop late onset dementia

Neuropathology

1. Atrophy of the cerebellar cortex and vermis, pons, and inferior olives
2. Purkinje cell loss
3. Glial cytoplasmic inclusions in the dentate nucleus
4. Neuronal intranuclear inclusions

Neuroimaging

1. MRI:
 - a. Vermian atrophy
 - b. Cruciate atrophy of the pons (atrophy of pontine nuclei and fibers of the middle cerebellar peduncles; the “hot cross bun sign”)
 - c. 30% of patients have cerebral atrophy
 - d. Atrophy does not correlate with either duration of illness or the severity of ataxia

Machado-Joseph Disease (MJD)**General Characteristics**

1. MJD, also known as spinocerebellar atrophy 3, is caused by a CAG trinucleotide expansion in the ataxin-3 gene that maps to chromosome 14q32.12. Inheritance is autosomal dominant
2. The gene encodes an abnormal polyglutamine (poly Q) repeat in the ataxin-3 protein
3. The length of the repeat correlates with both the severity of the disorder and age of onset (anticipation)
4. The ataxin-3 protein functions in the:
 - a. Chaperone system
 - b. Ubiquitin-proteasome system
 - c. Aggregation autophagy

Clinical Manifestations

1. Variable age at onset; adult onset is most frequent
2. There is pronounced phenotypic heterogeneity
3. The core clinical features include:
 - a. Gait ataxia
 - b. External ophthalmoplegia
 - c. Nystagmus
 - d. Bulging eyes
4. Variable manifestations:
 - a. Dementia
 - b. Generalized muscle and joint pain
 - c. Amyotrophy
 - d. Early onset Parkinsonism
 - e. Axonal sensory and motor neuropathy (in patients with fewer CAG repeats)
 - f. Restless leg syndrome

Neuropathology

1. The SCA3 pathogenic form of ataxin-3 (ataxin-3(exp)) impairs the clearance of misfolded protein that are either dependent or independent of its deubiquitinase activity. The result is an accumulation of misfolded protein that leads to neuronal death in the cerebellum
2. Demyelination of spinocerebellar tracts and the dorsal columns
3. Loss of neurons in the pons
4. The severity and loss of Purkinje and olivary cells is variable in different kindreds
5. The subthalamopallidal system may be affected

Laboratory Evaluation

1. EMG:
 - a. Sensorimotor neuropathy (some kindreds)

Neuroimaging

1. MRI:
 - a. Enlargement of the IVth ventricle
 - b. Diffusion MRI imaging with voxel-based morphometry demonstrates:
 - i. Loss of both gray and white matter in the cerebellar hemispheres, brainstem, pons and lateral thalamus

Differential Diagnosis of Cerebellar Diseases with Associated Dementia

1. Ataxia telangiectasia
2. Friedreich's ataxia
3. Marinesco-Sjögren's disease
4. MSA-C
5. SCA3 (Machado-Joseph disease)
6. Cerebroxanthomatosis (CTX)
7. OPCA
8. DRPLA

Thalamic Dementia**General Characteristics**

1. Thalamic dementia is most often caused by cerebral vascular disease that infarcts the anterior and medial thalamic nuclei but also occurs with lesions of the paramedian, intralaminar and pulvinar nuclei. The left thalamus may be particularly important for cognitive function

Clinical Manifestations

1. Onset in middle age
2. Progressive intellectual deterioration
3. Personality change
4. Bizarre behavior
5. Movement disorder

Neuropathology

1. The dorsomedial nucleus is usually the most severely affected
2. Associated involvement of:

- a. Cortex, brainstem, basal ganglia cerebellum, and white matter
- 3. Many patients have neuronal loss and gliosis in the anterior thalamic nuclei; often the lesions are bilateral
- 4. The cortical neuronal loss is of the linear spongy type

Neuroimaging

1. MRI:
 - a. Infarction of the artery of Percheron with paramedian nuclear involvement
 - b. Dural arteriovenous fistula with venous hypertension due to excessive drainage into the Vein of Galen that causes edema of paramedian nuclei bilaterally
2. T2-Weighted and FLAIR sequences demonstrate lesions in the Papez circuit as well as the anterior thalamic nuclei, intralaminar nuclei and the pulvinar

Differential Diagnosis of Thalamic Dementia with Neuronal Loss and Astrogliosis

1. Friedreich's ataxia
2. Some spinocerebellar degenerations
3. Multiple system atrophy
4. Membranous lipodystrophy
5. Creutzfeldt-Jakob disease
6. Fatal familial insomnia
7. Isolated thalamic degeneration of Shulman

Cerebral Amyloid Angiopathy

Overview

In cerebral amyloid angiopathy, amyloid deposits form in the walls of CNS blood vessels and are not related to systemic forms of amyloidosis. Congophilic angiopathy (CAA) can occur sporadically in elderly patients or in familial kindreds such as the Flemish, Iowa, Icelandic, and Dutch variants. It causes deposition of A-beta amyloid in both the leptomeningeal and cerebral blood vessels. The Flemish variant is different as there are associated dense-core plaques in the parenchyma of the brain.

A-beta amyloid is cleared from the brain by four mechanisms:

1. Endocytosis by astrocytes and the microglia
2. Enzymatic degradation by neprilysin or insulin
3. Cleared through the blood-brain barrier
4. Drained along periarterial spaces. The mechanisms involved in the deposition of A-beta amyloid in sporadic CAA are unclear

In the genetic form of CAA, it is posited that the basic mechanism of CAA is overproduction rather than inadequate clearance.

The Boston Criteria for the Diagnosis of Cerebral Amyloid Angiopathy (CAA)

1. Definite CAA:

- a. Post-mortem examination reveals lobar, cortical or subcortical hemorrhage and evidence of severe CAA
- 2. Probable CAA:
 - a. The clinical data and pathologic biopsy or evacuated tissue demonstrate the characteristics of definite CAA and some degree of vascular amyloid deposition
- 3. Probable CAA:
 - a. Clinical data and MRI findings demonstrate multiple hematomas (lobar primarily) in a patient older than 60
- 4. Possible CAA:
 - a. The patient is >60 years of age, MRI reveals a single lobar, cortical or cortico-subcortical hemorrhage without another cause; multiple hemorrhages with a possible, but not definite cause or some hemorrhage in an atypical location

Dementia in Familial Cerebral Amyloid Angiopathies

Hereditary Cerebral Hemorrhage with Amyloidosis-Icelandic Type (HCHWA-I)

General Characteristics

1. HCHWA-Icelandic type is caused by mutation in the cystatin C gene that maps to chromosome 20p11.21
2. The gene encodes a protein that is similar to a human protein termed gamma-trace or cystatin C

Clinical Manifestations

1. Recurrent primarily lobar cerebral hemorrhage with focal deficits
2. Slowly progressive dementia secondary to parenchymal destruction

Neuropathology

1. Amyloid is deposited in the walls of arteries and arterioles in:
 - a. Leptomeninges
 - b. Cerebral cortex
 - c. Deep gray and white matter
 - d. Brainstem
 - e. Cerebellum
2. Repeated hemorrhage in these areas but predilection for the cortex
3. No parenchymal amyloid plaques or neurofibrillary tangles
4. Cystatin-C amyloid may be found in lymphoid tissue, spleen, salivary glands and seminal vesicles

Laboratory Evaluation

1. Low CSF cystatin C
2. Molecular genetic analysis

Neuroimaging

1. MRI:
 - a. Lobar microbleeds
 - b. Lobar hemorrhages

Hereditary Cerebral Hemorrhage with Amyloidosis (Dutch Type)

General Characteristics

1. APP-related cerebral amyloid angiopathy (CAA) Dutch type is caused by mutation in the APP gene that maps to chromosome 21q21.3
2. It is found in Dutch, Italian, Iowa (kindred), Flemish, Arctic variants
3. It is the most common form of CAA

Clinical Manifestations

1. Acute cerebral hemorrhage that occurs between 45–60 years of age
2. Approximately 2/3 of patients succumb and the remainder develop focal deficits and dementia
3. Rarely dementia is a presenting feature of the disease
4. TIA's may occur

Neuropathology

1. Vascular amyloid deposits are related to the beta-protein that is associated with Alzheimer's disease and Down syndrome
2. Small vessels may have thickened or split walls due to hyaline congophilic material
3. Abnormal vessels are in the leptomeninges and the cerebral and cerebellar cortex
4. Amyloid-beta 40 is seen in the cortical capillaries while amyloid-beta 42 is deposited in the neuropil of gray matter
5. In general, hemorrhage and infarcts are noted in the temporal and occipital lobes
6. Amyloid is deposited in arteries and arterioles:
 - a. Leptomeninges
 - b. Cerebrum and cerebellum
 - c. Cerebral cortex:
 - i. As diffuse A-beta Amyloid plaques
 - ii. Little neuritic pathology
7. An Iowa and Spanish kindred demonstrated:
 - a. Spanish kindred:
 - i. Tram-track bilateral occipital calcification
 - ii. Leukoencephalopathy
 - iii. Bilateral external carotid artery dysplasia
 - iv. EM evaluation of brain biopsy:
 1. Multilayered round microcalcifications in the basal lamina
8. It has been suggested that more than 15 amyloid-beta severely stenotic blood vessels in 5 frontal cortical sections are sufficient to cause dementia in the Dutch Variant

Neuroimaging

1. MRI:
 - a. Primarily cortical microbleeds with lobar hemorrhage
 - b. Rare variants (Spanish and Iowa kindreds):
 - i. Occipital lobe calcifications
 - ii. Leukoencephalopathy
 - iii. Bilateral external carotid artery dysplasia

Point Mutation of the APP gene at Codon 618

General Characteristics

1. The G to C transversion at codon 618 that encodes the extracellular portion of APP 695, produces an amino acid substitution of glutamine instead of glutamic acid

Clinical Manifestations

1. Symptoms develop in the fifth decade
2. Progressive dementia
3. Spastic paralysis
4. Ataxia
5. Memory impairment is rare
6. Stroke-like episodes are uncommon

Neuropathology

1. Atrophy of cerebral and cerebellar hemispheres
2. Cystic infarcts of the deep white matter
3. Arteries demonstrate:
 - a. Fibrotic thickening and obstruction
 - b. Fragmentation of the elastic lamina
 - c. Periarteriolar microhemorrhage
4. Ischemic neurons are found in the:
 - a. Cerebral cortex and white matter
 - b. Thalamus
 - c. Cerebellum
5. Non-neuritic amyloid plaques occur in the:
 - a. Cerebral and cerebellar cortex
6. Neurofibrillary tangles are demonstrated in the hippocampus and amygdala

Neuroimaging

1. MRI:
 - a. Atrophy of the cerebral and cerebellar hemispheres
 - b. Cortical microbleeds
 - c. Multiple simultaneous lobar hemorrhages

Familial Amyloid Angiopathy with Deafness and Ocular Hemorrhage (Danish type)

General Characteristics

1. Danish familial dementia is caused by mutation in the ITM2 gene that maps to chromosome 13q14.2
2. Possible function as an intracellular signaling molecule
3. The gene is also the site of mutation in familial British dementia (FBD)

Clinical Manifestations

1. Cataracts early in life (posterior polar)
2. Deafness by age 30–50 years of age
3. By the fifth and sixth decades patients manifest:
 - a. Ataxia
 - b. Dementia
 - c. Rare ocular hemorrhages
 - d. Rare stroke-like episodes
 - e. Paranoid psychosis
 - f. Most patients succumb in the fifth to sixth decade

Neuropathology

1. Diffuse brain atrophy
2. The cerebral cortex, cerebellum and white matter are affected
3. Thin and demyelinated cranial nerves
4. Amyloid angiopathy in:
 - a. Cerebrum
 - b. Choroid plexus
 - c. Cerebellum
 - d. Spinal cord
 - e. Retina
 - f. The amyloid is deposited in the endothelial and basement membrane
5. Neuritic plaques and neurofibrillary tangles are present in the hippocampus

Laboratory Evaluation

1. Proteins of the complement system and their proinflammatory activation products are found in the CNS
2. Genetic analysis for the mutation in the ITM2 gene

Familial British Dementia (FBD)**General Characteristics**

1. FBD is caused by heterozygous mutation in the ITM2 gene that maps to chromosome 13q142
2. A point mutation at the stop codon of ITM2B generates an ABR1 peptide that is deposited as amyloid fibrils

Clinical Manifestations

1. Onset is between 40–60 years of age
2. Early spasticity
3. Muscle rigidity is seen late in the course of the illness (legs are maintained in extension)
4. Truncal ataxia
5. Positive Romberg sign
6. Progressive loss of cognitive function

Neuropathology (Autopsy of 1 Patient)

1. Widespread demyelination most marked around small hyalinized blood vessels
2. Minimal neuronal loss except for Purkinje cells
3. Neurofibrillary tangles in the hippocampal formation but less than that found in Alzheimer's disease
4. Severely thinned corpus callosum; spared U-fibers
5. Hyalinization of small vessels in the white matter and pia
6. Congophilia in perivascular plaques
7. Parenchymal plaques and cerebrovascular amyloid aggregates in both FDD and FBD contain complement activation products of both the classic and alternative pathways

Neuroimaging

1. MRI (1 patient):
 - a. Periventricular white matter abnormal signal; sparing of U-fibers
 - b. Abnormal signal intensity in the brainstem and cerebellar white matter

Laboratory Evaluation

1. Slightly increased CSF protein

Differential Diagnosis of the Familial Amyloid Angiopathies

1. Alzheimer's disease (sporadic and familial)
2. Point mutation of the amyloid precursor protein at codon 618
3. Amyloidosis – Icelandic type
4. Amyloidosis – Dutch type with variants
5. Flemish amyloidosis
6. Familial Danish amyloidosis
7. Familial British amyloidosis
8. Gerstmann-Sträussler-Scheinker syndrome
9. Familial cerebral amyloid angiopathy with non-neuritic plaque formation

Secondary Dementia**General Characteristics**

1. A secondary dementia is a form of dementia that develops as a peripheral manifestation of a pre-existing mental illness or organic condition. Thus secondary dementias are those caused by or closely related to some other recognizable disease
2. Mild cognitive impairment (MCI) is a transitional stage between normal aging (usually age-associated memory impairment) and dementia. It is now clear that both neuropathological changes and subtle cognitive deficits are present up to two decades prior to the onset of dementia in many neurodegenerative diseases. Patients with MCI are at a greater risk of developing dementia than normal cognitively functioning individuals. The clinical criteria of MCI are:
 - a. Subjective cognitive changes corroborated by an informant
 - b. Impairment in one or more cognitive domains that are compatible with age and educational level
 - c. Normal activities of daily living are attained
 - d. Absence of dementia; the cognitive difficulties are mild with no significant social or occupational impairment

Vascular Dementia**Overview**

Cognitive impairment caused by vascular disease includes subclinical brain injury, silent brain infarction (SBI) and both large and small vessel stroke, as well as cerebral hemorrhage. MRI neuroimaging reveals a prevalence of covert small-vessel disease in the elderly population of 21% for silent lacunes and 95% for incidental white matter hyperintensities, both of which are associated with an increased risk of stroke and dementia. Pathologically, large cortical infarcts, lacunar infarcts, subcortical white matter disease, strategic subcortical infarcts, and hemorrhages all cause cognitive im-

pairment. Vascular lesions are frequently found in association with Alzheimer's disease and may lower the threshold for its clinical expression.

Cognitive syndromes associated with vascular disease have two core features:

1. Demonstration of the cognitive disorder by neuropsychological testing
2. History of clinical stroke or presence of vascular disease by neuroimaging

A memory deficit is not required for the diagnosis of vascular cognitive impairment or vascular dementia.

Research classification systems suggest that vascular cognitive impairment (VCI) includes a spectrum of cognitive main deficits that may be biased more to executive dysfunction than memory loss. The most severe form of VCI causes vascular dementia (VaD).

The most important cerebral vascular pathology that causes cognitive impairment is infarction. Macroscopic chronic infarctions occur in approximately 1/3 of older individuals. Microscopic infarctions, small vessel disease, and white matter lesions on MRI are vastly more common in community-based epidemiologic studies. As a general rule, larger loss of parenchymal brain tissue and an increased number of macroscopic infarcts are associated with vascular cognitive impairment. It has been suggested that loss of 100 mg of tissue is associated with dementia but it clearly has been evident with loss of much smaller brain volumes. There is not a good correlation between volume loss, the number of infarcts and cognitive impairment. This has generated the concept of strategic infarction whereby lesions in specific locations such as the thalamus, cingulate gyrus, and basal ganglia rather than other nuclear areas are more likely to cause dementia. Recent work with functional MRI (fMRI) suggests that specific distributed loops with hubs, small or large world connections, support specific brain oscillations required for attention, memory, and executive function. A small infarction that disrupts a specific distributed loop may have a major effect on cognition. The phenotypic and pathologic spectrum of vascular disease is wide and includes:

1. Primary vessel disease:
 - a. Arteriolosclerosis
 - b. Lipohyalinosis
 - c. Atherosclerosis
 - d. Cerebral angiopathy
 - e. Cerebral microbleeds

Primary vessel disease may be associated with strategic infarction (the disruption of specific distributed loops), diffuse tissue damage (white matter pathway damage), or functional deficits from hypoperfusion.

In most hospitals, present MRI resolution detects macroscopic infarcts of approximately 3 mm but is incapable of resolving microscopic infarcts and arteriolosclerosis. White matter degeneration and microbleeds are associated with VCI and Alzheimer's disease; pathologically both are related to lipohyalinosis. Hippocampal atrophy may also be caused by

Alzheimer's disease or ischemia. There is a complex interplay between vascular and Alzheimer's disease in determining the manifestations of VCI, dementia and Alzheimer's disease.

The neurovascular unit is altered in both Alzheimer's disease and vascular cognitive impairment. In both disorders, microvessels have thickened basement membranes, are tortuous and reduced in density. Arterioles undergo lipohyalinosis (hyaline degeneration). Periventricular white matter demonstrates microglial activation and astrogliosis due to the expression of hypoxia-inducible genes. Accumulation of amyloid-beta in the media of cortical arterioles in both congophilic angiopathy (cerebral amyloid angiopathy) and Alzheimer's disease is a cause of microbleeds and lobar hemorrhage (basal ganglia microbleeds are from hypertension).

A β (amyloid-beta) found in Alzheimer's disease and CAA (cerebral amyloid angiopathy) causes:

1. Suppression of endothelium-dependent responses such as functional hyperemia and autoregulation
2. Vasoconstriction
3. Increased constrictor tone of smooth muscle (Alzheimer's disease)

The key pathogenic factors in the neurovascular dysfunction seen in vascular cognitive impairment are oxidative stress and inflammation. The free radicals generated under ischemic conditions are thought to be produced from inefficiencies in oxidative phosphorylation and by nicotinamide adenine dinucleotide phosphate oxidase. Free radicals activate redox-sensitive proinflammatory transcription factors; endothelial dysfunction induced by oxidative stress releases vascular endothelial growth factor (VEGF) and prostanooids that increase vascular permeability, protein extravasation and cytokine production and release. Further pathology is caused by inflammatory process enhancement of oxidative stress that upregulates reactive oxygen species producing enzymes and downregulates antioxidant defenses.

The A β (amyloid-beta) clearance receptor (low-density lipoprotein receptor-related protein-1), is downregulated in Alzheimer's disease blood vessels that allows amyloid-beta accumulates around blood vessels and exacerbates their dysfunction. Oxidative stress and the inflammatory cascade are deleterious for the proliferation, migration, and differentiation of oligodendrocyte progenitor cells, which impairs white matter repair.

Recent clinical and experimental evidence support a significant role of the neurovascular unit in VCI and may exacerbate Alzheimer's disease by:

1. Altering the regulation of the local blood supply
2. Disrupting the kinetics of the blood-brain barrier
3. Decreasing the trophic support of neurotrophic factors

There is a strong correlation between age and the structure and physiology of large extra- and intracranial vessels. The selected parameters for investigation have included carotid wall thickening and aortic stiffness that putatively measure athero- and arteriosclerosis, respectively. There is a strong

correlation between the parameters of vascular aging and cognitive impairment and silent cerebral small vessel disease. There is linkage between large artery dysfunction and cerebral small vessel disease that are independent of both age and cardiovascular risk factors.

Midlife hypertension is a clear risk factor for later cognitive impairment and vascular dementia. Systolic increased blood pressure appears to be a more consistent biomarker of cognitive impairment than diastolic variability and failure of the nocturnal dip of systolic pressure. A history of hypertension and total cholesterol level are also biomarkers of vascular cognitive impairment.

Associated disorders of vascular dementia include:

1. Coronary and peripheral arterial disease
2. Atrial fibrillation
3. Renal disease, and
4. Cardiac failure

Dementia from Strategic Vascular Lesions

General Characteristics

1. In some patients mental impairments are the presenting or only manifestation of stroke:
 - a. Approximately 15% of strokes may have minimal or transient motor or sensory symptoms and signs
 - b. Small cortical or subcortical infarcts that are asymptomatic but disrupt important distributed networks that subserve executive function, attention and language, may be silent

Clinical Manifestations

1. Middle cerebral artery:
 - a. Acute confusional states occur more frequently with R > L hemisphere infarction
 - b. Confusional state may occur from infarction of the:
 - i. Middle frontal gyrus
 - ii. Middle temporal gyrus
 - iii. Inferior parietal lobule
 - iv. Head of the left caudate nucleus
 - v. Right temporoparietal occipital cortex
 - c. Global deficits of selective attention causes confusion with associated clinical deficits of:
 - i. Attention to relevant stimuli
 - ii. Distractibility
 - iii. Normal arousal
 - iv. Lack of concern for the illness
 - v. Disorientation
 - vi. Anomia
 - vii. Inability to maintain coherent thought
 - viii. Restless, agitated, and at times aggressive behavior
 - ix. Most acute confusional states last days to weeks; rarely they are permanent
 - x. Disruption of distributed language loops, attentional loops, and components of the DMN (default mode network) lead to vascular dementia

2. Anterior cerebral artery:

- a. ACA branch occlusions that cause dementia include the:
 - i. Frontopolar artery
 - ii. Callosomarginal artery
- iii. Neuroanatomical structures that are involved are:
 1. The orbital cortex
 2. Medial frontal cortex (a major hub of the DMN)
3. Clinical signs:
 - a. Mental inertia (abulia)
 - b. Indifference and apathy
 - c. Emotional blunting
 - d. Infarcts cause subtle deficits of:
 - i. Divergent thinking
 - ii. Temporal organization
 - iii. Executive and planning strategies
4. Behavior may be triggered by environmental stimuli:
 - a. Imitation behavior
 - b. Utilization behavior

3. Posterior Cerebral Artery

- a. Infarction of the posterior cerebral artery causes ischemia to a varying degree in:
 - i. Mediotemporal areas (P₁)
 - ii. Midline mesencephalon (interpeduncular artery)
 - iii. Thalamic nuclei (DM and anterior):
 1. Thalamogeniculate arteries
 - iv. Occipital/temporo/parietal junction:
 1. TPO branch of the inferior division of the DCA
- b. Occipital lobe lesions and behavior:
 - i. Color vision (lingual and fusiform gyri)
 - ii. Color naming
 - iii. Alexia without agraphia (visual field deficit in the left occipital lobe with concomitant damage of the corpus callosum)
 - iv. Visual distortions and hallucinations (perceived in the hemianopic or entire VF)
 - v. Bilateral lesions of the occipital lobe cause:
 1. Visual agnosia
 2. Cortical blindness
- c. Medial temporal lobe infarction:
 - i. Severe amnesic deficit:
 1. Often bilateral involvement
 2. Severe hippocampal formation damage
 3. Rarely occurs in isolation: usually a consequence of anoxia due to the ischemia of cardiac arrest or severe hypotension during prolonged heart or abdominal surgery

Subcortical Infarction and Dementia

General Characteristics

1. Thalamic vascular disease
2. Interpeduncular artery infarction from involvement of top of the basilar artery (usually embolic)

3. A single arterial stem that supplies both paramedian thalamic nuclei (the thalamic peduncle of Percheron)
4. Small artery infarction from penetrators of the posterior communicating artery

Clinical Manifestations

1. Bilateral involvement (midline thalamic nuclei)
 - a. Disturbance of consciousness acutely
 - b. Eye movement deficits (eyes looking down at the tip of the nose) and other vertical gaze palsies
2. Unilateral thalamic infarction (DM, anterior nuclei)
 - a. Inattention
 - b. Motor neglect
 - c. Anterograde amnesia
 - d. Left-sided lesions (aphasia):
 - i. Fluent paraphasic speech
 - ii. Perseverative speech
 - iii. Anomia
 - iv. Spared repetition
 - e. Right-sided lesions:
 - i. Hemineglect of the left side of the body and personal and extrapersonal space (VPL nucleus with the parietal projection)

Neuropathology

1. Infarction of thalamic nuclei:
 - a. The intralaminar nuclei: deficits of arousal and attention
 - b. Medial dorsal nuclei: short-term memory loss
 - c. Anteroventral nuclei: disruption of Papez circuit of the anterior limbic system:
 - i. Personality change
 - ii. Episodic memory loss
 - iii. Insomnia and sleep-wake cycle alterations

Caudate Lesions

General Characteristics

1. Disruption of caudate frontal lobe projections

Clinical Manifestations

1. Left caudate head:
 - a. Acute agitation (R caudate > left)
 - b. Thalamic type of aphasia
 - c. Frontal lobe syndrome

Neuropathology

1. Infarction of the thalamoperforate artery (origin is P2 segment of the PCA)

Multi-Infarct Dementia

General Characteristics

1. The most common form of multi-infarct dementia is that from small vessel disease that most often occurs without a specific clinical deficit and is manifest by:

- a. White matter hyperintensities throughout the brain
- b. Lacunar infarction
- c. Supra- and infratentorial microbleeds
- d. Enlarged perivascular spaces
- e. Microinfarction of arterioles

Clinical Manifestations

1. Patients are usually older than 50 years of age: men > women
2. Episodic lacunar infarctions with focal deficits that include:
 - a. Hemiparesis
 - b. Hemisensory deficit
 - c. Rarely aphasia
 - d. Dysarthria
 - e. Confusion
 - f. Ataxia
 - g. Diplopia
 - h. Dizziness
3. Cognitive deficits may occur early or late in the course, depending on the disruption of the specific distributed loop that is affected
4. In general, there are usually minimal residual deficits from each episode
5. Cognitive deficits include:
 - a. Slowed psychomotor processing
 - b. Decreased attention
 - c. Decreased concentration
 - d. Poor memory
 - e. Inertia
 - f. Loss of executive function
6. Prior to cognitive decline there is:
 - a. Gait disturbance
 - b. Urinary incontinence
7. Variable neurologic signs include:
 - a. Pyramidal tract dysfunction
 - b. Spasticity
 - c. Parkinsonism
 - d. Pseudobulbar palsy
 - e. Hypomimia
 - f. Instability of gait
8. Accumulation of cortical lesions cause:
 - a. Aphasia
 - b. Visuospatial deficits
 - c. Various apraxias:
 - i. Ideomotor (frontal lobe)
 - ii. Limb kinetic (both frontal and parietal lobe)
 - iii. Ideational (parietal lobe)
 - iv. Oral buccal and speech apraxia (supplementary motor area and frontal lobe)
 - v. Eye opening and closing apraxia:
 1. Frontal lobe (second frontal convolution)
 - vi. Sympathetic apraxia (anterior corpus callosum) – inability to follow commands with the left hand
 - vii. Both cortical and subcortical deficits:

1. May have an abrupt onset
2. Stepwise deterioration
3. Association with nocturnal confusion
4. Depression and inertia
5. Fluctuating course
- viii. Concomitant medical associations in most patients:
 1. HCVD
 2. CHF
 3. Diabetes mellitus
 4. Intermittent claudication
 5. Angina
 6. Myocardial infarction
 7. Generalized vascular disease
 8. Valvular heart disease (less frequently)
 9. Chronic kidney disease
 10. Atrial fibrillation
 11. Prior stroke

Neuropathology

1. Microbleeds
 - a. In the basal ganglia due to hypertensive vascular disease
 - b. Lobar cortical distribution due to CAA
2. CAA
3. Increased perivascular spaces
4. Lacunar infarction (“état lacunaire”) if severe
5. Associated hypertensive changes in large vessels
6. Generalized atherosclerosis
7. Numerous microscopic infarcts in the cortex have been associated with cortical granular atrophy
8. Territorial infarction of large vessels with atherosclerosis and arteriolar sclerosis
9. Ventricular enlargement
10. Hippocampal atrophy:
 - a. Alzheimer’s disease > frequency than vascular disease
11. Loss of 50–100 grams of brain tissue has been correlated with vascular dementia

Laboratory Evaluation

1. Carotid intima-media thickness
2. Arterial stiffness (arteriosclerosis): Carotid-femoral pulse wave velocity is increased with stiffened atherosclerotic vessels
3. Associated:
 - a. Hyperglycemia
 - b. Insulin resistance
 - c. Metabolic syndrome
 - d. Diabetes
 - e. Lipids: midlife total cholesterol is a risk factor
 - f. Inflammation: plasma levels of inflammatory proteins:
 - i. α 1-antichymotrypsin
 - ii. C-reactive protein
 - iii. Increased interleukin-6

Neuroimaging

1. MRI techniques:
 - a. FLAIR
 - b. Diffusion tensor
 - c. Magnetization transfer
 - d. NMR spectroscopy
2. Infarction in multiple cortical areas (topographical distribution)
3. Lacunar infarction of the basal ganglia, thalamus, internal capsule, and centrum semiovale
4. FLAIR or T2-weighted sequences white matter hyperintensities around the ventricles (“ventricular capping”)
5. Strategic infarcts
6. White matter hyperintensities throughout the brain on FLAIR or T2-weighted sequences

Inherited Vascular Diseases Associated with Dementia

Small Vessel Syndromes

1. CADASIL:
 - a. Missense mutations of the Notch 3 gene
 - b. Deposition of granular eosinophilic aggregation in the arteriolar media
2. CAA:
 - a. Mutations or duplication of the APP amyloid-beta precursor protein gene
3. Autosomal dominant retinal vasculopathy with cerebral leukodystrophy due to frame shift deletions in the exonuclease TREX1 gene
4. Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy from missense or nonsense mutations of the transforming growth factor β 1 repressor HTRA1 gene
5. COL4A1 type IV collagen subunit gene mutations are associated with:
 - a. Congenital porencephaly
 - b. Leukoencephalopathy
 - c. Intracerebral hemorrhage
6. HCHWA (Icelandic); cystatin c gene
7. HCHWA (Danish) – ITM2B gene
8. HCHWA (British) – ITM2B gene
9. HERNs – TREX1 gene
10. Moyamoya – RNF213 gene
11. Fibromuscular dysplasia:
 - a. Autosomal dominant inheritance
 - b. Approximately 10% of patients have an affected relative
12. Pseudoxanthoma elasticum:
 - a. ABCC6
 - b. XYLT1 – modifier of severity
 - c. XYLT2 – modifier of severity
13. Homocystinuria:
 - a. Autosomal recessive inheritance
 - b. Homozygous or compound heterozygous mutation in the cystathionine beta synthase gene (CBS)

Binswanger Disease*General Characteristics*

1. Subcortical arterioleukoencephalopathy of the Binswanger type that may be associated with confluent white matter lesions
2. Diffuse white matter damage of vascular etiology

Clinical Manifestations

1. Patients are between 50–70 years of age
2. Males and females are equally affected
3. Subacute neurologic symptoms and signs
4. Progressive longstanding dementia
5. Most prevalent in hypertensive patients
6. Occipital lobe preponderance

Neuropathology of White Matter Disease

1. Triad of demyelination, axonal loss, and lacunar infarction is the pathology of WML (white matter lesions) that when confluent, constitute “leukoaraiosis”
2. This pathologic process is located in:
 - a. The periventricular white matter
 - b. Subcortical white matter
3. It has a wide phenotypic expression from dilation of the Virchow-Robin spaces to diffuse myelin pallor (demyelination) and microinfarction that spares subcortical U-fibers (connect adjacent convolutions)
4. The lesions are putatively caused by microvascular changes of arteriosclerosis, hyalinosis, and focal fibrinoid necrosis, with or without occlusion of small penetrating arterioles
5. White matter lesions are putatively also caused by chronic ischemia due to hypoperfusion and disruption of the blood-brain barrier
6. The process is often associated with atherosclerosis of large cerebral blood vessels
7. The myelin changes are most severe in:
 - a. Frontal, occipital and parietal lobes
 - b. The distribution is most often bilateral and symmetrical
8. Lacunes are often seen in the deep gray matter of the pons, caudate, putamen, centrum semiovale and internal capsule
9. Minor degree of cortical infarction

Neuroimaging

1. MRI:
 - a. Lateral ventricular enlargements are prominent posteriorly
 - b. Diffuse and at times WML that are confluent
 - c. Cortical atrophy

Cerebral Microbleeds (CMB)*General Characteristics*

1. CMBs are defined histologically as blood extravasation into the perivascular and/or Virchow-Robin space without disruption of the surrounding brain parenchyma. They may also be very small intracerebral hemorrhages of <5 mm in diameter

2. Hemosiderin-laden macrophages and hemosiderin deposits within the perivascular space indicate post-resolved microbleeds

Clinical Manifestations

1. If predominate in the basal ganglia they are most often due to prolonged hypertension. Hemorrhage in this distribution is associated with severe neurological deficits of hemiparesis, hemisensory deficits associated with aphasia if left-sided and visuospatial deficits with hemineglect if right-sided
2. Cortical microbleeds in a lobar distribution in patients older than 60 years of age are most often due to congophilic angiopathy:
 - a. Minimal focal neurologic deficit depending on location
 - b. No alteration of mental status
 - c. May be multiple

Neuropathology

1. Arterioles that have ruptured walls demonstrate:
 - a. Thickened acellular walls
 - b. A deficient muscular layer with AB1-40 deposition
2. Hemosiderin-laden macrophages and deposition of hemosiderin within perivascular spaces
3. Activation of surrounding microglial cells, late complement activation and apoptosis

Neuroimaging

1. MRI:
 - a. Most effectively detected with gradient echo sequences
 - b. Only a few CMB may be clinically significant
 - c. Lack of a signal on GE sequences (due to cancellation effects of hemosiderin) in lesions <5 mm are characteristic
 - d. A gliotic lesion with a surrounding hemosiderin ring located superficially in the cortex in a lobar distribution is characteristic of CAA

Normal Pressure Hydrocephalus*General Characteristics*

1. The incidence (estimated from a Norwegian population) is 5.5/100,000 of the population
2. Normal pressure hydrocephalus is now separated into idiopathic NPH and secondary NPH
3. Possibility 1% of dementia

Clinical Manifestations

1. Occurs most frequently in the sixth and seventh decade
2. Gait disturbance:
 - a. Initiation difficulties
 - b. “Foot grasp” of the floor
3. Subcortical type dementia:
 - a. Slow information processing
 - b. Decreased attention
 - c. Poor concentration

- d. Poor abstract thought
- e. Memory is relatively well preserved
- f. Falling backwards
- g. Urinary incontinence (precipitate micturition; deficit of inhibition from the paracentral lobule)

Neuropathology

1. Ventricular enlargement causes:
 - a. Stretch of the long descending corticospinal leg fibers that are periventricular (increased reflexes; gait apraxia)
2. Bladder fibers:
 - a. Paracentral lobule bladder inhibitory afferents to the frontal lobe become dysfunctional
3. Distributed loops associated with executive functions are affected:
 - a. Cortico-cortical-fibers
 - b. Transcallosal fibers
4. Normal brain weight
5. Well preserved cortical ribbon
6. Minimally thinned corpus callosum
7. Mild pallor of periventricular white matter
8. Concomitant features:
 - a. Vascular pathology
 - b. Amyloid plaques; neurofibrillary tangles
 - c. Hypertension
 - d. Peripheral vascular disease
 - e. Posterior circulation insufficiency
 - f. Arrhythmia, valvular disease, congestive heart failure, myocardial infarction aortocoronary bypass
 - g. Secondary NPH:
 - i. Predisposes to obstruction of CSF flow or reabsorption from:
 1. Subarachnoid hemorrhage
 2. Head injury
 3. Meningitis
 4. Aqueductal stenosis
 5. Syringomyelia

Neuroimaging

1. MRI:
 - a. Severely dilated lateral and IIIrd ventricles
 - b. Absence of significant cortical atrophy
 - c. Dilated temporal horns out of proportion to dilatation of the other ventricles
 - d. Transventricular edema
 - e. MRI Aqueductal flow:
 - i. Aqueductal flow values are elevated which is seen in idiopathic NPH
 - ii. Persistent ventricular stasis on radioisotope cisternography (in the lateral ventricles)

Metabolic Disease Associated with Dementia

Uremia

General Characteristics

1. Associated, HCVD and anemia

2. Blood uremia nitrogen >60 mg/dl
3. Parathyroid hormone may be involved in the cognitive deficits

Clinical Manifestations

1. Cognitive deficits in all spheres
2. Memory deficits
3. Process fluctuates
4. Usually a slowly progressive course that fluctuates
5. Associated with:
 - a. Dysarthria
 - b. Myoclonus
 - c. Seizures
 - d. Dysphagia
 - e. Asterixis
6. Dialysis patients:
 - a. Uremic encephalopathy
 - b. Dialysis disequilibrium disorder
 - c. Associated:
 - i. Atherosclerosis
 - ii. Stroke
 - iii. Peripheral neuropathy
 - iv. Restless leg syndrome

Neuropathology

1. Subclinical hemorrhage is seen in 1–3% of patients
2. Generalized and variable neuronal loss
3. Perivascular necrosis and demyelination
4. Neuroanatomical areas of involvement:
 - a. Cerebral cortex
 - b. Subcortical brainstem nuclei
 - c. Cerebellum
5. Alzheimer type 2 astrocytes are prominent
6. Calcification of large and medium-sized blood vessels
7. Infarctions of both large and medium-sized cerebral vessels as well as widespread small vessel disease

Neuroimaging

1. MRI:
 - a. Uremic encephalopathy may cause irreversible posterior leukoencephalopathy
 - b. Basal ganglia involvement is rare
 - c. Supratentorial white matter involvement is rare
 - d. Calcification of extracranial blood vessels is common and often severe
 - e. Bilateral cytotoxic edema in the centrum semiovale

Laboratory Evaluation

1. Increased blood urea nitrogen and creatinine
2. Increased parathyroid hormone
3. Acidosis
4. X-ray of bones demonstrate severe osteoporosis
5. EEG:
 - a. Paroxysmal sharp waves and polyspikes

Hepatic Encephalopathy (HE)

General Characteristics

1. Hepatic encephalopathy (HE) may be minimal or overt and occurs with liver disease or portosystemic shunting
2. Overt HE presents with a wide phenotype from mild confusion to coma
 - a. Minimal hepatic encephalopathy may cause neurocognitive impairment in patients with cirrhosis and portal-systemic shunting that have a normal neurologic and psychiatric examination

Clinical Manifestations

1. Acquired hepatolenticular degeneration:
 - a. Occurs in patients that have had several episodes of hepatic encephalopathy; usually in cirrhotic patients
 - b. Subcortical type dementia
 - c. Falling backwards
 - d. Parkinsonism
 - e. Severe dysarthria
 - f. Choreoathetosis

Neuropathology

1. Patchy cortical laminar involvement with pseudolaminar necrosis
2. Polymicrocavitation at the corticomedullary junction and in the striatum
3. Diffuse Alzheimer type 2 astrocytosis
4. Neuronal loss in the cortex, cerebellum and basal ganglia
5. Ammonia has a central role in both hepatic encephalopathy and minimal hepatic encephalopathy; it is felt that other processes contribute to the neurocognitive deficits that include:
 - a. Infection
 - b. Oxidative stress
 - c. Manganese accumulation
 - d. Intestinal bacterial overgrowth
 - e. Benzodiazepine-like toxins

Laboratory Evaluation

1. Elevated systemic and CSF ammonia
2. EEG:
 - a. Triphasic waves

Neuroimaging

1. MRI:
 - a. High signal intensity in the globus pallidus in T1-weighted images (most often posited to increased tissue concentrations of manganese)
 - b. In some patients the hypothalamus and pituitary gland have shown high signal intensity
2. MR Spectroscopy (proton):
 - a. Elevated glutamine/glutamate peaks
 - b. Decreased myoinositol and choline signals

Thyroid Failure with Dementia

General Characteristics

1. Hypothyroidism is one of the most important causes of treatable dementias
2. Psychosis is occasionally an associated manifestation and is termed myxedema madness
3. Other specific forms of thyroid disease with dementia are:
 - a. Hashimoto's encephalopathy
 - b. Apathetic hyperthyroidism

Clinical Manifestations of Myxedema

1. Lethargy and bradyphrenia
2. Psychotic behavior that ranges from depression to severe agitation
3. Most often in a setting of severe long standing hypothyroidism
4. Subcortical dementia
5. Associated neurologic signs and symptoms:
 - a. Proximal myopathy
 - b. Ataxia (Purkinje cell loss)
 - c. Hearing loss
 - d. Rarely facial pain (mucopolysaccharide deposition in the Vth nerve)
 - e. Bilateral carpal and tarsal tunnel syndromes
 - f. Sensorimotor neuropathy
 - g. Delayed relaxation phase of reflexes
 - h. Scleromyxedema:
 - i. Generalized popular eruption
 - ii. Dermal fibroblast proliferation
 - iii. High fever
 - iv. Seizures
 - v. Coma

Hashimoto's Thyroiditis

General Characteristics

1. Hashimoto's encephalopathy is an encephalopathy that is posited to be autoimmune and associated with high titers of antithyroid peroxidase antibodies
2. It is more common in women than men and may be seen in pediatric, adult and elderly patients

Clinical Manifestations

1. Often a relapsing and remitting course that includes:
 - a. Seizures
 - b. Stroke-like episodes
 - c. Neuropsychiatric disorders
 - d. Myoclonus
 - e. Progressive cognitive decline
 - f. Response to corticosteroids
 - g. Peak incidence is between 45–65 years of age

Neuropathology

1. The disorder depends on an immune defect in a genetically susceptible patient triggered by environmental factors

2. Gradual atrophy of thyroid tissue due to lymphocytic cell invasion
3. Follicular atrophy
4. Oncocytic metaplasia of follicular cells

Laboratory Evaluation

1. Elevated antibody titers against thyroid tissue that include:
 - a. Anti-TPO (thyroperoxidase)
 - b. Anti-Tg (anti-thyroglobulin)
 - c. Rarely TSH-stimulation blocking antibody (TSBAbs)
 - d. The antibody titers often correlate with an increased inflammatory reaction in the thyroid parenchyma and resultant hypothyroidism
 - e. Inflammatory cytokines are detected in thyroid follicular cells
 - f. Increased CSF protein
 - g. EEG:
 - i. Severe slowing

Hypothalamic-Pituitary Disorders

General Characteristics

1. Usually associated with symptoms due to endocrine dysfunction prior to neurological features

Clinical Manifestations

1. Adrenal failure:
 - a. Personality change
 - b. Apathy
 - c. Cognitive impairment
 - d. Severe fatigue (asthenia)
 - e. Flexed posture
 - f. Thin muscles
 - g. Abnormal body mass index and decreased growth velocity in children

Neuropathology (Causes)

1. Craniopharyngioma
2. Optic pathway glioma
3. Suprasellar arachnoid cyst
4. Germ cell tumor
5. Astrocytoma

Neuroimaging

1. MRI:
 - a. To evaluate intracranial lesions

Laboratory Evaluation

1. Increased potassium concentration and decreased sodium concentration in the serum
2. Depressed thyroid and gonadal hormones; decreased growth hormone
3. ACTH and cortisol levels are low

Adrenal Insufficiency

General Characteristics

1. Primal adrenal insufficiency:
 - a. 80% are secondary to autoimmune mechanisms
2. Secondary adrenal insufficiency:
 - a. Most common cause in the West is exogenous steroid use (in general at least 3 weeks of >25 mg hydrocortisone/day with an inadequate taper)
3. Tertiary adrenal insufficiency:
 - a. Due to hypothalamic disease and decrease in corticotrophin releasing hormone (CRH)

Clinical Manifestations

1. Medical signs and symptoms:
 - a. Hypoglycemia
 - b. Weight loss
 - c. Dehydration
 - d. Hypotension
 - e. Nausea, vomiting
 - f. Diarrhea
 - g. Associated goiter and vitiligo
 - h. Hyperpigmentation of buccal mucosa, scars and skin creases
2. Decreased cognition is most often due to concomitant thyroid or electrolyte disturbances

Neuropathology

1. Adrenal dysgenesis:
 - a. Mutations of the SF1 transcription factor
 - b. Congenital adrenal hypoplasia (CAH) due to DAX-1 gene mutations
 - c. Mutation of the ACTH receptor gene or Triple A gene
 - d. DAX-1 may be a component of concomitant gene mutations that include glycerol kinase deficiency
2. Impaired synthesis:
 - a. Smith-Lemli-Opitz syndrome and abetalipoproteinemia impair the delivery of cholesterol from which cortisol is synthesized
 - b. 21-hydroxylase, 11 β -hydroxylase, 17 β -hydroxylase, 3 β -hydroxysteroid dehydrogenase and lipoid CAH congenital adrenal hypoplasia (due to STAR and DNA mutations) are the major enzymatic deficiencies that cause failure of synthesis
3. Destruction of the adrenal gland:
 - a. Autoimmune adrenalitis (immune impairment of 21-hydroxylase) can be isolated or occurs with autoimmune polyendocrine syndrome type 1 or 2
 - b. Adrenoleukodystrophy
 - c. Waterhouse-Friderichsen syndrome
 - d. Antiphospholipid syndrome
 - e. Tuberculosis, coccidioidomycosis and histoplasmosis
 - f. Amyloidosis

Laboratory Evaluation

1. Serum cortisol, ACTH, aldosterone, renin, potassium and sodium concentration

2. CT of the adrenal gland
3. MRI of the pituitary
4. ACTH simulation test
5. 21-hydroxylase autoantibody test for Addison's disease

Hyperthyroidism

General Characteristics

1. Thyrotoxicosis is caused by the secretion of excess thyroid hormone from any cause
2. Grave's disease causes 50–80% of hyperthyroidism in the USA; possibly 1% of the population is affected

Clinical Manifestations

1. May be asymptomatic
2. Increased heat rate
3. Hyperhidrosis
4. Thinning of the skin
5. Brittle hair
6. Increased bowel movements
7. Weight loss
8. Menstrual cycle abnormalities
9. Heat intolerance
10. Neurologic complications:
 - a. Anxiety and depression
 - b. Proximal myopathy
 - c. Sleep disruption
 - d. Tremor
 - e. Cognitive impairment (inattention)
 - f. Panic attacks
 - g. Panic and paranoia (rare)
 - h. Periodic paralysis (primarily Asian patients)
 - i. Associated with myasthenia gravis
11. Ophthalmopathy:
 - a. Pathologic lid retraction
 - b. Exophthalmos
 - c. Extraocular muscle weakness
 - d. Eye muscle swelling
 - e. Lid lag and failure of convergence

Neuropathology

1. Thyroid inflammation (Hashimoto's leading to hypothyroidism) and subacute (De Quervain's) inflammation
2. Exogenous consumption
3. Amiodarone (can cause hyper- or hypothyroidism)
4. Post-partum thyroiditis
5. A struma ovarii
6. Excess iodine consumption (kelp algae)
7. Pituitary edema with increased TSH

Laboratory Evaluation

1. TSH (low)
2. Increased T3 and T4
3. Anti-TSH-receptor antibody in Grave's disease; anti-thyroid peroxidase antibodies in Hashimoto's disease
4. Thyroid scintigraphy

Hyperparathyroidism

General Characteristics

The neurologic manifestations of parathyroid disease are associated with serum calcium levels:

1. Hyperparathyroidism is caused by excessive PTH (parathyroid secretion in respect to calcium homeostasis)
2. Familial forms of the disease are caused by mutations in:
 - a. MEN gene for type 1 disease and RET gene for MEN (multiple endocrine neoplasia) type 2 disease
 - b. Calcium-sensing receptor gene for familial hypocalcemic hypercalcemia
 - c. Parafibromin (HRP2 oncosuppressor gene) for PHPT-jaw tumor and carcinoma
 - d. 80% of patients have sporadic adenomas most commonly found with mutation of the menin gene for activation of the PRAD1 oncogene
 - e. Rarely HRPT2 and CASR gene mutations

Clinical Manifestations

1. Bone involvement is more prominent at skeletal sites that have an increased concentration of cortical tissue; trabecular skeletal sites are relatively spared
2. General medical signs and symptoms are primarily due to hypercalcemia and include:
 - a. Fatigue
 - b. Anorexia
 - c. Thirst
 - d. Polyuria
 - e. Kidney stones
 - f. Constipation
 - g. Peptic ulcer

Neurologic Manifestations

1. Psychiatric disorders
2. Patients with bipolar disorder on long term lithium may become hyperparathyroidotic (usually caused by a single adenoma)
3. Muscular weakness (proximal)
4. Cognitive impairment with encephalopathy
5. Bone pain
6. Muscle soreness
7. Secondary hyperparathyroidism:
 - a. Due to hypocalcemia from vitamin D deficiency (decreased calcium absorption from the intestine)
8. Chronic renal disease:
 - a. Failure to convert vitamin D to its active form (occurs in the kidney)

Neurologic Manifestations of Hypocalcemia

1. Cognitive impairment
2. Neuromuscular irritability:
 - a. Chvostek's and Trousseau's sign
 - b. Hyperactive reflexes
3. Seizures
4. Asterixis
5. Basal ganglia dysfunction

Neurologic Manifestations of Hypercalcemia

1. Lethargy progressing to stupor
2. Early stages poor cognitive function primarily that of a subcortical dementia
3. Associated neurologic features:
 - a. Absent reflexes
 - b. Absent bowel sounds
 - c. Very rare pseudo ALS syndrome
 - i. Fasciculating tongue
 - ii. Proximal muscle weakness
 - iii. Hyperactive reflexes
 - iv. Associated with primary hyperparathyroidism

Neuropathology

1. Primarily hyperparathyroidism is caused by oversecretion of PTH from:
 - a. Parathyroid adenoma
 - b. Parathyroid hyperplasia
 - c. Rarely as a component of multiple endocrine neoplasia (MEN) syndrome
2. Secondary hyperparathyroidism:
 - a. Vitamin D deficiency
 - b. Malabsorption (from the intestine)
 - c. Chronic renal failure

Laboratory Evaluation

1. Parathyroid immunoassay:
 - a. PTH is elevated or inappropriately normal in the face of an elevated calcium concentration
2. Increased serum calcium levels with abnormally low serum phosphate due to decreased renal tubular phosphate reabsorption
 - a. In secondary hyperparathyroidism the phosphate may be elevated due to renal disease
3. Alkaline phosphatase is usually elevated in primary hyperparathyroidism
4. Parathyroid scan

Diabetes*General Characteristics*

1. Astrocytes convert glucose into lactate and transfer it to neurons that is essential for neuronal metabolism, the formation of synapses, dendrites and the expression of genes that are involved in memory
2. Severe hyperglycemia is associated with alterations in osmotic pressure and diabetic ketoacidosis may cause cerebral edema

Clinical Manifestations

1. Cognitive impairment and dementia have recently been posited to be complications of diabetes mellitus
2. Obesity and insulin resistance may increase the risk of both vascular dementia and possibly Alzheimer's disease

Neuropathology

1. Chronic hyperglycemia and hyperinsulinemia cause the formation of advanced glycation end products (AGEs) that cause overproduction of reactive oxygen species
2. Insulin is neurotrophic at normal concentrations but at higher concentrations may impair amyloid-beta clearance from alterations in insulin degrading enzyme availability. This is posited to be a component of the A β amyloid clearing mechanism. Glucose has a much higher affinity for the enzyme
3. Hyperglycemia and hyperinsulinemia may accelerate brain aging by:
 - a. Microangiopathy
 - b. Induction of tau hyperphosphorylation
 - c. Amyloid oligomerization
4. Diabetic patients have a higher propensity to develop leukoaraiosis that is associated with cognitive impairment
5. Pathologic hyperglycemia may induce:
 - a. Mitochondrial production of free radicals
 - b. Oxidative stress
 - c. Activation of neuronal apoptosis
 - d. Increased proinflammatory cytokines may be produced during insulin resistance that may cross the BBB to induce inflammation
 - e. Glycogen-synthetase kinase (GSK-3) is increased in diabetes and is a component of the regulation of tau phosphorylation and A β peptide production

Laboratory Evaluation

1. Hyperglycemia and insulin resistance
2. High metabolic index

Neuroimaging

1. MRI:
 - a. Large and small vessel atherosclerosis
 - b. Microangiopathy
 - c. Leukoaraiosis

Episodic Hypoglycemia*General Characteristics*

1. Hypoglycemia is most often encountered in patients with poorly controlled diabetes mellitus that are utilizing insulin
2. Extremely rarely it is caused by an insulinoma
3. Hypoglycemia occurs in a setting of hepatic and renal insufficiency, starvation and rarely with suicide attempts (medical personnel)

Clinical Manifestations

1. Multiple episodes of seizures and coma lead to the neurological sequelae
2. Gradual deterioration of cognitive function
3. Associated with:
 - a. Motor neuropathy
 - b. Ataxia
 - c. Involuntary movements

Neuropathology

1. Neuroanatomical areas of neuronal loss:
 - a. Neocortex layers III–VI
 - b. Purkinje cells
 - c. Globus pallidus internus
 - d. Anterior horn cells

Laboratory Evaluation

1. Episodic hypoglycorrhachia (CSF) with blood sugar concentration of less than 30 mg/dl

Neuroimaging

1. MRI (head):
 - a. To rule out bacterial, fungal or tuberculosis meningitis

Differential Diagnosis of Hypoglycorrhachia in Adult Patients (Tertiary Center)

1. Bacterial meningitis:
 - a. Most often in patients following neurosurgical procedures
2. Stroke and hemorrhage
3. Carcinomatosis
4. Lymphoma and leukemia
5. Immunosuppressed patients more likely to have fungal meningitis
6. Sarcoidosis
7. Viral meningitis:
 - a. Herpes simplex
 - b. Mumps
 - c. Enterovirus
8. GLUT1 deficiency
9. Neurosyphilis:
 - a. May not affect the CSF sugar

Cushing's Syndrome*General Characteristics*

1. Definition:
 - a. Cushing's disease or pituitary dependent Cushing's syndrome is caused by a corticotroph pituitary tumor and accounts for approximately 70% of chronic endogenous hypercortisolism
 - b. Cushing's disease is caused by increased secretion of cortisol from the adrenal glands due to excessive ACTH stimulation from a pituitary tumor. The usual tumor is a pituitary adenoma
 - c. Microadenomas account for 90% of patients; macroadenomas account for 10%; rarely pituitary carcinoma is causative
 - d. The incidence of CD is 1.2 to 2.41 million of the population/year
 - e. CD is three times more prevalent in women than men

Clinical Manifestations

1. Medical complications:

- a. Weight gain with central obesity
- b. Fatigue
- c. Proximal myopathy
- d. Thin skin with purple striae
- e. Medical comorbidities:
 - i. Arterial hypertension
 - ii. DM
 - iii. Dyslipidemia
 - iv. Osteoporosis
 - v. Depression
 - vi. Impaired sexual function in men
 - vii. Menstrual irregularities in women
2. Neurocognitive disorders:
 - a. Neurocognitive impairment occurs in:
 - i. The memory domain
 - ii. Visual and spatial abilities
 - iii. Executive function
 - iv. Verbal learning
 - v. Language domains

Neuropathology

1. Decreased brain and hippocampal volume
2. Nuclei involved in cognitive functions have a high density of glucocorticoid receptors
3. Endogenous Cushing's syndrome is caused by:
 - a. Pituitary adenoma that causes excess adrenocorticotrophic hormone secretion
 - b. Increased secretion of corticotropin releasing hormone (CRH)
 - c. Adrenocortical tumors or hyperplasia
4. Exogenous Cushing's syndrome:
 - a. Iatrogenic steroid administration

Lysosomal Storage Disorders and Dementia***Overview***

There are more than 50 lysosomal storage disorders primarily arising from abnormal function of lysosomal enzymes. They are caused by genetic mutations which cause a decreased or lack of activity of proteins that belong to four functional groups:

1. Acid lysosomal hydrolases that degrade macromolecules
2. Proteins that are involved in lysosomal transport
3. Proteins that deliver enzymes into lysosomes
4. Activation of lysosomes

These deficiencies cause complete or partial failure of degradation of macromolecules which accumulate in lysosomes with consequent physiologic and pathologic dysfunction in cells, tissues and organs. The lysosomal storage diseases are autosomal recessive with 3 exceptions: 1. Fabry's disease and Hunter's disease (mucopolysaccharidosis type II) that are X-linked recessive diseases and 2. Danon disease which is an X-linked dominant disorder.

Lysosomal function is a component of the endosomal-lysosomal system. This system accomplishes the internalization, recycling, transport and decomposition of cellular and extracellular molecules as well as dissociating receptor ligand bonds. The lysosome is the major component of endocytic and phagocytic enzymes that are found in both endosomes and lysosomes but are more effective in the latter due to its greater acidity.

Lysosomal enzymes are synthesized in the rough endoplasmic reticulum, are N-glycosylated and enter the Golgi compartment and, through a series of actions, acquire the M6P ligand. The receptor protein complex then enters the late endosomes where the final steps of proteolysis, folding and aggregation occur.

Adult Lysosomal Disorders with Dementia

GM1 Gangliosidosis

General Characteristics

1. GM1-Gangliosidosis is autosomal recessive and is caused by mutations in the GLB1 gene that maps to chromosome 3p22.3
2. The 3 major variants are:
 - a. Infantile form (Type I)
 - b. Late infantile form (Type II)
 - c. Adult onset (Type III)
3. Mutations in both the infantile and adult forms interfere with the phosphorylation of precursor beta-galactosidase. The precursor is secreted instead of being compartmentalized into lysosomes and processed further

Clinical Manifestations (Adult Form)

1. Onset may be in the first decade (3–30 years of age)
2. Slowly progressive
3. Dystonia
4. Spasticity
5. Ataxia
6. Myoclonus
7. Cognitive impairment
8. No visual involvement

Neuropathology

1. Minimal storage of gangliosides in the cerebral cortex
2. Atrophy of the caudate, putamen and globus pallidus (neuronal loss with gliosis)
3. Meganeurite formation is noted in the basal ganglia and pyramidal neurons of the cortex
4. The stored ganglioside is PAS-positive
5. No vacuolated lymphocytes

Laboratory Evaluation

1. Vacuolated lymphocytes are described in Type I but not in Type III

Neuroimaging

1. MRI:

- a. Progressive atrophy in the cerebrum and cerebellum
2. Quantitative MRS:
 - a. Deficit of N-acetyl aspartate in both late infantile and juvenile patients

GM2 Gangliosidosis

General Characteristics

1. The GM2 gangliosidosis are three related genetic diseases that are caused by a deficiency of the enzyme beta-hexosaminidase. They are:
 - a. Tay-Sachs disease:
 - i. Mutation of the HEXA gene that maps to chromosome 15q23 and causes a deficiency of hexosaminidase A
 - b. Sandhoff disease:
 - i. Mutations in chromosome 5 of the HEXB gene
 - ii. Encodes the lysosomal enzymes beta-N-acetyl hexosaminidase A & B
 - c. AB variant:
 - i. Mutations in the GM2A gene cause this variant that maps to chromosome 5
 - ii. Encodes an enzyme cofactor in the GM2 activator that is essential for the function of beta-hexosaminidase A

Clinical Manifestations

1. Infantile form (all types have similar signs)
 - a. Onset at 3–6 months of age with developmental delay
 - b. Cognitive impairment
 - c. Macrocephaly
 - d. Exaggerated startle response
 - e. Blindness
 - f. Cherry red spot in the retina
 - g. Seizures
2. Juvenile onset:
 - a. Spinocerebellar symptoms

Hexosaminidase A Deficiency in Adults (Type B)

General Characteristics

1. Mutations in the alpha-subunit that causes failure of association with the beta-subunit
2. Low hexosaminidase A activity

Clinical Manifestations

1. Slowly progressive deterioration from early childhood
2. Cognitive impairment
3. Ataxia
4. Dysarthria
5. Recurrent psychotic episodes
6. No seizures
7. The most common presentation is motor neuron disease
8. No ocular abnormalities
9. Peripheral neuropathy

Neuropathology

1. Large increase of GM2 ganglioside in neurons

- a. Less storage in the cortex of ganglioside than is seen in the infantile or juvenile forms
- b. Storage in the brainstem, cerebellum, basal ganglia and the spinal cord
- c. Concomitant lipofuscin storage

Laboratory Evaluation

1. Molecular genetic testing (MGT)
2. Absent to near absent HEXA enzymatic activity in the serum

Kufs Disease

General Characteristics

1. Kufs disease is an adult onset neuronal ceroid lipofuscinosis that is genetically heterogeneous
2. Mutations in the gene CLN6:
 - a. Autosomal recessive inheritance
 - b. Maps to chromosome 15q23
3. The type A phenotype of mutation in CLN6 gene causes progressive myoclonic epilepsy while type B is associated with dementia and motor dysfunction
4. Recent exome sequencing has revealed homozygous and compound heterozygous missense mutations in the CTSF gene that maps to chromosome 11q13.2
 - a. Encodes cathepsin F, a lysosomal cysteine protease
5. Mutations in the DNA JC5 gene that maps to chromosome 20q13.33 and causes dominant Kufs disease

Clinical Manifestations

1. The phenotype of CTSF/CLN3 of Kufs disease type B
 - a. Onset in the second and third decades
2. Cerebellar syndrome with tremor
3. Ataxia and dysarthria
4. Tonic-clonic seizure
5. Progressive cognitive impairment

Neuropathology

1. Diffuse cerebral atrophy
2. Neuronal loss and astrogliosis most severe in the cerebral cortex and cerebellum
3. Autofluorescent material in the cytoplasm of neurons in the cortex, thalamus, striatum, brainstem nuclei and Purkinje cells
4. Deposition in meganeurites of the basolateral amygdaloid complex
5. Storage may be in layers III–VI of the cerebral cortex
6. No vacuolated lymphocytes

Laboratory Evaluation

1. Sequence analysis reveals the CLN6 gene maps to chromosome 15q21-q23

Neuroimaging

1. MRI:

- a. Kufs disease type B (CTSF)
 - i. Brain volume reduction
 - ii. Periventricular deep white matter hyperintensities
 - iii. Atrophy of the corpus callosum
- b. Similar MRI alterations are seen in adult-onset neuroceroid lipofuscinosis due to mutation in DNAJ CS, CLN6 and CLN5 and patients with mutations in GRN

Niemann-Pick Disease

General Characteristics

1. Niemann-Pick disease type A is caused by mutation in the sphingomyelin phosphodiesterase-1 gene that maps to chromosome 11p15.4
2. Niemann-Pick disease type B is allelic
3. Both types A and B are caused by a deficiency of acid sphingomyelinase

Clinical Manifestations

1. Persistent early jaundice with an enlarged abdomen
2. Developmental delay
3. Hepatosplenomegaly
4. Related physical growth and mental development delay
5. Neurologic features:
 - a. Hypotonia
 - b. Rigidity
 - c. Severe cognitive impairment
 - d. Demise by 3 years of age
 - e. Cherry red spot
 - f. Corneal opacification and brown discoloration of the anterior lens capsule
6. Clinical features of Niemann-Pick Type B
 - a. Thrombocytopenia (most patients)
 - b. Leukopenia and anemia less common
 - c. Decreased HDL cholesterol
 - d. Decline in pulmonary function

Neuropathology

1. Sphingomyelin accumulates in:
 - a. Reticuloendothelial cells throughout the body
 - b. Increased sphingomyelin is found in the bone marrow, skin and amniotic cells
2. Slight brain atrophy in NP type A; the brains of type B patients are normal
3. Neuronal and glial ballooning
4. Gliosis and storage cells in the white matter
5. Foamy histiocytes that contain cholesterol esters are found in the globus pallidus, substantia nigra, and the dentate nucleus
6. Niemann-Pick cells (a foamy storage cell) are found in most organs
7. Ganglion cells of the CNS are affected

Laboratory Evaluation

1. Molecular genetic testing to identify the gene mutation
2. Cell culture that demonstrates increased sphingomyelin in bone marrow or skin cells

Adult Form of Niemann-Pick Disease Type C (NP-C)*General Characteristics*

1. NP-C is a neurovisceral lysosomal storage disease with an estimated incidence of 1/120,000 live births
2. NP-C has autosomal recessive inheritance and is caused by mutations in the NPC1 gene that maps to chromosome 18q11.2 (in 95% of families) or mutations in the NPC2 gene (occurs in 5% of families) and is mapped to chromosome 14q24.3
3. Niemann-Pick disease type D (the Nova Scotia type) is caused by mutation in the NPC1 gene
4. The exact function of the encoded proteins from the mutants is not known. It is posited that they are involved in post-lysosomal and late endosomal transport of cholesterol

Clinical Manifestations

1. Clinical features of NP-C are varied
2. The age of onset varies from the perinatal period to the seventh decade. The average age of onset in the adult form is 59 years of age
3. Systemic disease, if present, precedes the onset of neurologic signs and symptoms. Systemic symptoms may be absent or slight in 15% of patients
4. Cerebellar ataxia
5. Dysarthria and dysphagia
6. Progressive dementia
7. Vertical supranuclear gaze palsy
8. Dystonia occurs in 25% of patients
9. Cataplexy (with or without narcolepsy) often laughter induced
10. Seizures
11. Isolated splenomegaly and lung involvement
12. A psychiatric presentation may be isolated for years prior to the onset of motor and cognitive impairment and includes:
 - a. Schizophrenia-like psychosis with paranoid delusions
 - b. Depression
 - c. Bipolar disorder
 - d. Obsessive-compulsive behavior
 - e. Behavioral problems
 - f. Visual hallucinations and confusion
 - g. Symptom fluctuation
 - h. Aggravation by neuroleptic drugs
13. The adult form is dominated by cerebellar and extrapyramidal rather than pyramidal signs

Neuropathology

1. Impaired utilization and processing of endocytosed cholesterol is a major component in the pathogenesis
2. Sphingomyelin accumulation is related to lysosomal storage
3. Cholesterol accumulation in the late endosomal/lysosomal compartment may impair the trafficking of late endosomal proteins Rab 9 and mannose-6-phosphate receptors

4. Generalized neuronal and glial ballooning
5. Foamy histiocytes containing cholesterol esters are found in the globus pallidus, substantia nigra and dentate nucleus

Laboratory Evaluation

1. Molecular genetic testing that identifies the mutations
2. Low HDL-cholesterol is a frequent but not a diagnostic finding
3. Chitotriosidase activity is mildly elevated
4. Impaired intracellular cholesterol transport is a diagnostic test for NP-C usually accomplished with skin fibroblast culture. The filipin test is the most sensitive and specific assay. It is a compound that forms specific complexes with unesterified cholesterol. Fluorescent microscopic examination of NP-C positive cells reveals positive cholesterol filled perinuclear vesicles
5. Foam cells and sea-blue histiocytes may be present in the bone marrow

Neuroimaging

1. MRI:
 - a. The callosal area and its mean thickness are reduced most severely in the genu, posterior body, isthmus and anterior splenium
 - b. Lower corpus callosum fractional anisotropy, volume and cross-sectional area correlate with clinical symptomatology

Gaucher's Disease*General Characteristics*

1. Gaucher's disease Type III is the subacute form of neuronopathic Gaucher's disease. Type II is caused by a homozygous or compound heterozygous mutation in the GBA gene that maps to chromosome 1q22
2. The gene encodes acid beta-glucosidase

Clinical Manifestations

1. Phenotypic subgroups of Type III Gaucher's disease
 - a. Type IIIA:
 - i. Myoclonus and dementia
 - b. Type IIIB:
 - i. Early onset of isolated horizontal supranuclear gaze palsy with aggressive systemic disease
 - c. Seizures occur
 - d. Norrbotten type:
 - i. Described from the Norrbotten province of Sweden
 - ii. Onset was 2.5 years of age (8 months to 14.5 years)
 - iii. Severe phenotypic variability and course among patients
 - iv. Affected patients have short stature, normal intelligence and seizures (some patients). There is later development of abnormal eye movements
 - e. Bone pain due to vascular changes in the metaphysics of long bones
 - f. Collapse of vertebral bodies with spinal cord compression
 - g. Parkinsonism and mood disorder

Neuropathology

1. Gaucher cells are seen perivascularly
2. Neuronal loss in cortex layers III and V, the cerebellum and basal ganglia
3. Gaucher cell:
 - a. 20–100 μ m in size
 - b. Cytoplasmic fibular material is PAS-positive

Laboratory Evaluation

1. Anemia, leucopenia and thrombocytopenia are seen in the Norrbotten variant
2. Deficit in enzymatic activity of glucocerebrosidase in circulating leukocytes
3. Molecular genetic analysis; patients with the L444P mutation in the GBA gene have a high incidence of neuralgic disease

Metachromatic Leukodystrophy*General Characteristics*

1. Metachromatic leukodystrophy is caused by mutation in the arylsulfatase A gene (ARSA) that maps to chromosome 22q13
2. There are 5 allelic forms of MLD that include:
 - a. Late infantile
 - b. Juvenile
 - c. Adult
 - d. Partial cerebroside sulfate deficiency
 - e. Pseudo arylsulfatase A deficiency
3. There are 2 non-allelic forms:
 - a. MLD due to saposin 13 deficiency
 - b. Multiple sulfatase deficiency

Clinical Manifestations of the Adult Form

1. Symptoms begin after age 16 years of age. Most adult patients have onset between 20–30 years of age
2. Patients present with a subtle organic brain syndrome:
 - a. Impaired concentration
 - b. Memory dysfunction
 - c. Schizophrenic behavior
 - d. Emotional liability
3. Rare seizures
4. Spasticity
5. Unusual movements
6. Increased reflexes
7. A rare presentation may occur without psychiatric symptoms
8. Variant of arylsulfatase A gene mutation:
 - a. D281Y in an adult patient
 - b. Slowly progressive psychiatric and cognitive decline
9. Pseudodeficiency of arylsulfatase A:
 - a. Mutations occur within the gene
 - b. No disease produced
 - c. Two patients have been reported with abnormal neurological findings that have arylsulfatase A deficiency

Neuropathology

1. Loss of myelin throughout the brain
2. Neuronal deposition of sulfatide in:
 - a. The basal ganglia
 - b. Dentate nucleus
 - c. Brainstem nuclei
 - d. Spinal cord neurons
 - e. μ fibers are spared
3. Loss of myelinated fibers in peripheral nerves
4. Sulfatides are in macrophages and Schwann cells

Laboratory Evaluation

1. Molecular genetic evaluation to determine the mutation
2. EMG:
 - a. Demyelinating neuropathy
 - b. The gallbladder may be non-functional

Neuroimaging

1. MRI:
 - a. Symmetric signal abnormalities of the periventricular and centrum ovale that spares fibers
 - b. Regional measurement of cortical atrophy:
 - i. The cingulate and frontal lobes are most affected in the adult form (measured by age-related volumetry)
 - ii. Frontal white matter involvement correlates with decreased cingulate, insular and frontal lobe cortical thickness
 - iii. Cerebellar atrophy is most pronounced in patients with an adult presentation
 - iv. Thalamic volumetric loss is present early in the disease

Krabbe's Leukodystrophy*General Characteristics*

1. Krabbe's disease is caused by homozygous or compound heterozygous mutations in the galactosylceramidase gene (GALC) that maps to chromosome 14q31.3
2. It is an autosomal recessive lysosomal disease that affects the myelin of both the peripheral and CNS
3. The disorder presents as:
 - a. An infantile form
 - b. Late onset disorder
4. The gene encodes galactosylceramide beta-galactosidase

Clinical Manifestations (Late Onset Form)

1. May have very late onset (up to 84 years of age)
2. Gait abnormality
3. Progressive spasticity (tetraparesis)
4. Visual dysfunction
5. Cognitive impairment (50% of patients)
6. No seizures
7. Optic disc pallor
8. Pes cavus

Neuropathology

1. Gross loss of CNS myelin
2. Astrocytic gliosis
3. Globoid macrophages that generally surround blood vessels
4. In late onset patients the appearance of globoid cells may be delayed
5. Globoid cells are PAS-positive
6. The cortex may be relatively normal
7. Loss of neurons in the dentate nucleus and the inferior olives
8. Straight or curved tubule crystalloid inclusions in Krabbe's globoid cells

Laboratory Evaluation

1. Neurophysiologic studies:
 - a. 20% of patients have slow nerve conduction studies
 - b. Brainstem auditory evoked potential abnormalities are seen in 40% of patients
 - c. Approximately 1/3 of patients have an abnormal EEG
 - d. Molecular genetic evaluation to determine the mutation
 - e. Globoid cells in brain tissue, derived from monocytes-macrophage stem cells from the bone marrow that contain psychosine and galactosylceramide
 - f. Enzyme assay of leukocytes or fibroblasts
 - g. Increased CSF protein

Neuroimaging

1. MRI:
 - a. Involvement of parieto-occipital periventricular white matter

Mucopolysaccharidosis*General Characteristics (Adult Form)*

1. The mucopolysaccharidoses are disorders in which there is a deficiency of enzymes that metabolize glycosaminoglycans (CAGs) which are long chains of sugar carbohydrates
2. The lysosomal enzyme deficits result in storage of glycosaminoglycans within liposomes of most tissues
3. There may be early death or survival into adulthood in all forms

Clinical Manifestations (Adult Form)

1. Severe and mild disease for all the various forms
2. Hepatosplenomegaly
3. Coarse features
4. Mild to severe cognitive impairment
5. Skeletal changes that may cause spinal cord compression
6. Corneal clouding in type I, IV, VI and VII
7. Carpal tunnel syndrome
8. Cardiomyopathy
9. Aortic and mitral valve incompetence
10. Normal intelligence in Scheie, Morquio and Maroteaux-Lamy disease

11. Sanfilippo

- a. Severe behavioral disturbance
- b. No skeletal abnormalities

*Adult Forms of Mucopolysaccharidoses with Dementia***General Characteristics**

1. Hurler syndrome
 - a. The mutated gene is IDUA that maps to chromosome 4p16.3. The mutations are homozygous or compound heterozygous
 - b. The encoded enzyme is alpha-L-iduronidase
2. There is a wide range of phenotypic expression with 3 subtypes:
 - a. Hurler (MPS 1H)
 - b. Scheie (MPS IS)
 - c. Hurler-Scheie (MPS IH/5)
 - d. Hurler and Scheie are the most severe and least affected (respectively) with Hurler-Scheie being the intermediate phenotype

Clinical Manifestations

1. Children appear normal at birth and develop clinical symptomatology during early life
2. Coarse faces
3. Corneal clouding
4. Cognitive impairment
5. Hernias
6. Dysostosis multiplex
7. Hepatomegaly
8. Nervous system
 - a. Developmental delay
 - b. Chronic hearing loss
 - c. Head circumference at or above the 95th percentile

Neuropathology

1. Dura and leptomeninges may be thickened
2. Perivascular areas contain foamy cells
3. There may be severe neuronal storage of glycosaminoglycan throughout the brain
4. Associated with increased neuronal lipopigment

Laboratory Evaluation

1. Molecular diagnosis
2. Quantitative dimethylmethylene blue test for determination of heparin sulfate and dermatan sulfate in the urine

Neuroimaging

1. MRI: (children)
 - a. Cystic low signal lesions on T1-weighted sequences and high signal intensity lesions on T2-weighted sequences perivascularly
 - b. Myelination delay
 - c. Cerebral atrophy
 - d. Enlarged ventricles

Hunter's Syndrome*General Characteristics*

1. Hunter's syndrome is caused by mutation in the IDS gene that maps to chromosome Xq28
2. The gene encodes the liposomal enzyme iduronate sulfatase
3. It is a multisystem disorder

Clinical Manifestations

1. Airway obstruction
2. Skeletal deformities
3. Cardiomyopathy
4. Most patients succumb by the second decade although some survive into the fifth and sixth decade
5. Two major phenotypes:
 - a. Severe phenotype MPS IIA:
 - i. Progressive cognitive decline
 - ii. Systemic involvement with death by age 15
 - b. Mild form (MPS IIB):
 - i. Survival into adulthood
 - ii. Mild cognitive impairment
 - c. Lack of corneal clouding
 - d. Mild dysostosis (adult form)
 - e. Aortic regurgitation
6. Variable features:
 - a. Patients with a complete deletion of the IDS locus:
 - i. Atypical phenotype that includes:
 1. Ptosis
 2. Obstructive sleep apnea
 3. Seizures

Neuropathology

1. Storage of glycosaminoglycans within liposomes of most tissues and organs
2. Neuronal glycosaminoglycans storage; minimal cortical storage in mild cognitively impaired patients
3. Neuronal storage throughout the brain
4. Hepatic fibrosis

Laboratory Evaluation

1. Molecular genetic evaluation to detect the mutation
2. Urinary excretion of heparin and dermatan sulfates

Sanfilippo Syndrome Type IIIA*General Characteristics*

1. Mucopolysaccharidosis type IIIA is caused by homozygous or compound heterozygous mutations in the SGSH gene that maps to chromosome 17q25.3
2. There are 4 types of MPS III due to deficiencies of different enzymes:
 - a. Heparin N-sulfatase (type A)
 - b. Alpha-N-acetylglucosaminidase (type B)
 - c. Acetyl CoA: alpha-glucosaminide N-acetyl transferase (type C)
 - d. N-acetylglucosamine 6-sulfatase (type D)

Clinical Manifestations

1. Wide phenotype variability with delineation of a severe, intermediate and mild forms
2. Intermediate and mild types live into adulthood
3. Attenuated adult form:
 - a. Achieve speech and ability to walk
 - b. Behavioral disorder
 - c. Seizures
 - d. Upper airway infections
 - e. Death occurs usually by 18 years of age
 - f. Spasticity

Neuropathology

1. The accumulated glycosaminoglycan is heparin sulfate

Laboratory Evaluation

1. Molecular genetic analysis to determine the gene mutation
2. Urinary excretion of heparin sulfate
3. Radiologic evaluation of the extremities:
 - a. Persistent biconvexity of the vertebral bodies
 - b. Thick calvaria

Morquio Syndrome (IVB)*General Characteristics*

1. Mucopolysaccharidosis type IVB is caused by mutation of the GLB1 gene that maps to chromosome 3p22.3
2. Incidence of both type IVA and IVB in one patient per 75,000 of the population
3. The gene encodes beta-galactosidase
4. Inheritance is autosomal recessive
5. Mucopolysaccharidosis type IVA is caused by mutation of the GALN gene that maps to chromosome 16q24.3 and has overlapping phenotypic features with type IVB
6. MPS IVB is an autosomal recessive disorder

Clinical Manifestations

1. Normal intelligence
2. No central nervous system involvement
3. Spondyloepiphyseal dysplasia
4. Corneal clouding
5. Short stature

Neuropathology

1. No CNS involvement
2. Accumulated keratan sulfate

Laboratory Evaluation

1. Bone X-rays
 - a. Flattening of the vertebral bodies and femoral heads
 - b. Coxa valga
 - c. Absence or hypoplasia of the odontoid process
 - d. Abnormal metacarpal epiphyses
 - e. Narrowed phalanges
2. Molecular genetic evaluation
3. Deficient B-galactosidase in leukocytes
4. Increased urinary sulfate excretions

Maroteaux-Lamy Syndrome (MPS VI)*General Characteristics*

1. Maroteaux-Lamy syndrome is caused by homozygous or compound heterozygous mutation in the ARSB gene that maps to chromosome 5q14
2. The gene encodes arylsulfatase B

Clinical Manifestations

1. Severe skeletal dysplasia
2. Short stature
3. Kyphosis
4. Heart defects
5. Hepatosplenomegaly
6. Corneal clouding
7. Usually normal intelligence
8. Facial dysmorphism
9. Spinal cord compression (some patients with severe kyphosis)
10. Joint contractures

Neuropathology

1. Ligamentum flavum hypertrophy due to deposition of glycosaminoglycans with spinal stenosis at multiple levels
2. Demyelination of optic nerves (reported in some patients)

Laboratory Evaluation

1. Alder granulations may be present in neutrophils (reddish violet granulation by Wright stain)
2. Residual N-acetylgalactosamine 4-sulfatase in cultured fibroblasts
3. Increased urinary excretion of chondroitin sulfate

Neuraminidase Deficiency*Sialidosis Type I**General Characteristics*

1. Sialidosis type I is caused by homozygous or compound heterozygous mutation in the NEV gene that maps to chromosome 6p21.33
2. Inheritance is autosomal recessive
3. There is storage of sialylated glycopeptides and oligosaccharides due to a deficiency of neuraminidase
4. Type I has a less severe phenotype, it is also referred to as cherry red spot-myoclonus syndrome

Clinical Manifestations

1. Presentation is often in the second to third decade
2. Bilateral cherry red spots in the macula
3. Progressive visual loss
4. Myoclonus (cherry red spot myoclonus)
5. Corneal clouding
6. Punctuate opacities of the lens
7. Red-green color blindness
8. Ataxia
9. No hepatosplenomegaly
10. Cystic long bone changes
11. Alternating periodic nystagmus
12. Usually normal intelligence

Neuropathology

1. Minimal neuronal storage in the cortex
2. Some vacuolation of neurons in:
 - a. Cortex
 - b. Basal ganglia
 - c. Thalamus
3. PAS-positive foam cells in the marrow

Laboratory Evaluation

1. Urinary excretion of N-acetylneuraminic acid covalently linked to oligosaccharides or glycoprotein
2. Molecular genetic evaluation to detect the mutation

*Sialidosis Type II**General Characteristics*

1. Sialidosis type II is caused by mutations of the NEV1 gene that maps to chromosome 6p21.33
2. It is a more severe phenotype than type I

Clinical Manifestations

1. Earlier onset than type I, autosomal recessive inheritance
2. Coarse facial features
3. Pectus carinatum
4. Thoracic kyphosis
5. Progressive loss of vision
6. Corneal cloudiness
7. Bilateral macular cherry red spots
8. Deafness
9. Ataxia
10. Joint contracture
11. Cortical myoclonus

Neuropathology

1. Neuronal storage:
 - a. Brainstem
 - b. Anterior horn cells
 - c. Nucleus basalis of Meynert (substantia innominata)
2. Rectal biopsy
 - a. Lamellar inclusion bodies
3. Foam cells in the marrow

Laboratory Evaluation

1. Molecular genetic analysis
2. Cytoplasmic vacuolization of peripheral lymphocytes
3. Enzyme assay of cultured fibroblasts
 - a. Decreased oligosaccharide sialidase activity
4. Increased urinary excretion of N-acetylneuraminic acid covalently linked to oligosaccharides or glycoproteins
5. Radiography:
 - a. Dysostosis multiplex
 - i. Vertebral anomalies

Galactosialidosis (GSL)*General Characteristics*

1. Galactosialidosis is caused by mutation in the CTSA gene that maps to chromosome 20q.13.2

2. Inheritance is autosomal recessive
3. The gene encodes cathepsin A
4. It is a lysosomal storage disease that has a combined deficiency of beta-galactosidase and neuraminidase due to a defect in protein: cathepsin A
5. 3 subtypes have been delineated:
 - a. Early infantile
 - b. Late infantile
 - i. Both subtypes associated with early demise
 - c. Juvenile/adult type
6. The majority of patients are Japanese and have the juvenile/adult form of the disorder

Clinical Manifestations (Adult Subtype)

1. Wide phenotype spectrum
2. Variable levels of cognitive impairment
3. Angiokeratoma
4. Ataxia
5. Myoclonus
6. Cherry red macular lesions
7. Coarse facies
8. Skeletal dysplasia

Neuropathology

1. In this disorder, there is a dramatic increase of degradation of beta-galactosidase from a half-life of 10 days to 1 day
2. The increased degradation of both neuraminidase and beta-galactosidase is due to a deficiency in a glycoprotein that is posited to be necessary for activation or protection of the two enzymes
3. Atrophic brain
4. Loss of cortical neurons
5. Lipofuscin is accumulated in layers III, V and VI of the cortex
6. Demyelination in the CNS
7. Vacuolated lymphocytes
8. Foamy cells in the bone marrow
9. Stored material resembles membrane cytoplasmic bodies

Laboratory Evaluation

1. Molecular genetic analysis
2. Vacuolated lymphocytes in the peripheral blood and foamy cells in the bone marrow
3. Enzyme analysis of cultured fibroblasts
4. Electron microscopy of skin biopsy and peripheral blood lymphocytes demonstrate:
 - a. Membrane-bound fibrillogranular inclusions
5. Sialyloligosaccharides in the urine

Mucopolipidosis II

General Characteristics

1. MLD (mucopolipidosis II) alpha/beta, also known as I-cell disease is caused by a homozygous or compound heterozygous mutation in the GNPTAB gene that maps to chromosome 12q28.2

2. Inheritance is autosomal recessive
3. The gene codes for N-acetylglucosamine-1-phosphotransferase

Clinical Manifestations

1. Similar phenotype to Hurler syndrome
2. Cognitive impairment
3. Skull and skeletal deformities:
 - a. Congenital dislocation of the hip
4. Thoracic deformities
5. Hernia
6. Short stature
7. Restricted joint movement
8. Clear cornea
9. Intrauterine fracture
10. Inter- and intrafamilial variability
11. Cardiomegaly
12. Developmental delay

Neuropathology

1. Mutations of the N-acetylglucosamine-1-phosphotransferase complex from defects in the alpha and beta subunits leads to decreased mannose-6-phosphate synthesis. This is the marker on the oligomannosyl type glycan side chains of lysosomal enzymes which targets them to the lysosomes of connective tissue cells
2. This is a disorder of lysosome function rather than of storage of undegraded materials
3. Abnormal inclusions in fibroblasts in some patients

Laboratory Evaluation

1. Skeletal X-rays:
 - a. Osteopenia and dysostosis multiplex
 - i. Diaphyseal widening
 - ii. Shortening of the tubular bones
 - iii. Long tubal and ischial bones (some patients)
 - iv. First and second lumbar vertebral abnormalities
2. Molecular genetic analysis that documents mutations in the GNPTAB gene
3. Cytoplasmic inclusions
4. Increased oligosaccharide urinary excretion

Neuroimaging

1. MRI:
 - a. Brain atrophy in some patients

Mucopolipidosis III Alpha/Beta

General Characteristics

1. Mucopolipidosis III alpha/beta (pseudo-Hurler polydystrophy) is caused by mutation in the GNPTAB gene that maps to chromosome 12q23.2
2. The gene encodes the alpha/beta subunit precursor gene of GlcNAc-phosphotransferase
3. The mucopolipidosis III variant MLIII gamma is due to the GNPTG gene that encodes the gamma subunit
4. Inheritance is autosomal recessive

Clinical Manifestations

1. A less severe phenotype than the allelic disorder mucopolysaccharidosis type II alpha/beta
2. Development of dystrophic features similar to Hurler syndrome
3. Severely stiff joints
4. Flexion contraction in the fingers and toes; reduced mobility of the ankles, wrists, elbows, hips, shoulders and spine
5. Rare corneal clouding
6. Carpal tunnel syndrome
7. Mild cognitive deficits
8. Developmental delay

Neuropathology

1. The disorder is caused by a defect in lysosomal enzyme phosphorylation and localization
2. Empty vacuoles in bone marrow cells
3. Increased glycosaminoglycan of skin lesions; coarse collagen fibers that consist of type I, III, and VI collagen
4. Myelination is normal in both CNS and PNS
5. Primarily a mesenchymal disease

Laboratory Evaluation

1. Radiographic features:
 - a. Dysostosis multiplex
 - b. Trabecular osteopenia
 - c. Subperiosteal bone resorption
 - d. Increased biochemical indices of increased bone turnover
2. Elevated serum levels of lysosomal enzymes
3. Molecular genetic analysis

Mucopolysaccharidosis III Gamma (MDL III)*General Characteristics*

1. MLD III is inherited as an autosomal recessive disorder
2. MLD III gamma is caused by mutation in the gene GNPTG that maps to chromosome 16p13.3
3. The gene encodes the gamma subunit of N-acetylglucosamine-1-phosphotransferase

Clinical Manifestations

1. Childhood onset
2. Joint stiffness with pain in the shoulders, hips and fingers
3. Gradual coarsening of facial features
4. Cardiorespiratory complications:
 - a. Restrictive lung disease
 - b. Thickening and insufficiency of the mitral and aortic valves
 - c. Left ventricular hypertrophy
5. Mild cognitive impairment in some patients
6. No organomegaly
7. Genu valgum

Neuropathology

1. Recent studies posit that the gamma subunit is important in the maintenance of alpha and beta subunits in the GlcNAc-6-phosphotransferase complex

Laboratory Evaluation

1. Skeletal radiographs:
 - a. Hypoplastic iliac bones
 - b. Dysplasia of the proximal femoral epiphyses that causes coxa valga
 - c. Diaphyses of metacarpal and phalanges are shortened
 - d. Widening of the costochondral junction of the ribs
 - e. Generalized platyspondyly
2. Increased activity of lysosomal hydrolases in the serum
3. Molecular genetic analysis to delineate the mutation in GNPTG

Mucopolysaccharidosis IV*General Characteristics*

1. Mucopolysaccharidosis type IV is caused by homozygous or compound heterozygous mutation in the MCOLN1 gene that maps to chromosome 19p13
2. It encodes the lysosomal Ca(2+) efflux channel TRPML1 (transient receptor potential mucolipin 1 (MCOLN1))
3. Inheritance is autosomal recessive
4. The lysosomal hydrolases in MLIV are normal. The defect is one of transport along the lysosomal pathway that affects membrane sorting or the late steps of endocytosis. Recent evidence supports a mechanism in which the target of rapamycin (TOR) targets and inactivates the TRPML1 channel which alters autophagy
5. 80% of patients with the disorder are of Ashkenazi Jewish descent

Clinical Manifestations

1. No skeletal abnormalities
2. Developmental delay
3. Severe cognitive impairment
4. Less severe juvenile and adult patients:
 - a. Corneal clouding (some patients)
 - b. Cognitive impairment
 - c. Ataxia
 - d. Hepatosplenomegaly (some patients)
5. Variable features:
 - a. Achlorhydria
 - b. Mucosal inflammation and atrophy in the stomach

Neuropathology

1. Autophagic alteration due to aberrant regulation of the lysosomal Ca(2+) efflux channel TRPML1
2. Hypoplasia of the corpus callosum (absent rostrum, dysplastic or absent splenium)
3. Demyelination of white matter
4. Atrophy of the cerebrum and cerebellum in long standing diseased patients

5. Electron microscopy of skin biopsies:
 - a. Membranous cytoplasmic bodies in Schwann cells, blood vessel walls, smooth muscle fibers and sweat glands
6. Neuronal storage of PAS-positive granules in both the CNS and PNS
7. Membranous cytoplasmic bodies in endothelial cells of blood vessels

Laboratory Evaluation

1. Retinal pigment abnormalities (some patients) in the macula and retinal vessel attenuation consistent with VEP and ERP documented retinal dystrophy
2. Abnormal fibroblast inclusions may be noted in conjunctival biopsy

Mannosidosis Alpha B

General Characteristics

1. Alpha-mannosidosis is caused by homozygous or compound heterozygous mutation in the MAN2B1 gene that maps to chromosome 19p13.13
2. The new classification:
 - a. Type I:
 - i. The least severe phenotype
 - ii. Onset after age 10
 - iii. No skeletal abnormalities
 - iv. Slow progression
 - b. Type II:
 - i. Onset prior to age 10
 - ii. Skeletal abnormalities
 - iii. Slow progression
 - iv. Ataxia by age 20
 - c. Type III:
 - i. The severest phenotype
 - ii. Onset is early infancy
 - iii. Skeletal abnormalities
 - iv. Death from neurologic CNS deficits or myopathy

Clinical Manifestations (Type I)

1. Onset after age 10; often the second decade of life
2. Cognitive impairment
3. Deafness
4. Pectus carinatum
5. Thoracolumbar gibbus
6. Lens opacities
7. Gingival hypertrophy
8. Ataxia
9. Recurrent infections
10. Retinal degeneration

Neuropathology (Type II and III)

1. Vacuolization of neurons in:
 - a. Cerebral cortex
 - b. Brainstem
 - c. Spinal cord
 - d. Vacuoles in astrocytes and endothelial cells
 - e. Diffuse gliosis and loss of myelin

Laboratory Evaluation

1. MRI (Type I):
 - a. Cerebellar atrophy and periventricular hyperintensity on T2-weighted sequences
 - b. Molecular genetic analysis to delineate the gene mutation
 - c. Alpha-mannosidase activity is decreased in patient lymphoblasts
 - d. Increased urinary excretion of oligosaccharides
 - e. Vacuolated lymphocytes in the peripheral blood

Beta Mannosidosis

General Characteristics

1. Beta-mannosidosis (MANSB) is caused by homozygous or compound heterozygous mutation in the beta-mannoside gene (MANB) that maps to chromosome 4q24
2. The gene encodes beta-mannosidase
3. Inheritance is autosomal recessive

Clinical Manifestations

1. Severe cognitive impairment in most patients
2. Deafness
3. Mild dysmorphic features (some)
4. Angiokeratoma (some patients)
5. Peripheral neuropathy (1 patient)

Neuropathology

1. Gross vacuolization is seen in many cell types
2. Fibroblasts show vacuolization by electron microscopy

Laboratory Evaluation

1. Molecular genetic analysis to delineate the mutation
2. Vacuolated lymphocytes are not seen
3. Direct enzyme assay of fibroblasts

Fucosidosis

General Characteristics

1. Fucosidosis is caused by homozygous or compound heterozygous mutation of the FUCA1 gene that maps to chromosome 1p36.11
2. The gene encodes alpha-L-fucosidase
3. Inheritance is autosomal recessive

Clinical Manifestations

1. There are two types:
 - a. Infantile severe form with death during the first decade (Type 1)
 - b. Type 2 with a less severe phenotype
2. Adult clinical manifestations:
 - a. Facial dysmorphism similar to the mucopolysaccharidosis
 - b. Angiokeratomas
 - c. Cognitive impairment
 - d. Vascular tortuosities in the conjunctiva and retina
 - e. Dysostosis multiplex
 - f. Hypohidrosis and poor temperature regulation

Neuropathology

1. Enlarged or small brain
2. Neural ballooning in all brain structures; olivary nucleus, thalamus, and dentate nuclei in particular
3. Granulovacuolar storage in all organs
4. Foam cells in the bone marrow
5. White matter may demonstrate loss of myelin and gliosis
6. Rosenthal fibers may be seen
7. Marked vacuolation in vascular endothelial cells, fibroblasts and sweat glands
8. Lamellar inclusions and empty occlusions are seen in neurons, astrocytes and Schwann cells

Laboratory Evaluation

1. Molecular genetic analysis to delineate the mutation
2. Decreased ability to degrade fucose-containing blood group H and Lewis substances. Lewis A and B antigens are high in both red cells and saliva
3. Enzyme evaluation in cultured fibroblasts
4. Vacuolated lymphocytes in the blood

Aspartylglucosaminuria*General Characteristics*

1. Aspartylglucosaminuria is caused by mutation in the AGA gene that maps to chromosome 4q34.3
2. The disorder is classified as one of Finnish disease heritage and is autosomal recessive

Clinical Manifestations

1. Common in Finland
2. Severe cognitive impairment
3. Sagging coarse skin (particularly in the cheeks)
4. Joint laxity
5. Short stature
6. Dysostosis multiplex
7. Rare hepatosplenomegaly
8. Macroglossia
9. Excitable psychotic behavior in adults
10. Spondylosis/spondylolisthesis (3 adolescents)
11. Angiokeratoma (some patients)
12. Bacterial infections

Neuropathology

1. No consistent macroscopic changes in the brain
2. Cranial hyperostosis
3. Some patients have thickened and crenated mitral valves
4. Neuronal cytoplasm is filled with vacuoles in:
 - a. The cerebral cortex
 - b. Basal ganglia
 - c. Less evident in the brainstem
5. Neurons and glial cells contain increased lipofuscin

Laboratory Evaluation

1. Molecular genetic analysis to delineate the mutation
2. Urinary excretion of aspartylglucosamine

3. Body fluid and tissue accumulation of glycoasparagines that are glycoconjugates with an aspartylglucosamine moiety at the reducing end
4. Vacuolated lymphocytes

Sialuria*General Characteristics*

1. Sialuria is caused by heterozygous mutation of the GNE gene that maps to chromosome 9p13.3. It is autosomal dominant
2. The gene encodes uridine diphosphate-N-acetylglucosamine 2-epimerase (UDP-GlcNAc 2-epimerase)
3. Putative defective feedback inhibition of an enzyme that is involved in sialic acid synthesis

Clinical Manifestations

1. Occurs primarily in Finland
2. Onset most often in infancy
3. Severe cognitive impairment
4. Adults most often have an IQ of less than 30
5. Spasticity
6. Ataxia
7. Athetosis
8. Mild coarse facies
9. Hepatosplenomegaly
10. Developmental delay

Neuropathology

1. Gyral atrophy of the cerebral cortex; atrophy of cerebellar folia
2. Loss of cortical neurons, astrocytosis and increased lipofuscin
3. Occasional NFT (neurofibrillary tangles)
4. The thalamus, basal ganglia and spinal cord are involved to a varying degree
5. Lysosomal storage of free sialic acid
6. The metabolic defect has been posited to be a loss of sensitivity of the rate-limiting enzyme uridine diphosphate-N-acetylglucosamine 2-epimerase (UDP-GlcNAc) to feedback inhibition by cmp-NANA (in fibroblast cultured cells from patients)

Laboratory Evaluation

1. Massive excretion of free sialic acid in the urine
2. Molecular genetic analysis to delineate the mutation

Neuroimaging

1. MRI:
 - a. Reduction of white matter; normal cortical ribbon; thin corpus callosum

Fabry's Disease*General Characteristics*

1. Fabry's disease is caused by mutations in the GLA gene that maps to Xq22.1 which encodes alpha-galactosidase A

2. The enzyme defect leads to the accumulation of globotriaosylceramide and other related glycosphingolipids in cellular lysosomes
3. Heterozygous female patients have severe medical complications

Clinical Manifestations

1. Systemic:
 - a. Angiokeratoma corporis diffusum:
 - i. Punctate reddish purplish telangiectasia primarily in a bathing suit distribution
 - ii. Mucous membranes
 - iii. Rarely, they are absent
 - b. Proteinuria to renal insufficiency
 - c. Hypertrophic cardiomyopathy; mitral insufficiency
 - d. A variant:
 - i. Left ventricular hypertrophy with or without renal failure that develops in the sixth decade
 - e. Minor to major manifestations occur in female heterozygotes
 - f. Autonomic dysfunction:
 - i. Decreased sweating (may lead to severe hyperthermia)
 - ii. Decreased saliva and tear formation
 - iii. Decreased intestinal motility
 - g. Retinal, conjunctival and corneal abnormalities
 - h. Sensorineural hearing loss
 - i. Neurologic complications:
 - i. Mental deterioration from renal failure, cardiomyopathy and stroke
 - ii. Burning pain and paresthesia of the extremities (small fiber neuropathy)
 - iii. Small and large vessel stroke
 - iv. Severe hyperthermia

Neuropathology

1. Accumulation of globotriaosylceramide in the plasma and cellular lysosomes of vessels, peripheral small diameter nerve fibers and visceral organs
2. Foam cells are present in bone marrow aspirates
3. Accumulation of globotriaosylceramide and related glycosphingolipids in the:
 - a. Amygdala
 - b. Hypothalamus
 - c. Brain stem
 - d. Anterior horn cells
 - e. Brain pathology is related to the vascular pathology that leads to primarily small vessel infarcts
 - f. Involvement of the leptomeninges
 - g. Small fiber peripheral nerve involvement
 - h. Corneal involvement
 - i. Whorl-like corneal dystrophy:
 1. Corneal involvement is equal in males and females (a marker for female heterozygotes)
 - ii. Atabrine and amiodarone cause similar changes

Laboratory Evaluation

1. Molecular genetic analysis to delineate the gene mutation
2. Increased serum myeloperoxidase (MPO) levels in male patients
3. Defects in thyroid, gonadal, adrenal and growth hormone/insulin-like growth factor-1 (higher circulating TSH and ACTH circulating levels)
4. Marked increase of plasma lyso-Gb3 in hemizygotes at a young age; female heterozygotes demonstrate mild lyso-Gb3 increase in the plasma
5. Deficient activity of alpha-galactosidase in leukocytes in both affected males and heterozygote females
6. Urinary trihexoside assay
7. Biopsy demonstrates PAS-positive deposits in the walls of blood vessels which also stain with Luxol fast blue

Neuroimaging

1. MRI:
 - a. Ectasia of large cerebral arteries; particularly in the basilar artery
 - b. White matter hyperintensities throughout the cerebrum
 - c. Small vessel > large vessel infarction

Schindler Disease

General Characteristics

1. Schindler disease types I and III are caused by homozygous or compound heterozygous mutation in the alpha-N-acetylgalactosaminidase gene (NAGA) that maps to chromosome 22q13
2. There are three subtypes:
 - a. Type I:
 - i. An infantile onset neuroaxonal dystrophy
 - b. Type II (Kanzaki disease):
 - i. Adult-onset with angiokeratoma corporis diffusum and mild cognitive impairment
 - c. Type III:
 - i. Intermediate form with a less severe phenotype than Type I
 - ii. Inheritance is autosomal recessive
 - iii. The gene encodes alpha-N-acetylgalactosaminidase

Clinical Manifestations

1. Type I (infants/children):
 - a. Infantile onset neuroaxonal dystrophy
 - b. Pyramidal tract signs
 - c. Hypotonia
 - d. Myoclonus
 - e. Early visual impairment
 - f. Severe cognitive impairment
 - g. Seizures
2. Clinical manifestations of the adult form of the disorder Kanzaki disease:
 - a. Onset in the second or third decade

- b. Mild cognitive impairment
- c. Hearing loss (sensorineural)
- d. Peripheral neuropathy
- e. Angiokeratoma
- f. Facial dysmorphisms:
 - i. Enlarged tip of the nose
 - ii. Depressed bridge of the nose
 - iii. Thick lips
 - iv. Lymphedema

Neuropathology

1. Type I:
 - a. Neocortical and peripheral autonomic axons reveal:
 - i. Tubulovesicular and lamelliform membranous arrays
 - ii. Acellular clefts
 - iii. Electron-dense axoplasmic matrix
 - iv. Spheroids are detected by light and electron microscopy in terminal axons of gray matter consistent with an infantile form of axonal dystrophy
 - v. Vacuolization of fibroblasts in type 2

Laboratory Evaluation

1. Molecular genetic analysis to identify the mutation in the NACA gene
2. Decreased alpha-NAGA activity in cultured leukocytes, fibroblasts and in the plasma
3. Abnormal urinary oligosaccharide pattern

Neuroimaging

1. MRI (children):
 - a. Atrophy of the cerebellum, brainstem and cervical spinal cord

Type II Glycogenosis (Acid Maltase Deficiency)

General Characteristics

1. Glycogen storage disease 2 (GSD2) is caused by homozygous or compound heterozygous mutation in the GAA gene that maps to chromosome 17q25.3
2. The gene encodes acid alpha-1-4 glucosidase

Clinical Manifestations of Adult Onset Glycogen Storage Disease 2

1. Proximal muscle weakness
2. Severe involvement of the diaphragm which is manifest early in the course of the disease
 - a. Severe dyspnea in the supine position
 - b. Nocturnal dyspnea
 - c. Mechanical ventilation is required in severely affected patients
3. Lingual weakness and scapuloperoneal phenotype have been reported
4. Ectasia of cerebral blood vessels as well as Wolff-Parkinson-White syndrome and second-degree atrioventricular block has been reported

5. Many adult onset patients report mild muscular symptoms during childhood although muscle signs in adults occur primarily in the 3rd decade

Neuropathology

1. Glycogen is enclosed in lysosomal membranes rather than in the cytoplasm as is characteristic of other glycogen storage disorders
2. The mutation is posited to affect the production or degradation of the enzyme rather than its catalytic properties
3. Severe vacuolization of skeletal muscle, liver and vascular smooth muscle is noted
4. There is glycogen deposition in vascular smooth muscle
5. Skeletal muscle:
 - a. Is affected in both the infantile and late onset forms
 - b. Vacuoles are filled with soluble B particle glycogen
 - c. Type 2 muscle fibers are more affected than type 1
6. There is no neuronal glycogen storage in the adult form of the disorder

Laboratory Evaluation

1. Peripheral blood lymphocytes have discrete cytoplasmic vacuoles
2. Molecular genetic analysis to delineate the mutation in the GAA gene
3. Enzyme activity can be assessed from skin fibroblast cultures
4. Elevated CK (creatine kinase)
5. Alpha-glucosidase activity can be assessed in dried blood spots
6. Diminished plasma methylation capacity and elevation of insulin that lead to a chronic catabolic state

Farber's Disease

General Characteristics

1. Farber lipogranulomatosis is caused by homozygous or compound heterozygous mutation in the ASAHL gene that maps to chromosome 8p22
2. The protein encoded is acid ceramidase; inheritance is autosomal recessive
3. Acid ceramidase is also referred to as N-acylsphingosine amidohydrolase which catalyzes the synthesis and degradation of ceramide

Clinical Manifestations

1. There are 6 clinical subtypes
2. Patients with type 3 may live to the end of the second decade
3. Infantile form:
 - a. Onset is in the early months of life
 - b. Painful swelling of joints
 - c. Subcutaneous nodules over the affected joints
 - d. Hoarse cry (laryngeal involvement)
 - e. Feeding difficulty

- f. Irritability
- g. Hepatosplenomegaly in some patients
- h. Patients with type 2 and 3 have the longest survival
- i. Cognitive impairment is noted in the more severe patients
- j. Macular cherry red spot may be seen in some infantile patients

Neuropathology

1. Neuronal storage:
 - a. Swollen neurons and glia with non-sulfonated acid mucopolysaccharide
 - b. Brainstem
 - c. Basal ganglia
 - d. Anterior horn cells
 - e. Cortical neurons and those of the GI tract are involved to a lesser degree
2. Subcutaneous nodules
 - a. Formed by collections of foam cells
3. Zebra-like bodies are detected in neurons

Laboratory Evaluation

1. Molecular genetic analysis to identify the mutation in the *ASAHI* gene
2. Direct assay of skin fibroblasts demonstrates ceramidase deficiency
3. Lymph nodes demonstrate histiocytic infiltration that does not involve sinusoids which is typical for proliferative histiocytic disease

Wolman's Disease/Cholesteryl Ester Storage Disease

General Characteristics

1. Lysosomal acid lipase deficiency is caused by homozygous or compound heterozygous mutation of the *LIPA* gene that maps to chromosome 10q23.31
2. Inheritance is autosomal recessive
3. There are two phenotypes:
 - a. Wolman's disease
 - b. Cholesteryl ester storage disease (CESD)

Clinical Manifestations

1. Wolman's disease:
 - a. Diarrhea, vomiting, failure to thrive in infancy
 - b. Hepatosplenomegaly
 - c. Anemia and fever
 - d. Adrenal calcification
 - e. Death usually by 1 year

Neuropathology

1. Massive infiltration of the liver, spleen and other organs by:
 - a. Macrophages filled with cholesteryl esters and triglycerides
2. Less severe involvement of the skin, retina and CNS

Laboratory Evaluation

1. Foam cells occur in the bone marrow
2. Vacuolated lymphocytes in the peripheral blood
3. Diffuse punctuate calcification of the adrenal glands
4. Molecular genetic analysis to delineate the mutation in the *LIPA* gene
5. Enzyme activity can be quantified in cultured fibroblasts. It is reduced approximately 200 fold in Wolman's disease

Cholesteryl Ester Storage Disease

General Characteristics

1. CESD is caused by homozygous or compound heterozygous mutation in the lysosomal acid lipase gene (*LIPA*) that maps to chromosome 10q23.31. Inheritance is autosomal recessive
2. Primarily a visceral disease

Clinical Manifestations

1. Later onset than Wolman's disease
2. Wide phenotypic spectrum
3. Hepatitis-like illness
4. Pulmonary vascular obstruction in some patients
5. Atherosclerosis with cardiovascular complications
6. Liver disease:
 - a. Altered liver function with jaundice
 - b. Steatosis, fibrosis and cirrhosis
 - c. Secondary hypersplenism
 - d. Malabsorption

Neuropathology

1. Failure of intracellular hydrolysis of cholesteryl esters and triglycerides primarily in hepatocytes and macrophages that causes accumulation of these lipids in lysosomes
2. Some fibrillary gliosis of white matter, although the brain demonstrates no gross changes
3. Calcification of the deeper layer of the adrenal gland
4. Lipid-laden foamy cells of the mononuclear phagocyte system

Laboratory Evaluation

1. Molecular genetic analysis to demonstrate the mutation in the *LIPA* gene
2. Serum lipid profile:
 - a. High total serum concentrations of cholesterol
 - b. Increased serum low-density lipoprotein and triglycerides
 - c. Low serum concentration of high-density lipoprotein
3. Deficient LAL enzyme activity can be measured in peripheral blood leukocytes, fibroblasts and dried blood spots

Cystinosis

General Characteristics

1. Nephrotic cystinosis is caused by mutation in the cystinosis gene (*CTSN*) that maps to chromosome 17p13.2
2. It differs from other lysosomal diseases because acid hydrolysis is not a mechanism in the accumulation of cystine
3. The protein encoded is cystinosin, a cystine transporter

Clinical Manifestations

1. Infant nephropathic form:
 - a. Failure to thrive
 - b. Fanconi syndrome
 - c. Photophobia due to crystals within the conjunctiva and cornea
 - d. Depigmentation of the retina
 - i. Slight decrease in visual acuity
 - e. Fair complexion and light hair
 - f. Hypothyroidism by age 10
 - g. Many patients succumb in the first decade
2. Intermediate form:
 - a. Later onset of renal disease
 - b. Survival to age 30
3. Benign cystinosis:
 - a. No renal involvement
 - b. Corneal and retinal changes
4. Long term survivors (usually on dialysis)
 - a. Photophobia from both corneal and conjunctival deposition of cystine refractile material
 - b. Patchy retinopathy
 - c. Cognitive impairment
 - d. Myopathy (severe)
 - e. Oral motor dysfunction
 - f. Decreased tongue and lip strength; deficits in swallowing
 - g. Children with nephropathic cystinosis:
 - i. Inability to produce the normal amount of sweat:
 1. Heat intolerance
 2. Flushing
 3. Hyperthermia
 - h. Decreased pulmonary function at 21–40 years of age
 - i. CNS calcifications at 21–40 years of age
 - j. Retinal blindness, diabetes mellitus and hypogonadism between 18–40 years of age

Neuropathology

1. Cystinosis deficient proximal tubular epithelial cells have:
 - a. Abnormal shape and distribution of the endolysosomal compartments
 - b. Impaired endocytosis
 - c. Decreased surface expression of multiligand receptors
 - d. Delayed lysosomal cargo processing
2. Multifocal cystic neuronal and spongy change in the cerebrum (autopsy of a 28 year old)
3. Necrosis of the internal capsule and brachium pontis
4. Deposition of cystine crystals that is widespread and is mainly within the mononuclear phagocytic system

Laboratory Evaluation

1. Moderate to severe visual field constriction
2. Decreased rod-and-cone electroretinographic responses
3. Molecular genetic analysis to delineate the mutation in the CTNS gene

4. Increased concentration of free cystine in the leukocytes of patients
5. CT evaluation:
 - a. Cerebral atrophy

Differential Diagnosis of Lysosomal Storage Disease

Most of the lysosomal storage diseases have an adult form that will manifest seminal neurological features. They are rare and will be intermingled with other dementing illnesses that make their diagnosis difficult.

Outstanding neurological features that suggest these disorders are:

1. Facial dysmorphism
2. Corneal clouding
3. Cherry red spot in the retina
4. Spasticity
5. Skeletal dysplasia (dysostosis multiplex)
6. Myoclonic epilepsy
7. Adrenal dysfunction or calcification
8. Angiokeratoma
9. Cardiac valve dysfunction

GM1 gangliosidosis has the combination of dystonia, ataxia and spasticity. The adult form of GM2 (hexosaminidase A) deficiency presents as anterior horn cell disease. Behavioral and psychiatric episodes may be prominent. Niemann-Pick (sphingomyelinase) type C is striking due to the vertical gaze ophthalmoparesis that is seen. Gaucher's disease in adults is often suspected due to long bone changes, myoclonic epilepsy and bleeding. Metachromatic leukodystrophy should be suspected in an adolescent or young adult with psychiatric problems and spasticity.

Facial coarseness, corneal clouding, skeletal dysostosis with normal intelligence suggests Morquio, Schie or Maroteaux-Lamy disease. Deficiencies of neuraminidase (sialidosis I and II) are suggested by cherry red spot myoclonic epilepsy, cystic long bone changes, skeletal dysostosis and deafness. Galactosidases have myoclonic seizures and cherry red spots in the retina but angiokeratoma of the skin in addition. Abnormal joint mobility with corneal clouding, suggest mucopolidosis II and III. Angiokeratoma of the skin are distinctive and are seen in fucosidosis, sialidosis, galactosialidosis, and alpha-N-acetylglucosaminidase deficiency. Fabry's disease is the most commonly encountered disorder with this physical finding and demonstrates angiokeratoma in the bathing suit distribution. A common early complaint of these patients is burning hands and feet from small fiber neuropathy. They are heat sensitive due to hypohidrosis. Strokes at an early age and renal involvement are prominent.

The mucosulfatidoses have ichthyosis, retinitis pigmentosa, and corneal clouding.

Wolman's disease (patients die by one year most often) and cholesteryl ester storage disease are associated with calcification of the adrenal glands. The latter is also associated with accelerated atherosclerosis.

Adult Krabbe's disease has the unusual combination of spasticity and features of a demyelinating neuropathy with MRI involvement of the parietal lobe.

Kufs disease (neural ceroid lipofuscinosis) is suspected in a middle-aged patient with myoclonic epilepsy, dementia, and ataxia.

Differential Diagnosis of Lysosomal Storage Disorders Presenting as an Adult or Persisting into Adulthood

1. Metachromatic leukodystrophy
2. Krabbe's disease
3. Fabry's disease
4. Niemann-Pick disease
5. GM1 (gangliosidosis)
6. GM2 (gangliosidosis)
7. Gaucher's disease
8. Mucopolysaccharidoses
9. Salla disease
10. Cholesteryl ester storage disease

Peroxisomal Disorders

Overview

Peroxisomes are oxidative organelles found in the cytoplasm in most mammalian cells. They utilize molecular oxygen in oxidative reactions that generates hydrogen peroxide. They contain peroxidase (catalase) which, in conjunction with H₂O₂, oxidizes substrates.

Peroxisomal enzymes catalyze anabolic and catabolic reactions that include:

1. Plasmalogen synthesis, which are the most abundant phospholipids in myelin
2. Beta oxidation of very long chain fatty acids (VLCFA), the products of which are used in the biosynthesis of cholesterol and bile acids
3. Glyoxylate transamination
4. Pipecolic acid oxidation
5. Glutamic acid oxidation
6. Phytanic acid α -oxidation
7. Dolichol synthesis
8. Alcohol dehydrogenase

The peroxisome consists of a single membrane that encloses its matrix. It is a lipid bilayer with embedded peroxisome membrane proteins. The peroxisomal membrane proteins and matrix enzymes are encoded by nuclear genes that are synthesized and then imported into the peroxisome. Peroxisomal proteins involved in biogenesis are called peroxins and are encoded by PEX genes. The peroxisomal disorders are caused by:

1. Single enzyme deficiency
2. Biogenic disorders (defects in their assembly) PBDs

The peroxisomal biogenetic disorders (PBD) are associated with deficiencies of multiple peroxisomal enzymes and often

a decrease of peroxisomal number. Most peroxisomal disorders are associated with migration deficits, myelin alterations and neuronal degeneration. The non-neurological abnormalities are dysmorphisms, liver dysfunction and skeletal deficits. Laboratory diagnostic features are elevated VLCFAs and decreased RBC plasmalogens. The only peroxisomal disorder that does not have autosomal recessive inheritance is X-linked adrenoleukodystrophy.

Several mutations of each gene may occur and mutations of different genes may cause a similar phenotype.

Peroxisome Single Enzyme Defects of Adolescence and Adulthood

X-linked Adrenoleukodystrophy

General Characteristics

1. X-linked adrenoleukodystrophy is caused by mutation in the ABCD1 gene that maps to chromosome Xq28
2. The ABCD1 gene encodes the peroxisomal transporter ATP-binding cassette subfamily D member 1
 - a. The transporter imports very long chain fatty acid (VLCFA) esters across the peroxisomal membrane. Mutation of the ABCD1 gene impairs VLCFA degradation with their consequent accumulation in different lipids and body tissues
3. Approximately 95% of patients inherit the ABCD1 pathogenic variant from one parent while 4% of patients have a de novo mutation
4. Affected male patients transmit the disorder to all of their daughters and none of their sons. Females who inherit the pathologic variant are carriers and usually are only mildly affected. Males that inherit the mutated gene are affected
5. The three major phenotypes in affected males are:
 - a. Childhood cerebral form
 - b. Adrenal myeloneuropathy
 - c. Addison's disease (in isolation)
6. Subtypes occur within families and within kindreds
7. Manifesting female carriers occur in approximately 20% of patients (carriers)

Clinical Manifestations

1. Childhood cerebral form:
 - a. Onset between four and eight years of age
 - b. Progressive cognitive impairment
 - c. Attention deficit hyperactivity symptoms
 - d. Decreased vision, hearing and motor abilities
 - e. Severe disability within two years
2. Adolescent form:
 - a. Onset from 11–21 years of age
 - b. Dementia
 - c. Hearing loss
 - d. Visual deficits
 - e. Pyramidal tract signs and symptoms
 - f. Extrapyrmidal dysfunction
 - g. Cerebellar signs

- h. Adrenal insufficiency manifested by:
 - i. Increased pigmentation
 - ii. Episodic vomiting and diarrhea
 - iii. Hypotension
 - iv. Severe weakness and fatigue
- 3. Adult cerebral type:
 - a. Schizophrenia-like symptoms
 - b. Dementia
 - c. Spasticity
 - d. Aphasia
 - e. Auditory and visual deficits
 - f. Patients may or may not have adrenal insufficiency
- 4. Adrenal insufficiency without neurologic symptoms:
 - a. Patients have a high risk of late neurologic disease
 - b. Oldest patient described with Addison's disease is 78
- 5. Asymptomatic carriers of the genetic deficit with elevated VLCFA:
 - a. High risk of later neurologic symptoms and signs
 - b. Oldest patients are males between 60–70 years of age
- 6. Adrenoleukodystrophy female heterozygotes:
 - a. Female carriers of the gene defect may develop neurologic symptoms
 - b. Non-random X-chromosome inactivation that favors expression of the mutant allele is the postulated mechanism
 - c. The usual phenotype is that of adrenomyeloneuropathy (AMN)
 - d. Onset is in the fourth decade
 - e. Mild signs
 - f. Slowly progressive course

Adrenomyeloneuropathy

General Characteristics

1. Affects approximately 40–45% of patients with X-linked adrenoleukodystrophy

Clinical Manifestations

1. Onset is between 20–40 years of age
2. Slowly progressive
3. Approximately 50% of patients have cerebral involvement
4. Often presents with clumsiness and leg stiffness
5. Spastic paraplegia
6. Impotence and incontinence
7. Sparing of the upper arms
8. Adrenal insufficiency occurs in 60–70% of patients
9. Adrenal symptoms may precede neurological signs and symptoms
10. In 10–20% of patients brain involvement is rapidly progressive that causes severe behavioral disorders and cognitive impairment

Isolated Addison's Disease

General Characteristics

1. Affects approximately 10% of X-linked ALD

Clinical Manifestations

1. Males may present with signs of adrenal insufficiency from age 2 years to adulthood. The most common age at presentation is 7.5 years
2. Most often patients present with vomiting and/or severe weakness. Occasionally the presentation is coma
3. There is variable hyperpigmentation of the skin (particularly skin creases and scars)
4. Males whose initial presentation is adrenal insufficiency develop signs of AMN by middle age
5. Adrenal function is abnormal in approximately 90% of symptomatic boys and 70% of men with AMN
6. Adrenal function is usually normal in female carriers

Variable Presentations with X-Linked Adrenoleukodystrophy

General Characteristics

1. Unusual presentations are seen in approximately 5–10% of patients with X-linked adrenoleukodystrophy

Clinical Manifestations

1. Age four to 10 years but occasionally in adolescents and adults:
 - a. Headache
 - b. Increased intracranial pressure (pseudotumor cerebri)
 - c. Hemiparesis
 - d. Visual field deficits
 - e. Aphasia
 - f. Focal neurological deficits
2. Adult patients:
 - a. Progressive behavioral disorder
 - b. Dementia with spastic paraparesis
 - c. Neurogenic bladder
 - d. Gastrointestinal dysmotility
 - e. Progressive incoordination and ataxia
 - f. Impotence without associated other neurologic or endocrine deficits; usually in at risk males with a positive family history
 - g. No neurologic or endocrine dysfunction
 - h. Cerebellobrainstem dominant form of X-linked ALD
 - i. Presentation is characteristic of multiple system atrophy
3. The Zellweger spectrum is the most severe part of the X-linked ALD clinical spectrum and is composed of:
 - a. Zellweger cerebrohepatorenal syndrome (ZS)
 - b. Neonatal adrenoleukodystrophy (NALD)
 - c. Infantile Refsum's disease
4. These entities are due to mutations of PEX genes that cause abnormalities of peroxisome biogenesis

Pathology of X-Linked ALD

1. Diffuse myelin loss, lipid laden histiocytes and perivascular lymphocytic infiltrates
2. VLCFA accumulation has been postulated to activate microglia which enhance inflammatory demyelination
3. Cellular inclusions are trilamellar membranes that contain VLCFA cholesterol esters

4. A caudal rostral progression of the leukodystrophy
5. The occipital parietal and temporal lobes are most severely involved
6. Bilateral symmetrical lesions
7. Severe demyelination of:
 - a. Optic nerves
 - b. Fornix
 - c. Hippocampal commissure
 - d. Posterior cingulum
 - e. Corpus callosum
 - f. Internal capsule
 - g. Partial sparing of the subcortical arcuate fibers
8. The brainstem and spinal cord are less affected:
 - a. Involvement of descending tracts only
9. Neuropathology of AMN:
 - a. Brainstem (minimally involved)
 - b. Cerebellum (moderate involvement)
 - c. Lumbar corticospinal tracts (demyelinated)
 - d. Cervical fasciculus opacities
 - e. Dorsal spinocerebellar tracts (demyelinated)
 - f. Advancing demyelination
 - i. Axons are spared
 - ii. PAS-positive macrophages
 - g. Peripheral nerves:
 - i. Loss of large and small diameter fibers
 - h. Adrenal glands are atrophic
 - i. Electron microscopy:
 - i. Trilaminar bodies
 - ii. These inclusions may also be found in nerves, conjunctiva and skin

Laboratory Evaluation

1. Molecular genetic analysis to detect the hemizygous ABCD1 pathogenic variant
2. The plasma concentration of very long chain fatty acids (VLCFA) is abnormal in males with X-linked ALD
 - a. The parameters that are analyzed are:
 - i. Concentration of C26:0 fatty acids
 - ii. Ratio of C24:0 to C22:0 fatty acids
 - iii. Ratio of C26:0 to C22:0 fatty acids

Neuroimaging

1. MRI:
 - a. Symmetric enhanced T2 signal in the parieto-occipital area with contrast enhancement at the margin in approximately 86% of patients
 - b. The corpus callosum is involved
 - c. Minimal if any involvement of the arcuate fibers
 - d. Primarily posterior involvement of the cerebrum

Unusual Leukodystrophies That May Be Seen in Adulthood with Dementia

Pelizaeus-Merzbacher Disease (PMD)

General Characteristics

1. PMD is caused by mutation in the PLP1 gene that maps to chromosome Xq22

2. The gene encodes proteolipid protein-1
3. There is wide genetic heterogeneity in the hypomyelinating leukodystrophies (> than 12 delineated genes at present)
4. There are 3 types of PMD:
 - a. A classic infantile form:
 - i. Onset in infancy and death in late adolescence or early adulthood
 - b. Connatal type
 - i. Fatal in infancy or childhood
 - c. Transitional type
 - i. Intermediate in severity

Clinical Manifestations

1. Onset of nystagmus in infancy (horizontal with a torsional rotary component)
2. Stridor early in life (some patients)
3. Developmental delay
4. Ataxia
5. Seizures (some patients)
6. Optic atrophy by age 5 (some patients)
7. Death may occur at any age up to the fifth decade
8. Heterozygous females may be symptomatic

Neuropathology

1. Various proteolipid protein 1 mutations that include duplications, point mutations and deletions cause oligodendrocytic dysfunction that underlies PMD
2. The phenotypic spectrum is determined by the type of proteolipid mutation. Duplications usually have a milder classic form compared with missense mutations associated with the connatal type
3. The greatest risk in females is with nonsense or null mutations
4. Atrophic brain
5. Cerebellar atrophy
6. Loss of myelin with a tigroid pattern of residual myelin
7. Decreased numbers of oligodendroglia
8. Increased astrocytes

Laboratory Evaluation

1. Abnormal brainstem auditory potentials
2. Molecular genetic analysis to delineate the mutation of the PLP1 gene

Neuroimaging

1. MRI:
 - a. Macrogyria
 - b. Lack of myelination
 - c. Iron deposition in the basal ganglia
 - d. Brain and cerebellar atrophy
2. Magnetic resonance spectroscopy
 - a. Increased concentrations of N-acetyl-aspartate
 - b. N-acetylaspartylglutamate, glutamine, myoinositol, creatine and phosphocreatine in affected white matter

3. Decreased choline-containing compounds
4. The white matter analysis is consistent with:
 - a. Increased neuroaxonal dystrophy
 - b. Astrogliosis
 - c. Decreased oligodendroglia
 - d. Hypomyelination
5. MRI of obligate carriers:
 - a. Periventricular and subcortical white matter hyperintensities

Pelizaeus-Merzbacher-Like Disease (PMLD)

General Characteristics

1. PMD-like disease is caused by homozygous or compound heterozygous mutation of the GJC2 gene that maps to chromosome 1q42.13
2. The gene encodes the gap function protein connexin 47 (CX47)
3. Inheritance is autosomal recessive
4. The protein is highly expressed in oligodendrocytes

Clinical Manifestations

1. Nystagmus
2. Developmental delay
3. Progressive spasticity
4. Ataxia
5. A CJC2 missense mutation causes a milder phenotype
 - a. AR spastic paraplegia type 44
6. Usually less cognitive and motor deficits than classic PMD although one variant is very severe and resembles congenital PMD

Neuropathology

1. Similar to PMD

Laboratory Evaluation (GJC2 Mutation)

1. Brainstem auditory evoked potentials deficits are less severe than in patients with classic PMD
2. Waves III, IV and V (generated in the pons and midbrain) are recordable in PMD-like disease but are usually absent in PMD
3. Delay in visual and somatosensory evoked potential conduction
4. Mild peripheral nerve conduction delay in some patients with PMD-like disorder and is normal in classic PMD
5. Molecular genetic analysis to delineate the mutation in the GJC2 gene

Neuroimaging

1. MRI
 - a. Similar to classic PMD

Alexander's Disease

General Characteristics

1. Alexander's disease is caused by heterozygous mutation in the gene GFAP that maps to chromosome 17q21.31
2. The gene encodes fibrillary acidic protein

3. There are infantile, juvenile and adult forms of the disease
4. Inheritance is autosomal dominant

Clinical Manifestations

1. Infant form:
 - a. Megalencephaly
 - b. Failure to thrive
 - c. Developmental delay
 - d. Seizures
 - e. Ataxia
2. Juvenile form:
 - a. A phenotypic spectrum
 - b. Some patients are asymptomatic
 - c. Onset between 5 and 9 years of age
 - d. Linear growth failure
 - e. Excessive sleepiness
 - f. Vomiting
 - g. Bulbar or pseudobulbar signs
 - h. Spasticity
 - i. Cognitive impairment
 - j. Megalencephaly
 - k. Seizure
 - l. Ataxia
3. Adult form:
 - a. Onset is in the third and fourth decade
 - b. Varied phenotype
 - c. Sleep disturbance (since childhood)
 - d. Dysautonomia
 - e. Bulbar signs
 - f. Brainstem cranial nerve dysfunction
 - g. Cognitive impairment
 - h. Ataxia
 - i. No macrocephaly
 - j. One reported kindred:
 - i. Progressive kyphosis
 - ii. Short neck
 - iii. High-arched palate
 - k. Focal brainstem involvement (some patients)
 - l. Palatal myoclonus

Neuropathology

1. Histologic findings:
 - a. Rosenthal fibers (elongated tapered rods that may be 30 microns in length) that are diffusely scattered throughout the cortex and white matter
 - b. Rosenthal fibers are:
 - i. Subpial
 - ii. Around blood vessels
 - iii. Subependymal areas
 - iv. Contain GFAP and alpha-beta-crystalline
 - v. Primarily located in astrocytes
2. Demyelination (rarefaction)
3. Hydrocephalus (some patients)
4. Differential diagnosis of Rosenthal fibers
 - a. Astrocytoma
 - b. Optic nerve glioma
 - c. Chronic reactive gliosis

Neuroimaging**1. MRI:**

- a. Extensive symmetric white matter hyperintensities that are predominantly in the frontal lobe
2. Basal ganglia and thalamic signal abnormalities
3. Brainstem lesions with atrophy
4. Lesions may enhance
5. Atypical MRI evaluation:
 - a. Predominantly posterior fossa lesions
 - b. Tumor-like brainstem lesions
 - c. Asymmetric frontal lobe involvement
 - d. Basal ganglia lesions
 - e. Predominant atrophy and signal changes in the medulla and spinal cord

Laboratory Evaluation

1. Molecular genetic analysis to delineate the mutation in the GFAP gene

Hereditary Diffuse Leukoencephalopathy with Spheroids (HDLS)**General Characteristics**

1. HDLS is due to mutations in the colony-stimulating factor-1 receptor gene (CSF-1R) that maps to chromosome 5q32
2. Missense and splice site mutations have been delineated in the tyrosine kinase domain
3. A frameshift mutation that causes nonsense-mediated mRNA decay has been described

Clinical Manifestations

1. Approximately 22% of patients are of Japanese ethnicity
2. Mean age of onset is 45 years (range 18 to 78 years)
3. Cognitive decline
4. Behavioral disorders
5. Pyramidal signs
6. Parkinsonism
7. Seizures
8. Ataxia (rare)

Neuropathology

1. Loss of myelin and microglial activation
2. Macrophage infiltration of the parenchyma
3. Axonal swellings and spheroids

Laboratory Evaluation

1. Electron microscopy:
 - a. Axonal swelling in the CNS and skin nerves
 - b. Pigment containing macrophages
2. Molecular genetic analysis to delineate the mutation in the CSF-1R gene

Neuroimaging**1. MRI:**

- a. Bilateral confluent white matter hyperintense signal on T2-weighted sequences in the cerebrum

Adult-Onset Autosomal Dominant Leukodystrophy (ADLD)**General Characteristics**

1. ADLD is caused by heterozygous tandem genomic duplication that causes an extra copy of the lamin B1 gene that maps to chromosome 5q23.2

Clinical Manifestations

1. Onset in the 5th and 6th decades
2. Cognitive impairment is usually mild
3. Autonomic failure is often a presenting feature and includes:
 - a. Postural hypotension
 - b. Neurogenic bladder
 - c. Impotence
 - d. Rectal incontinence
 - e. Heat intolerance (some patients)
4. Spasticity
5. Ataxia (cerebellar type)
6. Clinical exacerbation often triggered by mild head trauma or viral infection
7. Personality change and depression
8. Ataxic gait
9. REM sleep behavior disorder (one patient)
10. Autonomic dysfunction that either precedes or is concomitant with gait and coordinative deficits
11. Motor deficits ascend from spastic paraplegia to tetraplegia and pseudobulbar palsy by the seventh decade

Neuropathology

1. Frontal and parietal lobes are preferentially affected
2. Demyelination occurs from the lateral margins of the corpus callosum that diminishes in severity to the occipital lobes
3. Vacuolar changes in the white matter
4. U-fibers are not affected

Neuroimaging**1. MRI:**

- a. MRI alterations of the brain and spinal cord may precede clinical symptoms
- b. Symmetric atrophy of the white matter of the frontal lobes, centrum semiovale and cerebellum
- c. Spared U-fibers and optic radiations
- d. Spinal cord involvement best appreciated on T2-weighted transverse sequences

Vanishing White Matter Disease**General Characteristics**

1. Leukoencephalopathy with vanishing white matter is caused by homozygous or compound heterozygous mutations in any of 5 genes that encode subunits of the translation initiation factor gene EIF2B that maps to:

- a. E1F2B1 – chromosome 12q24
- b. E1F2B2 – chromosome 14q24
- c. E1F2B3 – chromosome 1p34
- d. E1F2B4 – chromosome 2p23
- e. E1F2B5 – chromosome 3q27
2. The adult form of the disease is due to mutation in E1F2B3
3. Inheritance is autosomal recessive

Clinical Manifestations

1. Classic phenotype:
 - a. Onset is between 1 and 5 years of life
 - b. Cerebellar ataxia
 - c. Spasticity
 - d. Slowly progressive course
 - e. Neurologic deterioration may be exacerbated by fever, infection, mild head trauma
2. Adult onset type:
 - a. A milder and insidious cause
 - b. Behavior disorders
 - c. Dementia
 - d. Seizures
 - e. Complicated migraine
 - f. Less frequent stress-related neurological deterioration
 - g. Ovarian failure is common and may precede neurological signs and symptoms
 - h. Female mutation carriers may manifest ovarian failure by primary or secondary amenorrhea associated with elevated gonadotropin levels at less than 40 years of age
 - i. Spastic paraparesis
 - j. Optic atrophy (some patients)

Neuropathology

1. Cystic degeneration of cerebral white matter with reactive changes
2. Primary axonopathy rather than demyelination
3. Hypomyelination, demyelination and gliosis
4. Decreased quantity of myelin specific proteins and lipids

Laboratory Evaluation

1. Molecular genetic analysis to delineate the mutation in the E1F2B gene subunit

Neuroimaging

1. MRI:
 - a. Symmetric involvement of cerebral hemispheric white matter
 - b. Some component of the white matter has a signal intensity similar to CSF on proton-density, T2 and T1-weighted sequences
 - c. Mild to severe vermian atrophy
2. MRS (magnetic resonance spectroscopy):
 - a. Decrease of all normal signals
 - b. Presence of lactate and glucose

Vascular Leukoencephalopathy Mapping to Chromosome 20q13

General Characteristics

1. This vasculopathy has been investigated in two sisters and 21 members of their kindred
2. The causative gene has been mapped to chromosome 20q13

Clinical Manifestations (5 Patients)

1. Gait disturbance
2. Transient movement disorders
3. Cognitive impairment
4. Stroke

Neuropathology

1. Cerebral arteriopathy that affects preterminal arterioles

Neuroimaging

1. MRI:
 - a. Symmetric white matter hyperintensities that increased with age

Differential Diagnosis of Adult-Onset Genetic Leukoencephalopathies

1. Vascular forms:
 - a. CADASIL
 - b. CARASIL
 - c. COL4A1
 - d. Retinal vasculopathy with cerebral leukodystrophy (RVCL)
 - e. Polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOS)
 - f. Cerebroretinal microangiopathy with cysts and calcifications (CRMCC); primarily infantile onset with vascular based myelin damage
2. Autosomal dominant forms of adult-onset leukoencephalopathy:
 - a. Hereditary diffuse leukoencephalopathy with spheroids (HDLS)
 - b. Autosomal dominant adult-onset leukoencephalopathy (ALDL)
 - c. CADASIL
 - d. Alexander's disease
3. Autosomal recessive forms of adult-onset leukoencephalopathy:
 - a. CARASIL
 - b. Vanishing white matter (VWM) with leukoencephalopathy
 - c. Nasu-Hakola disease
 - d. Metachromatic leukodystrophy
4. X-chromosome-linked disorders
 - a. Fragile X-associated tremor and ataxia syndrome (FXTAS)
 - b. Adrenoleukodystrophy

Differential Diagnosis of Genetic Inborn Errors of Metabolism That Present into Adulthood and May Manifest Cognitive Impairment

1. Lysosomal disorders:
 - a. Metachromatic leukodystrophy
 - b. Krabbe's disease
 - c. Fabry's disease
 - d. Niemann-Pick disease
 - e. GM1 gangliosidosis
 - f. GM2 gangliosidosis
 - g. Gaucher's disease
 - h. Mucopolysaccharidoses
 - i. Salla disease
2. Peroxisomal disorders
 - a. Adrenoleukodystrophy
 - b. Adrenomyeloneuropathy
3. Mitochondrial disorders:
 - a. MELAS
 - b. MERRF
 - c. Leigh's syndrome
 - d. PEO
 - e. MNGIE
 - f. Kearns-Sayre syndrome
 - g. POLG
 - h. Diabetes with deafness
4. Urea cycle disorders
5. Organic acidemias:
 - a. Phenylketonuria
 - b. Methylmalonic acidemia
 - c. Propionic acidemia
 - d. 3-methylglutaconic aciduria
 - e. 2-hydroxyglutaric aciduria
6. Cytoskeletal or transporter molecular defects
 - a. Alexander's disease
 - b. Pelizaeus-Merzbacher disease
 - c. Wilson's disease
 - d. Huntington's disease
7. Disorders of iron accumulation
8. Unusual and rare disorders:
 - a. Megalencephalic leukoencephalopathy with subcortical cysts (Van der Knaap disease)
 - b. Polymerase-III gene defect ("4H syndrome")
 - c. Childhood ataxia with central nervous system hypomyelination (vanishing white matter disease)
 - d. Cockayne syndrome

Toxic and Physical Disorders with Dementia

General Characteristics

1. Aluminum toxicity usually seen in patients with impaired renal function

Clinical Manifestations

1. No longer thought to be significant in Alzheimer's disease
2. Dialysis encephalopathy:
 - a. Possibly associated with osteomalacia

- b. An increased concentration of aluminum has been documented in hemodialysis patients from hemodialysis solutions with high levels of aluminum

Neuropathology

1. Mechanism of action:
 - a. Increases oxidative stress
 - b. Increases the phosphorylation of heavy and medium neurofilament subunits
 - c. Induces cross linking between neurofilaments
 - d. Posited inhibition of enzyme activity and decreased protein synthesis

Laboratory Evaluation

1. Aluminum brain concentration should be lower than 2 ug/g
2. Secondary hyperparathyroidism
3. Anemia
4. Aluminum in the bone marrow confirms the diagnosis

Alcohol and Dementia

General Characteristics

1. There has been a reported increase rate of alcohol abuse in older people and increased consumption in women
2. There are two main forms of alcohol-associated cognitive disorders
 - a. Alcohol-related dementia (ARD)
 - b. Alcohol-induced persisting amnesic syndrome (Wernicke-Korsakoff syndrome)
3. Neuropathological and neuroimaging studies demonstrate that excessive and prolonged alcohol abuse leads to structural and functional brain damage
4. The controversy has been: is there a direct alcohol-induced dementia or is it the associated thiamine deficiency or other nutritional deficiencies
5. Alcohol-related dementia patients:
 - a. Most often are male
 - b. Have comorbid mental and medical complications such as liver and gastrointestinal disorders
 - c. Diagnosed often by hospital admissions
 - d. Are socially isolated and unmarried
6. Wernicke-Korsakoff patients (WKS):
 - a. Most patients have alcohol abuse difficulties but there are multiple non-alcohol medical causes
 - b. Prevalence rates are between 1–2% (post-mortem studies) of the general population and approximately 10% of severe alcohol abuse patients in Western countries

Clinical Manifestations

1. Alcohol-related dementia
 - a. Direct intoxication:
 - i. Impairs almost all cognitive function
 - ii. Alcohol in excess often leads to stupor and respiratory depression
 - b. Acute withdrawal in severe alcohol abuse patients causes:

- i. Tremor
- ii. Hallucinations (small green insects)
- iii. Seizures
- iv. Severe agitation, paranoia and fear
- v. Fluctuating levels of consciousness
- vi. In a setting of severe autonomic dysregulation
- c. Neuropsychological evaluation:
 - i. Language is spared (as opposed to many other forms of dementia)
 - ii. Some deficits on semantic tasks that include:
 - 1. Confrontational naming
 - 2. Category fluency
 - 3. General knowledge
 - 4. Verbal recognition
 - 5. Delayed recall
 - iii. Deficits in visuospatial tasks:
 - 1. Decreased working memory, executive function and motor speed
 - 2. Clinical profile supports both cortical and sub-cortical deficits
- 2. Other non-alcoholic causes of WKS include:
 - a. Starvation diets
 - b. Prolonged IV treatment without thiamine supplementation
 - c. HIV (AIDS)
 - d. Gastric stapling
 - e. Renal dialysis
 - f. Prolonged vomiting

Neuropsychology of Wernicke-Korsakoff Syndrome

- 1. Profound anterograde amnesia
- 2. Impaired recall (better for remote time period events)
- 3. Implicit and procedural memory are more intact
- 4. Impaired executive function
- 5. Visuospatial deficits
- 6. Decreased working memory

Classic Wernicke-Korsakoff Syndrome

- 1. Ophthalmoplegia
- 2. Nystagmus
- 3. Ataxia
- 4. Encephalopathy

Core Clinical Manifestations of Korsakoff's Psychosis

- 1. Amnesic state
- 2. Deficits in memory:
 - a. Anterograde episodic memory deficit
 - b. Normal semantic memory
 - c. Relatively intact non-declarative memory
 - d. Normal intelligence and implicit and procedural memory
 - e. Retrograde amnesia may be severe (years or decades)
 - f. Confabulation (minority of patients)

Neuropathology

- 1. Alcohol-related dementia:

- a. Approximately 80% of patients with chronic alcoholism have some degree of brain pathology
- b. White matter loss occurs in the:
 - i. Prefrontal cortex
 - ii. Corpus callosum
 - iii. Cerebellum
- c. Neuronal Loss:
 - i. Superior frontal association cortex
 - ii. Hypothalamus
 - iii. Cerebellum (particularly the anterior vermis)
- d. Partial recovery of white matter deficits can occur with abstinence that correlates with clinical improvement
- e. Although controversial, lesions of the mammillothalamic tract and the mediodorsal thalamic nuclei are most closely correlated with the memory deficit (evidence from thalamic infarction primarily)
- f. Possible mechanisms of neuronal degeneration include:
 - i. Glutamate excitotoxicity
 - ii. Oxidative stress
 - iii. Decreased neurogenesis
 - iv. Possibly associated with thiamine deficiency
 - v. Pathology of Wernicke's encephalopathy
 - 1. Neuronal loss and hemorrhagic lesions in the mammillary bodies, paraventricular and periaqueductal gray matter
 - 2. Wernicke's encephalopathy can include Korsakoff's syndrome if there is concomitant thalamic and hippocampal circuit disruption
 - 3. Korsakoff's psychosis
 - a. The medial dorsal nucleus is severely affected: subnucleus > lateral dorsal > medial pulvinar

Neuroimaging

- 1. MRI:
 - a. Structural changes, volume loss of frontal association areas
 - b. Small mammillary bodies (loss of signal T1 and T2) weighted sequences due to paramagnetic effects due to hemosiderin
 - c. Anterior vermian loss (lingua, culmen, and centralis lobules)
 - d. Frontal lobe volume loss
 - e. Functional MRI: (Patient with WK)
 - i. No hippocampal activation during encoding or recognition memory tasks
 - ii. Decreased activation of the ventrolateral prefrontal cortex
 - f. Elevated serum transketolase

Marchiafava-Bignami Disease

General Characteristics

- 1. Marchiafava-Bignami disease is most often associated with chronic severe alcohol abuse. It can occur in the absence of alcohol particularly in malnourished patients

Clinical Manifestations

1. Acute:
 - a. Seizures
 - b. Disorder of consciousness
2. Chronic:
 - a. Progressive dementia
 - b. Interhemispheric disconnection syndrome

Neuropathology

1. Necrotizing and cystic lesions of
 - a. Corpus callosum
 - b. Optic chiasm
 - c. Centrum semiovale
 - d. Middle cerebellar peduncle
 - e. Demyelination with axonal sparing
2. Other diseases that cause similar findings include:
 - a. Cyanide poisoning
 - b. Sepsis
 - c. Malnutrition and vitamin B deficiency
 - d. Sickle cell disease
 - e. Plasmodium infection

Neuroimaging

1. MRI:
 - a. Hyperintensity of the corpus callosum on FLAIR sequences
 - b. Frontal white matter may be concomitantly involved
 - c. Positive lesions demonstrated by diffusion-weighted-imaging
 - d. Atrophic corpus callosum in the chronic state; bleeding may occur in the subacute state
 - e. Extracallosal lesions occur in:
 - i. Frontal cortex
 - ii. White matter
 - iii. Putamen

Methyl Alcohol Poisoning*General Characteristics*

1. Methanol is a component of household products that include:
 - a. Paint remover
 - b. Windshield washer fluid
 - c. The usual patient exposure follows ingestion by alcoholics who filter it through various substances
 - d. Methanol is metabolized to formic acid

Clinical Manifestations

1. Acute intoxication:
 - a. Formic acid is six times more toxic than methanol
 - b. Symptoms usually begin within 30 minutes but occasionally they are delayed up to a day
 - c. Systemic symptoms:
 - i. Nausea and vomiting
 - ii. Headache

- iii. Abdominal pain
- iv. Dyspnea and cyanosis
- d. Neurologic signs and symptoms:
 - i. Edema of the optic discs (bloody)
 - ii. Loss of visual acuity
- iii. Acute coma
- iv. Parkinsonism (survivors)
- v. Dementia (survivors)
- vi. Focal neurologic signs from bilateral putaminal hemorrhage

Neuropathology

1. Edema and petechial hemorrhage throughout the brain
2. Loss of retinal ganglia cells
3. Hemorrhagic necrosis and hemorrhagic leukoencephalopathy
4. Bilateral necrosis of the putamen with cystic change
5. Gliosis and axon loss of the optic nerves
6. Bilateral necrosis of the putamen may also be seen in:
 - a. Carbon monoxide poisoning
 - b. Ethylene glycol poisoning (antifreeze; eluted from car radiators utilized during the manufacture of "moon shine")

Neuroimaging

1. MRI:
 - a. Swollen optic discs with bilateral putaminal and/or other brain hemorrhage
 - b. Severe metabolic acidosis with large anion gap
 - c. Serum drug level of methanol
 - i. <20 mg/dl may cause severe poisoning
 - ii. 8 g (10 ml, 10%) and 10 g (30 ml, 40%) of washer fluid may cause blindness and death

Volatile Solvents or Drugs of Abuse with Consequent Cognitive Impairment*General Characteristics*

1. Volatile solvents that are components of fuels, paints and thinners have worldwide usage and are often inhaled in high concentrations to produce an altered mental status
2. Solvents have an effect on channels and neural circuits that are involved in reward and cognition
3. Classification of abused solvents
 - a. Aromatic hydrocarbons
 - i. Industrial uses:
 1. Adhesives
 2. Spray paint
 3. Paint thinner
 4. Leather tanning
 5. Some disinfectants
 6. Petroleum
 7. Cleaner
 8. Octane booster
 - ii. Halocarbons:

1. Trichloroethylene (TCY):
 - a. Degreasing agent
 - b. Coffee decaffeination
 2. 1,1,1 Trichloroethylene (TCE):
 - a. Film cleaner
 - b. Correction fluid
 3. Tetrachloroethylene (PERC):
 - a. Dry Cleaning
 - b. Degreasing
 4. n-Propyl Bromide (NPB):
 - a. Metal cleaner
 - b. Adhesive
 - iii. Aliphatic
 1. Propane
 2. Domestic and industrial fuel
 - iv. Hydrocarbons
 1. Butane
 - a. Lighter fluid
 2. n-Hexane
 - a. Adhesive
 3. Iso-octane
 - a. Automotive fuel
 4. Chemical properties
 - a. Low vapor pressure and high volatility at room temperature that encourages their use as a euphorogenic inhaled agent:
 - i. Nitrous oxide:
 1. An adjunct anesthetic to promote relaxation
 2. Is utilized in aerosol propellants
 3. Street name is "laughing gas" or "whippets"
 - ii. Mechanism of action
 1. Increased GABA-ergic and opioidergic transmission
 2. Inhibition of NMDA glutamate receptors
 3. Possible nitric oxide-like actions
 - iii. Alkyl nitrites
 1. Street name is "poppers"
 2. String vasodilators most commonly used for ischemic heart disease
 3. Epidemiology
 - a. Volatile solvents are a major source of abuse and are the most commonly used class of abused inhalants
 - b. The majority of solvents contain a mixture of chemical volatile agents
 - c. Toluene is the dominant chemical in glues and paint thinners, is popular and is strongly psychoactive
 4. These agents have a major effect on the mesocortical and mesolimbic systems
3. Approximately 11% of chronic users demonstrate signs of withdrawal with cessation of use
4. Most patients report euphoria or "drunkenness" feelings with use, drug seeking as well as craving and restlessness
5. Psychotic symptoms with use include:
 - a. Emotional volatility
 - b. Hallucinations
 - c. Delusions
6. Cognitive impairment occurs with chronic use and includes
 - a. Loss of short term memory
 - b. Attention deficits
 - c. Response inhibition
 - d. Executive function
 - e. Comorbidity with:
 - i. Mood disorders
 - ii. Major depression
 - iii. Antisocial personality disorder
 - f. Dementia
 - g. Long term toluene abuse symptoms and signs include:
 - i. Cognitive impairment
 - ii. Short term memory loss
 - iii. Ataxia
 - iv. Nystagmus
 - v. Tremor
 - vi. Hearing loss that is also seen with styrene and trichloroethylene (often associated with Vth nerve involvement concomitantly)
 - h. A common mixture of abused solvents include
 - i. Toluene
 - ii. Styrene
 - iii. Trichloroethylene
 - iv. Xylene
 - i. Cognitive impairment and dementia may precede other neurological signs

Neuropathology

1. Loss of white matter throughout the brain
2. It is estimated that approximately 3% of the vapor concentration reaches the brain, the majority is excreted through the lungs or is metabolized
3. Cerebral atrophy
4. Ventricular enlargement
5. Cerebellar and brainstem atrophy
 - a. More cerebellar atrophy with toluene than other solvents
6. Trilaminar inclusions may be detected within PAS-positive macrophages
7. VLCFAs may accumulate in white matter
8. U-fibers may be involved
9. Toluene and possibly all volatile solvents act as CNS depressants
 - a. Potency and sites of action differ between solvent type
10. Toluene, benzene, m-xylene, ethylbenzene and 1,1,1-trichloroethene (TCE)

Clinical Manifestations

1. Chronic solvent use can lead to substance abuse disorder (DSM-IV)
2. 10% of patients develop tolerance to solvents

- a. Reversibly inhibit NMDA receptors (Glu N1/2B.Glu N1/2A)
- b. Toluene, TCE and trichloroethylene (TCY) increase GABA and glycine receptor function
 - i. Chronic use induces NMDA increased currents and decreased GABA-ergic activity
- 11. Toluene's major action is putatively increasing intracellular calcium concentration in both glutamatergic and GABA-ergic neurons
- 12. Toluene also affects:
 - a. Nicotinic acetylcholine receptors (inhibition)
 - b. Enhances 5-HT₃ serotonin receptors (as do TCE, TCY and ethanol)
 - i. Enhancement of 5-HT₃ receptor function may increase dopamine in the NAc which may underlie its rewarding properties
- 13. Anesthetics, toluene, TCE and tetrachloroethylene (PERC) inhibit voltage-sensitive calcium and sodium channels
- 14. Putatively toluene and other volatile substances
 - a. Affect fast synaptic transmission
- 15. The prefrontal cortex is inhibited by solvents which
 - a. Enhances DA neuronal activity
 - b. Disinhibits the mesolimbic DA circuit which leads to their psychoactive and reinforcing properties

Neuroimaging

- 1. MRI:
 - a. Diffuse cerebral and cerebellar atrophy
 - b. Ventricular enlargement

Differential Diagnosis of Drugs and Toxins That Impair Cognition

- 1. Arsenic
- 2. Barbiturates
- 3. Hypnotic sedatives
- 4. MPTP
- 5. Chemotherapeutic agents
- 6. Lead

Neoplasms Causing Dementia

General Characteristics

- 1. Dementia may occur with both malignant and benign tumors
- 2. Dementia is determined primarily by the site of the neoplasm
- 3. Slow growing tumors most frequently cause diagnostic confusion

Clinical Manifestations

- 1. Location

- a. Midline
 - i. Colloid cysts
 - 1. Severe positional headache
 - ii. Pinealoma
 - 1. Eye movement defects (failure of vertical gaze)
 - 2. Hearing loss (compression of the inferior colliculus)
 - 3. Aqueductal stenosis with hydrocephalus
 - iii. Pituitary tumors
 - 1. Panhypopituitarism
 - 2. Chiasmatic visual field defects
 - 3. Hydrocephalus
 - 4. Dementia is primarily from thyroid failure
 - 5. Midline thalamic glioma
 - a. Somnolence
 - b. Aphasia
 - c. Memory loss and cognitive impairment
 - d. Fluctuating levels of consciousness

Subfrontal Frontal Lobe Meningioma

- 1. Subfrontal tumors (planum sphenoidale)
 - a. Pressure and irritation of the limbic orbitofrontal cortex
 - b. Seizures
 - c. Personality change and behavioral disorders
 - d. Rarely Foster-Kennedy syndrome
 - e. Subcortical dementia
- 2. Dorsolateral prefrontal cortex
 - a. Frontal lobe syndrome:
 - i. Poor memory retrieval
 - ii. Deficits of planning, execution and attention
- 3. Global decrease of cognitive function

Glioblastoma Multiforme

- 1. Bilateral frontal lobe involvement:
 - a. Crosses to the contralateral side through the corpus callosum
 - b. Frontal lobe syndrome
 - c. Seizure
 - d. Focal neurologic signs
 - i. Contralateral hemiparesis
 - ii. Ideomotor, limbkinetic and callosal apraxia
 - e. Abulia

Lymphoma

- 1. Primarily noted in AIDS patients
- 2. Crosses the midline through the corpus callosum
- 3. More necrotic on MRI than the usual lymphoma
- 4. Frontal lobe syndrome

Paraneoplastic Syndromes with Dementia

General Characteristics

- 1. Primarily immune-mediated

- a. Both cell surface and intracellular epitopes
- b. Small cell carcinoma of the lung is the most frequent tumor, but breast, GI, ovary and blood dysplasias are also common

Clinical Manifestations

- 1. Limbic encephalitis
- 2. Bilateral involvement of the hippocampal formation, parahippocampal gyrus, cingulate gyrus
- 3. Memory loss
- 4. Personality and behavioral change
- 5. Seizures

Neuropathology (Limbic Encephalitis)

- 1. Neuronal loss:
 - a. Hippocampus
 - b. Cingulate gyrus
- 2. Lymphocytic perivascular cuffing

Laboratory Evaluation

- 1. Antibody serum analysis for paraneoplastic epitopes particularly anti-Hu, anti-NMDA, anti-AMPA
- 2. Increased lymphocyte pleocytosis and CFS protein

Neuroimaging

- 1. MRI:
 - a. Increased signal intensity on T-2 weighted sequences bilaterally in the medial temporal lobe, insular and cingulate cortex that are most often gadolinium enhancing

Chronic Traumatic Encephalopathy as a Cause of Dementia (CTE)

General Characteristics

- 1. Definition:
 - a. CTE is a progressive neurodegenerative disease most often seen in association with the contact athletics, military combat, and trauma
 - b. Clinical symptoms most often begin after a latent period of years (decades)
 - c. The chronic neurodegeneration may be initiated from minor brain trauma

Clinical Manifestations

- 1. Early clinical investigation of boxers detailed a symptom complex that resulted from repeated sublethal head trauma that was characterized by:
 - a. An unsteady gait
 - b. Impaired cognition
 - c. Bradykinesia
 - d. Hesitant speech
 - e. Tremor of the hands and head
 - f. The complex was defined as “dementia pugilistica”

- g. Further clinical studies demonstrate:

- i. Subcortical dementia
- ii. Ataxia
- iii. Pyramidal tract dysfunction
- iv. Pseudobulbar palsy:
 - 1. Increased gag reflex
 - 2. Bilateral corticospinal dysfunction
 - 3. Emotional lability (laughing without mirth and crying without tears)
- v. Dysarthria
- vi. Shuffling gait
- vii. Hypopituitarism:
 - 1. Common after moderate to severe traumatic brain injury

Neuropathology

- 1. General features:
 - a. Cerebral atrophy
 - b. Enlarged lateral and third ventricles
 - c. Thinning of the corpus callosum
 - d. Fenestration of the cavum septum pellucidum
 - e. Cerebellar scarring
- 2. Histology
 - a. Neuronal loss in the cerebellar tonsils and substantia nigra
 - b. Neurofibrillary tangles in the substantia nigra and cerebral cortex
- 3. Topographic and cellular pattern of tau neurofibrillary pathology:
 - a. Neurofibrillary tangles (NFT) are predominant in layer II and upper IIIrd of neocortical areas (also seen in post-encephalitic Parkinsonism and Guamanian amyotrophic lateral sclerosis (ALS) Parkinsonism dementia)
 - b. This distribution supports the involvement of short distance, forward projecting cortico-cortical neurons
 - c. The size of individual NFTs is larger in CTE than in Alzheimer's disease
 - d. Neurites are more spindle-shaped than in Alzheimer's disease
 - e. The phosphorylated tau is perivascular and concentrated in the depths of the sulci
 - f. Medial temporal lobe p-tau is not an early manifestation of CTE
 - g. There is immune-reactivity to both three and four repeat tau
 - h. Subpial regions are affected early in CTE
 - i. There is astrocytic tau pathology

Stage I Chronic Traumatic Encephalopathy

- 1. Isolated perivascular foci of p-tau-NFTs, neuritic threads and astrocytic tangles
- 2. Tau pathology is formed at the depths of the sulci in:
 - a. Superior, dorsolateral and inferior frontal cortices

- b. P-tau-positive astrocytes are in the subpial region overlying the perivascular foci
- c. P-tau pathology occurs in the locus coeruleus
- 3. Approximately 50% of patients have TDP-43 inclusions in the subcortical frontal white matter and fornix
- 4. Gliosis of white matter at the apex of gyri and at the junction between the deep layers of the cortex and white matter
- 5. Hemosiderin accumulation may be seen in arterioles and venules in proximity to perivascular p-tau pathology

Stage II Chronic Traumatic Encephalopathy

- 1. Mild enlargement of the frontal horns of the lateral ventricles and IIIrd ventricle
- 2. Pallor of the substantia nigra and the locus coeruleus
- 3. Multifoci of tau pathology in the depths of the sulci in the:
 - a. Superior, dorsolateral, lateral and inferior frontal, anterior inferior cortices
 - b. Temporal, parietal, insular and septal cortices
 - c. Similar microscopic location as is seen in stage I
- 4. NFTs spread to superficial layers of adjacent cerebral cortex that extends into the gyral crest
- 5. NFTs are detected in the substantia innominata
- 6. Mild neurofibrillary degeneration is seen in the substantia nigra, dorsal and median raphe and the thalamus
- 7. TDP-43 pathology occurs in a large proportion of patients in a similar distribution to tau pathology
- 8. There is no AB pathology and no substantial NFT pathology in medial temporal lobe structures

Stage III Chronic Traumatic Encephalopathy

- 1. Decreased brain weight, atrophy of the frontal and temporal lobes
- 2. Enlarged lateral and IIIrd ventricles
- 3. Cavum septum and septal fenestrations are common
- 4. Pallor of the locus coeruleus and substantia nigra
- 5. Atrophy of the mammillary bodies, thalamus and hypothalamus
- 6. Thinning of the corpus callosum
- 7. NFTs are seen diffusely in the frontal, temporal and parietal cortices
- 8. They are concentrated around blood vessels at the depths of sulci
- 9. Involvement of similar cortices as seen in stage II
- 10. Involvement of the hippocampus, entorhinal cortex, amygdala, nucleus basalis of Meynert and locus coeruleus with extensive NFTs in the hypothalamus, mammillary bodies, substantia nigra, dorsal and median raphe nuclei
- 11. In approximately 1/3 of patients NFTs are seen in the dentate nucleus of the cerebellum and in the spinal cord
- 12. The majority of patients have TDP-43 positive neuritis and inclusions in the cerebral cortex, medial temporal lobe, thalamus and brainstem
- 13. In less than 20% of patients there is AB deposition that is sparse and diffusely distributed

Stage IV Chronic Traumatic Encephalopathy

- 1. The brain weight is decreased and there is marked atrophy of the frontal and temporal lobes, the medial temporal lobe and anterior thalamus
- 2. Generalized white matter atrophy
- 3. Disproportionate thinning of the posterior corpus callosum
- 4. Severe spongiosis of the layer 2 of the cerebral cortex
- 5. Widespread myelin loss and astrocytosis of the cerebral hemispheres
- 6. Severe tau deposition throughout all structures involved in the earlier stages
- 7. Heavy density of NFTs in the hippocampal formation which is sclerotic and almost devoid of neurons
- 8. The cerebellum is involved with tau pathology in the dentate nucleus granule cell layer
- 9. The medulla demonstrates tau pathology in the medial lemniscus and inferior olives
- 10. TDP-43 deposition is widespread and dense with dot-like and thread-like inclusions in neurites and neuronal cytoplasm

Pathogenesis of Traumatic Brain Injury

- 1. The mechanism of traumatic brain injury neurodegeneration is not known, but posited causes include:
 - a. Axonal injury
 - b. Tau hyperphosphorylation
 - c. Misfolding and aggregation of proteins
 - d. Cytoskeletal disruption
 - e. Deficiency of axonal transport
 - f. Acute traumatic brain injury (TBI):
 - i. The brain is subjected to shear stress that:
 - 1. Elongates and injures axons
 - 2. Damages small blood vessels and astrocytes
- 2. Traumatic axonal injury causes:
 - a. Changes in axolemmal permeability
 - b. Ionic shifts with a large influx of calcium
 - c. Release of caspases and calpains that triggers:
 - i. Misfolding, truncation and phosphorylation of multiple proteins that include tau and TDP-43
 - ii. Disruption and degeneration of microtubules and neurofilaments that interrupts axonal transport
- 3. Repetitive injury with accumulation of misfolded proteins or p-tau aggregates is posited to:
 - a. Overwhelm clearance mechanisms
 - b. P-tau spreads transsynaptically and interneuronally by possible template mechanisms and cerebrospinal fluid clearance pathways
 - c. Inflammation and microhemorrhage from damage to small blood vessels

Neuroimaging

- 1. MRI:
 - a. Grade I diffuse axonal injury (DAI):

- i. Wide-spread axonal damage in the:
 1. Corpus callosum
 2. Cerebral hemisphere white matter
 3. Brainstem
 - b. Grade II DAI:
 - i. All of the abnormalities noted in grade I DAI
 - ii. Focal abnormalities of the corpus callosum with small hemorrhage (a tissue tear hemorrhage)
 - c. Grade III DAI:
 - i. All of the findings of grade II DAI
 - ii. Axonal abnormalities in the rostral brainstem
2. fMRI:
 - a. A frontal vulnerability in mTBI:
 - i. Decreased activity in the MFG, ACC (anterior cingulate cortex and right precentral gyrus)
 - ii. Bilateral decreased activity in the DLPFC (dorsolateral prefrontal cortex)
3. Magnetic Resonance Spectroscopy:
 - a. Reduced n-acetylaspartate (NAA) in white matter:
 - i. Disruption of neuronal integrity
 - ii. Alterations in cellular energy metabolism
 - b. Increased white matter choline:
 - i. Repair and inflammation of myelin
 - c. Altered metabolic integrity in the splenium of the corpus callosum is associated with reduced functional interhemispheric connectivity
4. Positron emission tomography (PET):
 - a. Decreased cerebral glucose metabolic rate in gray matter
5. Disrupted modular organization of resting state functional networks has been demonstrated in blast traumatic brain injury
6. Diffusion weighted imaging:
 - a. Demonstrates an anterior to posterior loss of white matter anisotropy

Vasculitic and Microangiopathic Forms of Dementia

General Characteristics

1. Deficits occur in:
 - a. Cranial nerves
 - b. Peripheral nerves
 - c. Spinal cord
 - d. Large or small vessel stroke
 - e. Often multiorgan involvement
 - f. Systemic signs and symptoms
2. Rarer presentations:
 - a. Depressed consciousness
 - b. Confusional state
 - c. Dementia

SLE

General Characteristics

1. Dementia occurs often with acute exacerbations and increased disease activity

Clinical Manifestations

1. Large and small cerebral infarcts may lead to multi-infarct dementia
2. Strokes in young adults
3. Libman-Sacks endocarditis (verrucous subvalvular fibrin deposits) that are associated with emboli

Neuropathology

1. Lupus anticoagulant and anticardiolipin antibodies are detected in the serum
2. Single- and double-stranded anti-DNA antibodies are detected in the serum
3. Prolonged PTT, false positive syphilis serology, and thrombocytopenia suggest an ACL antibody state
4. Increased sed rate and C-reactive protein are seen during exacerbations
5. CSF:
 - a. Increased protein, lymphocytic pleocytosis and IgG
 - b. Decreased complement
6. Neuroimaging:
 - a. Large and small vessel topographic strokes
 - b. Atrophy
 - c. Normal MRI in some patients

Polyarteritis Nodosa

General Characteristics

1. CNS involvement:
 - a. 20% of patients
 - b. Involvement of large intra- and extracranial vessels and intracranial arterioles

Clinical Manifestations

1. Global encephalopathy
2. Multifocal deficits
3. Dementia
4. Seizures
5. Large vessels stroke (rare)
6. Stupor and coma

Neuropathology

1. Necrotizing vasculitis in small- and medium-sized muscular arteries
2. Segmental arterial lesions
3. Endothelial proliferation
4. Polymorphonuclear and mononuclear cell infiltration of blood vessel walls
5. The kidneys may be severely involved in some patients with consequent severe HCVD

Laboratory Evaluation

1. Elevation of acute phase reactants (approximately 50% of patients)
2. A percentage of patients have:
 - a. Hemoglobin <12 grams/dl

- b. WBC > 12,000/ μm^3
- c. CRP > 5 mg/dl
- d. Thrombocytosis > 400,000/ μl
- e. Sedimentation rate > 40 mm/hr
- f. Positive rheumatoid factor, anti-nuclear antibody, ANCA antibody concentrations in the serum
- g. Elevated C3 complement
- h. HBs-Ag positivity

Neuroimaging

1. MRA:
 - a. Microaneurysms in a segmental pattern of medium-sized blood vessels
 - b. Cerebral arteries often have a beaded appearance with variable degrees of stenosis and occlusion with or without contrast enhancement in their walls
2. MRI:
 - a. Small ischemic change to topographical infarction, hemorrhage and white matter edema

Primary Arteritis of the CNS (PACNS)

General Characteristics

1. An idiopathic inflammatory process that only affects CNS vasculature
2. There is no systemic inflammatory response

Clinical Manifestations

1. Affects adults in the fifth to eighth decade
2. A subacute cognitive decline
3. Seizures
4. Focal neurological deficits
5. Headache
6. Impaired consciousness (with acute exacerbations)
7. Rare cranial neuropathy
8. Spinal cord infarction (rare)
 - a. Amnesic syndrome

Neuropathology

1. Confirmed PACNS patients have been reported in association with:
 - a. Hodgkin's disease
 - b. Amyloid angiopathy
 - c. Graft-versus-host disease
2. Primarily a leptomeningeal and cortical vasculitis which involves small and medium leptomeningeal and cortical arteries
3. Granulomatous angiitis with Langhans giant cells, or a necrotizing lymphocytic vasculitis
4. Inflammation leads to occlusion of the involved blood vessel with consequent thrombosis and infarction in its territory

Laboratory Evaluation

1. Entities to be excluded prior to the diagnosis include:
 - a. Infections

- b. Neoplasm
 - c. Drug exposure
 - d. Vasospastic disorders
 - e. Systemic vasculitis
 - f. Vasculopathies
2. No blood studies are diagnostic
 3. CSF evaluation:
 - a. CSF is abnormal in 80–90% of patients with PACNS
 - b. Modest lymphocytic pleocytosis with an elevated protein

Neuroimaging

1. MRI:
 - a. Bilateral infarcts in the cortex, deep white matter and leptomeninges with or without contrast enhancement
 - b. High resolution multicontrast wall and lumen MRI (inflammatory lesions encompass the circumference of the arterial wall)
2. Angiography:
 - a. Beading
 - b. Absence or cut off of one or more vessels

Giant Cell Arteritis (GCA)

General Characteristics

1. Giant cell arteritis is an inflammatory vasculopathy that occurs in medium and large arteries
2. The affected vascular beds are the:
 - a. External carotid branches, most often the temporal and occipital arteries
 - b. Ophthalmic, vertebral, distal subclavian and axillary arteries and the thoracic aorta
 - c. Often occurs in association with polymyalgia rheumatic (PMR)
 - i. Approximately 50% of patients with giant cell arteritis present with PMR before, concomitant with, or after the diagnosis of GCA

Clinical Manifestation

1. Peak incidence for GCA is between 70–80 years of age
2. Severe headache (often a burning scalp with mechanoallodynia and hyperalgesia)
3. Unilateral blindness:
 - a. Infarction of the posterior ciliary arteries that form a watershed with the central retinal artery at the optic disc
4. Rarely there is involvement of the carotid, vertebral arteries and the arch of the aorta
5. Brainstem, the cerebellum and rarely the spinal cord may be involved
6. Ischemic optic neuropathy causes vision loss in 10–15% of patients
7. Vascular dementia

Neuropathology

1. Dendritic cells of the vessel wall initiate the pathological cascade by recruiting T-cells and macrophages that form a granulomatous infiltrate

2. Vascular lesions of inflamed temporal arteries contain:
 - a. Inflammatory cytokines and mediators which include:
 - i. Interleukin-12-type; helper T-cells (Th1); interferons of the gamma axis
 - ii. Interleukin-6 and T-cell (Th17) and the interleukin-21 axis (which can be suppressed by glucocorticoids)
3. Effect of cytokines that are released into the arterial wall:
 - a. Activate inflammatory cells which target:
 - i. Endothelial cells
 - ii. Vascular smooth muscle cells
 - iii. Fibroblasts
 - b. The above cellular events lead to intimal hyperplasia and vessel obstruction
4. Remodeling of the vascular wall is produced by:
 - a. Matrix metalloproteinases
 - b. Vascular endothelial growth factor
 - c. Platelet-derived growth factor

Laboratory Evaluation

1. Marked elevation of the erythrocyte sedimentation rate (usually between 80–120 mm/hr) and the level of C-reactive protein
2. Anemia and thrombocytosis
3. Elevated IL-6
4. Color Doppler:
 - a. Visualizes superficial arteries but has limited value in deep blood vessels:
 - i. Vessel wall edema produces a halo sign
5. Temporal artery biopsy is the definitive test

Neuroimaging

1. MRA:
 - a. Evaluation of the aortic arch and its branches to rule out stenosis, dissection or aneurysm
 - b. Inflammation of the vessel wall is suggested by intramural delayed enhancement and thickening

Thrombotic Thrombocytopenic Purpura

General Characteristics

1. Familial thrombotic purpura is caused by mutation in the ADAMTS12 gene that maps to chromosome 9q342
2. It encodes the von Willebrand factor (VWF)-cleaving protease (VWFPCP)
3. In the majority of patients it is acquired in which antibodies against ADAMTS13 are detected in the patient's serum that decreases ADAMTS13 enzyme activity (often less than 5%)
4. ADAMTS13 is a metalloproteinase that cleaves the von Willebrand factor (VWF) into small fragments. Decreased enzyme activity, VWF multimers induce platelet accumulation and activation that induces microangiopathic hemolytic anemia and thrombocytopenia

Clinical Manifestations (Acquired Form)

1. Acute confusion state
2. Psychosis
3. Seizures
4. Purpuric skin lesions
5. Fever
6. Rare vascular dementia

Neuropathology

1. The enlarged multimers of VWF resemble huge VWF proteins that are secreted by human endothelial cells
2. The multimers effect adhesion of platelets to the subendothelium if there is vascular damage
3. The inhibitors against the metalloproteinase ADAMTS13 are IgG antibodies
4. Terminal arterioles and capillaries are occluded by hyaline thrombi that are primarily composed of platelets
5. There is no perivascular inflammation or endothelial desquamation

Laboratory Evaluation

1. Peripheral blood smear:
 - a. Schistocytes
 - b. Platelet count of $<30,000/\text{mm}^3$
 - c. High reticulocyte count
2. High indirect bilirubin and LDH levels
3. Low haptoglobin
4. Direct antiglobulin test is negative
5. Decrease in ADAMTS13 activity is less than 10% of a normal value with anti-ADAMTS13 antibodies

Differential Diagnosis of Acquired TTP

1. Congenital TTP (Upshaw-Shulman syndrome)
2. Atypical hemolytic uremic syndrome
3. Disseminated intravascular coagulation (DIC)
4. Antiphospholipid syndrome
5. Cobalamin deficiency
6. During pregnancy the HELLP syndrome
7. Evans syndrome

Central Nervous System Angioendotheliosis

General Characteristics

1. Neoplastic angioendotheliosis often affects the systemic vasculature and is rapidly fatal
2. CNS involvement may be insidious

Clinical Manifestations

1. Subacute dementia over months
2. Focal neurologic deficits
3. Renal involvement
4. Skin ulcerations

Neuropathology

1. Small infarctions

2. Medium-sized arterial involvement
3. Intravascular proliferation of atypical cells with proliferation of blood vessels
4. Electron microscopy:
 - a. Weibel-Palade bodies and factor VIII-related antigen in intravascular and extravascular neoplastic cells

Laboratory Evaluation

1. CT evaluation:
 - a. Diffuse lucencies compatible with ischemic lesions
 - b. The predominance of the lesions are in the white matter
2. Angiographic abnormalities are in medium-sized arteries
3. Some patients have an elevated sedimentation rate and modest renal impairment

Infectious Causes of Dementia

HIV

General Characteristics

1. After infection, the HIV virus rapidly enters the brain and induces widespread inflammation and neuronal damage that leads to cognitive impairment
2. Cognitive impairment occurs in 35–70% of patients with HIV-1 infection regardless of treatment or non-treatment
3. Combination antiretroviral therapy has decreased the prevalence of HIV-associated dementia (HAD) but milder forms of HIV-associated neurocognitive disorders (HAND) remain a major problem
4. At present, there are no diagnostic tests or specific biomarkers that can specifically diagnose HAND
5. Virus may be detected in the CSF within 7–10 days of infection
6. Severe immunosuppression is concomitant with cognitive impairment
7. Viremia reaches peak levels within 21–28 days after infection and is accompanied by a massive loss of CD4+T cells and an excessive increase in proinflammatory cytokines
8. Abnormalities of the caudate nucleus and the hippocampus may be appreciated with structural MRI and fMRI evaluation within 4–12 months
9. Atrophy in the basal ganglia is correlated with duration of the infection
10. There is evidence that ongoing brain damage occurs during systemic viral suppression that supports the hypothesis of a viral reservoir in the brain that may preclude total viral eradication

Clinical Manifestations

1. Deficits occur in:
 - a. Gross motor ability (timed gait)
 - b. Fine motor function (grooved pegboard)
 - c. Language (WRAT 4 reading)

- d. Verbal learning (Hopkins Verbal Learning Test)
- e. Verbal memory (HVLT-R, delayed recall)
- f. Speed of processing (Trail making-A, digit symbol)
- g. Attention and working memory (paced auditory serial addition task)
- h. Executive function (verbal fluency, Stroop and trail making-B)

The Frascati Criteria for Neurocognitive Disorders in HIV Patients

1. Impairment of cognitive function in at least two domains:
 - a. Usually the impairment is in multiple domains
 - b. Particularly severe deficits in:
 - i. New information learning
 - ii. Slow information processing
 - iii. Attention and concentration
 - c. Ascertainment of deficits by neuropsychological testing with at least two domains that are two standard deviations or more below the mean
2. The cognitive impairment interferes with activities of daily living
3. There is no delirium
4. There is no pre-existing cause for the dementia

Neuropathology

1. Diffuse white matter changes
2. Macrophage invasion, multinucleated cells and reactive gliosis in the affected areas
3. Neuronal loss in the basal ganglia and subcortical gray matter as well as the cerebral cortex
4. Associated pathologic processes:
 - a. Lymphoma
 - b. Progressive multifocal leukoencephalopathy (PML)
 - c. Infections:
 - i. Toxoplasmosis
 - ii. Tuberculosis
 - iii. Syphilis
 - iv. Cryptococcosis
 - v. Herpes simplex
 - vi. Herpes Zoster
 - vii. Epstein-Barr Virus
5. Infected macrophages in the meninges, subarachnoid space and parenchyma induce inflammatory cascades that involve:
 - a. Cytokines (TNF α and IL-6)
 - b. Chemokines (fractalkine and MCP-1)
 - c. Viral proteins:
 - i. Metalloproteinases may modulate the neurotoxicity of HIV viral proteins and are elevated throughout the course of the infection

Laboratory Evaluation

1. Positive serum, ELISA test
2. Confirmatory Western blot
3. Viral Load Test (primarily to monitor treatment):

- a. Reverse transcriptase (PCR)
- b. Branched DNA (test)
- c. Nucleic acid sequence based amplification assay (NASBA)
- 4. CSF:
 - a. Lymphocytic pleocytosis
 - b. Moderately elevated protein
 - c. Task switching paradigm:
 - i. HIV-infected patients were slower than controls in adapting to the task demand
 - ii. The deficits are correlated to less activation in the dorsal area of the anterior cingulate cortex
 - d. Neurovascular coupling may be abnormal in HIV-infected patients, which makes BOLD investigations less reliable as an index of neuronal activity
- ii. The regulatory region of the JCV archetype consists of one 98-bp element, whereas the regulatory region of pathogenic PML prototype have tandem repeats of a 98-bp element
- iii. Each individual patient has a unique regulator rearrangement. This attribute of the virus supports a mechanism in which the pathogenic prototype emerges within the host from the original commonly acquired JCV archetype, and is not a newly acquired infection from the environment
- f. The distinct PML risk populations include:
 - i. The HIV-positive population:
 - 1. 1 per 1000 person years in the post-cART era
 - 2. The mortality rate with cART treatment:
 - a. Approximately 30% after 1 year and 50–60% after 2 years
 - 3. The population of HIV+ patients with a low CD4+T-cell count are at a higher risk of developing PML
 - ii. The second largest risk population is patients with hematological malignancies, that account for approximately 10% of PML patients:
 - 1. Most of these patients succumb very rapidly
 - iii. The third largest population at risk is patients taking natalizumab for relapsing-remitting multiple sclerosis. The risk is estimated to be 3.96 per 1000 patients:
 - 1. The risk is primarily in patients with anti-JCV antibody and increases to 5.3 per 1000 patients after 2–4 years of treatment
 - 2. Prior immunosuppression increases the risk
 - iv. Other disease associations include:
 - 1. Organ transplantation
 - 2. Solid malignancies
 - 3. Sarcoidosis
 - 4. Autoimmune diseases

Neuroimaging

- 1. Functional MRI:
 - a. fMRI studies during attention and working memory in HIV-infected patients reveals:
 - i. Greater activation within the frontal and parietal cortices during performance of the paradigms
 - ii. HIV patients demonstrated less activation in the primary sensory cortices
- 2. Structural MRI:
 - a. Global atrophy of both gray and white matter
 - b. Basal ganglionic atrophy
 - c. Diffuse white matter increased signal on T2-weighted sequences (primarily periventricularly)
- 3. Magnetoencephalography:
 - a. HIV-infected patients exhibit reduced neural synchronization in the 6–12 Hz frequency range across the dorsolateral prefrontal cortex, frontal eye fields and posterior cingulate gyrus:
 - i. This frequency band includes a component of the 4–7 Hz and alpha bands that have been associated with working memory and visual attention
 - ii. Alpha-frequency activity may be critical for network coordination during cognitive processing

Progressive Multifocal Leukoencephalopathy

General Characteristics

- 1. JCV is a polyomavirus:
 - a. Genetically related to BK virus (BKV) and simian virus 40 (SV40) that is composed of a 15–13 Kb double-stranded DNA enclosed in a capsid that lacks a lipoprotein envelope
 - b. Probable oral-fecal route of transmission
 - c. Most individuals are infected by age 30–40
 - d. The JCV archetype is not pathogenic although it is spread through the community
 - e. The pathogenic prototype variant:
 - i. Differs from the archetype in the non-coding region of the viral DNA

Clinical Manifestations

- 1. Cognitive impairment
- 2. Ataxia
- 3. Hemiparesis
- 4. Hemianopia and central visual loss
- 5. Rare brainstem signs and symptoms
- 6. A few patients have a remission and a long survival

Neuropathology

- 1. The parieto-occipital lobes are most commonly affected
- 2. Serpiginous coalescent white matter lesions
- 3. Large bizarre multi-nucleated oligodendrocytes with intranuclear lesions
- 4. The subcortical white matter is primarily affected
- 5. Oligodendrites are destroyed
- 6. Bizarre astrocytes

Laboratory Evaluation

- 1. JC virus DNA is in the spinal fluid

2. Anti-JCV antibodies are in the serum
3. Rarely a brain biopsy is needed for diagnosis

Neuroimaging

1. MRI:
 - a. The cortical white matter of the parieto-occipital and frontal lobes are most often affected
 - b. Lesions may be seen anywhere in the brain and include:
 - i. Basal ganglia
 - ii. External capsule
 - iii. Brainstem
 - iv. Cerebellum
 - c. Periventricular white matter is also frequently involved
 - d. Lesions have a scalloped lateral margin when they involve the subcortical white matter
 - e. Lesions are hypointense and well-demarcated on T1-weighted sequences
 - f. Lesions typically do not enhance or have mass effect; rarely there is slight enhancement

Subacute Sclerosing Panencephalitis (SSPE)

General Characteristics

1. SSPE is a chronic encephalitis after measles virus infection
2. The prevalence of disease varies with vaccination rates
3. Measles can induce a “slow virus” infection that occurs years after the initial exposure
4. It remains a common cause of progressive myoclonus with cognitive impairment in regions with incomplete measles immunization

Clinical Manifestations

1. Childhood form:
 - a. The age of presentation is usually between 8–11 years
 - b. The onset is between 2–10 years after measles infection
 - c. Cognitive impairment
 - d. Progressive myoclonus
 - e. School failure (often the earliest cognitive sign)
 - f. Visuospatial impairment
 - g. Apraxias
2. Adult-onset SSPE:
 - a. May have atypical features
 - b. Presentation is at a mean age of 25.4 years (range of 20–35 years)
 - c. Higher proportion of a negative measles infection history than in children
 - d. These patients may be infected at a younger age (<3 years old) or at an older age (>9 years of age)
 - e. Long intervals from exposure to the virus and the onset of SSPE that ranges from 14–22 years
 - f. None of the patients follow a measles vaccination
 - g. Visual symptoms are prominent
 - h. Fewer patients have behavioral disorders

- i. Possibly a higher rate of remission although the course is progressive and fatal
- j. Motor manifestations include:
 - i. Myoclonus
 - ii. Spastic hemiparesis
 - iii. Bradykinesia
 - iv. Rigidity

Neuropathology

1. There is predominant cortical occipital lobe involvement, although the thalamus and putamen are affected
2. Dawson’s inclusion bodies:
 - a. Cowdry A bodies
 - b. Large intranuclear inclusions with a halo
 - c. Diffuse white matter demyelination

Laboratory Evaluation

1. Positive measles antibody titers
2. EEG:
 - a. Diffuse high-amplitude bursts of periodic slow-wave complexes every 3 to 5 seconds
3. CSF:
 - a. Positive IgG index > 7%/dl
 - b. Slightly elevated protein
 - c. No pleocytosis; may have a few lymphocytes

Neuroimaging

1. MRI:
 - a. Patchy areas of hyperintense signal on FLAIR sequences in periventricular areas and throughout white matter

Chronic Rubella Encephalitis

General Characteristics

1. Usually occurs after a congenital infection, although it may follow an acquired infection in an adult

Clinical Manifestations

1. Progressive rubella panencephalitis most often occurs in a child with congenital rubella
2. Most often manifests between 8–19 years of age
3. Child develops:
 - a. Progressive spasticity
 - b. Cognitive impairment
 - c. Ataxia
 - d. Seizures (rarely myoclonic)
 - e. There is no myoclonus
 - f. Retinopathy with optic atrophy in some patients

Neuropathology

1. Neuronal loss in the cortex, cerebellum and brainstem
2. Perivascular lymphocytic infiltration
3. Myelin destruction with axon sparing
4. Similar to the pathology of SSPE but without intracellular inclusion bodies

Laboratory Evaluation

1. Enzyme immunoassay of the serum for IgM; elevated rubella antibody titers in the serum and CSF

Neuroimaging

1. MRI:
 - a. Early cerebellar lesions
 - b. Ventricular enlargement
 - c. DWI with hyperintense ovoid lesions in the splenium of the corpus callosum

Neurosyphilis*General Characteristics*

1. The number of new patients with syphilis per year is approximately 20,000 in the USA
2. The highest rates occur among men who have sex with men; approximately 50% of new patients have a concomitant HIV infection

Clinical Manifestations

1. Neurological signs and symptoms may occur 15–20 years after the original infection
2. Cognitive impairment includes:
 - a. Memory loss
 - b. Apathy
 - c. An expansive paranoid state
 - d. Dysphasia
 - e. Apraxias
 - f. General paresis
3. Associated neurological features:
 - a. Seizures
 - b. Dysarthria
 - c. Tremor
 - d. “Trombone” tongue tremor (the tongue protrudes rhythmically)
 - e. Hypertonia
 - f. Vth nerve involvement with mid-face numbness
 - g. Paretic pupil with optic atrophy
 - h. Argyll Robertson pupil
 - i. Brainstem strokes
 - j. Gummas with focal features
4. Clinical manifestations of neurosyphilis in AIDS patients
 - a. There is a telescoped pattern of infection:
 - i. Primary and meningoencephalitic pattern may develop concomitantly
 - ii. Neurosyphilis may develop although the primary infection was adequately treated
 - b. Ocular involvement is prominent
 - c. Syphilitic meningitis is common
 - d. Gummatous arteritis occurs
 - e. A fulminant necrotizing hyperinfection (during an anergic state) has been delineated as “quaternary” syphilis

Neuropathology

1. Meningovascular syphilis:
 - a. Diffuse or localized to the base of the brain

- b. Lymphocytes and plasma cells associated with fibrous tissue form perivascular infiltrates around small blood vessels
- c. The inflammatory process may extend into the cranial and spinal nerves
- d. Associated hydrocephalus from the meningeal fibrosis
- e. Gummas:
 - i. Infrequently occur in the meninges
 - ii. Usual locations are:
 1. The cerebral convexity
 2. Less commonly found in the cerebral peduncles, hypothalamus and spinal cord
 3. Most often they attach to the dura mater and are embedded in the brain parenchyma
 - iii. Histology of gummas:
 1. Central gummatous necrosis in which there are dead cells and reticulin
 2. The core is surrounded by densely cellular epithelial cells, fibroblasts, and scattered multinucleated giant cells
 3. Syphilitic meningitis may be confined to the spinal cord; vascular involvement may cause transverse myelitis
4. Huebner’s arteritis:
 - a. Is the vascular component of meningovascular syphilis
 - i. An endarteritis obliterans
5. Parenchymatous neurosyphilis:
 - a. General paresis (paretic dementia)
 - b. Tabes dorsalis
 - i. Selective degeneration of posterior spinal nerve roots with dorsal root ganglia involvement
 - ii. Demyelination and shrinkage of the posterior columns
 - iii. Rarely the degeneration is more severe in cervical nerve roots
 - c. Parenchymal syphilis:
 - i. A severely shrunken atrophic brain with a thick and opaque pia-arachnoid
 - ii. Severe frontal gyral atrophy
 - iii. Ventricular enlargement
 - iv. Extensive granular ependymitis
 - d. Loss of the laminar pattern of the cerebral cortex
 - e. Loss of neurons in the cortex with astrocytic and microglial proliferation (cells are hypertrophied and rod-like)
 - f. Perivascular lymphocytic cuffing of blood vessels
 - g. Plasma cells in both the cortex and the meninges

Laboratory Evaluation

1. The VDRL (Venereal Disease Research Laboratory test) is the gold standard

2. Other serum and blood tests include:
 - a. Fluorescent treponemal antibody absorption test (FTA-ABS)
 - b. Rapid plasma reagin (RPR)
 - c. Treponema pallidum particle agglutination assay (TPPA)

Neuroimaging

1. MRI:
 - a. Patients with neuropsychiatric symptoms have:
 - i. Diffuse cerebral atrophy
 - ii. Parenchymal mesial temporal signal change
 - iii. Signal changes in basifrontal areas
 - iv. Topographical infarction
 - v. Non-specific white matter changes
 - vi. Cerebral gummas
 - b. Patients with meningovascular syphilis have:
 - i. Diffuse cerebral atrophy
 - ii. Topographical infarction
 - iii. Signal changes in the medial temporal lobe
 - iv. Sulcal exudates
 - c. Diagnostic pattern for cerebral neurosyphilis:
 - i. Cerebral gummas:
 1. Dural-based that are similar to meningioma
 2. Medial temporal lobe lesions that may be misdiagnosed as herpes encephalitis

Whipple's Disease

General Characteristics

1. A systemic disorder caused by the bacterium *Tropheryma whipplei*
2. Its classic presentation is with diarrhea, abdominal pain and weight loss
3. Involvement of other systems include:
 - a. The lymphatic system
 - b. Heart
 - c. Large joints
 - d. Central nervous system
4. Rarely, it may involve the brain without systemic involvement, and in association with a negative small bowel biopsy

Clinical Manifestations

1. Neurologic manifestations:
 - a. Onset is usually in men in the 4th-6th decades (87% of patients)
 - b. Neurologic signs and symptoms may occur without associated systemic features
 - c. Neurologic involvement may be silent (only found at autopsy)
 - d. Dementia
 - e. Myorhythmia (side to side jaw movement)
 - f. Ophthalmoplegia
 - g. Ataxia

- h. Hypothalamic syndrome
2. Systemic manifestations:
 - a. Lymphadenopathy
 - b. Hyperpigmentation
 - c. Large joint arthritis (asymmetric)
 - d. Steatorrhea with malabsorption and weight loss
 - e. May occur concomitantly with AIDS

Neuropathology

1. *T. whipplei* is an actinomycete that is most common in farmers and patients that are exposed to soil and animals
2. CD11b cells are deficient in patients
 - a. Have a role in the activation of macrophages that destroy intracellular bacteria
3. PAS-positive macrophages in the lamina propria that contain non-acid fast gram-positive bacilli
4. Disseminated lesions throughout the CNS that are noted in:
 - a. Subpial regions of the cortex
 - b. Basal ganglia
 - c. Hypothalamus
 - d. Dentate nuclei of the cerebellum
 - e. Brainstem nuclei
5. Small infarcts (less than 5 mm) are scattered throughout the brain

Laboratory Evaluation

1. Jejunal biopsy that identifies the gram-positive bacilli
2. PCR-based assay that may be utilized on blood, vitreous fluid, synovial fluid and CSF

Neuroimaging

1. MRI:
 - a. Multiple nodular enhancing lesions
 - b. Solitary mass lesion

Lyme's Disease Encephalopathy and Dementia

General Characteristics

1. Lyme's disease is caused by the *Borrelia* bacteria, a spirochete
2. Transmission to humans is from the bite of infected ticks of the *Ixodes* genus. The tick usually has to be attached for 36 to 48 hours
3. In the USA (and North America), the bacterium involved is *Borrelia burgdorferi*. In Europe and Asia it is *Borrelia afzelii* and *Borrelia garinii*
4. Nervous system involvement occurs in approximately 8% of patients affected with *B. burgdorferi*

Clinical Manifestations

1. There are 3 stages of the disease:
 - a. Stage 1:
 - i. Erythema marginatum of the skin associated with arthralgias

- b. Stage 2:
 - i. Occurs weeks or months after the initial infection
 - ii. Onset of neurologic and cardiac involvement occurs in this stage
 - iii. The neurologic signs include:
 - 1. Meningitis
 - 2. Cranial nerve involvement (bilateral or unilateral VIIth nerve palsy)
 - 3. Radiculoneuritis
- c. Stage 3:
 - i. Occurs several years after the infection
 - 1. Arthritis
 - 2. Cognitive impairment (rare and controversial)
- d. Patients with *B. garinii* > *B. afzelii*
 - i. Radicular pain
 - ii. Meningeal signs
 - iii. Less dizziness

Neuropathology

- 1. Nerve biopsy:
 - a. Perivascular lymphocytic infiltration around small endoneurial, perineurial, and epineurial blood vessels
 - b. Axonal degeneration
- 2. Lymphocytic meningitis

Laboratory Evaluation

- 1. The serological laboratory tests most widely used are the Western blot and ELISA:
 - a. The Western blot IgM has a specificity of 94%
 - b. ELISA has a sensitivity of 70%
- 2. CSF:
 - a. Lymphocytic pleocytosis

Neuroimaging

- 1. MRI:
 - a. Late stage disease:
 - i. Some patients demonstrate periventricular white matter hyperintense signals
 - ii. Ventricular enlargement
 - iii. Cortical atrophy

Cysticercosis

General Characteristics

- 1. The most common helminth with CNS involvement
- 2. A significant problem in immigrants from Mexico, Central and South America to the USA
- 3. Seen in approximately 1–3% of post-mortem studies in Mexico
- 4. The infection is caused by the larval stage of the pig tapeworm *Taenia solium*

Clinical Manifestations

- 1. Seizures

- 2. Acute and focal neurological signs
- 3. Increased intracranial pressure
- 4. Hydrocephalus
- 5. Meningeal form
- 6. Involves the diaphragm
- 7. Muscle enlargement from inflammation
- 8. Chronic dementia from the severe lesion load

Neuropathology

- 1. Most cysts are parenchymal; they vary from one to several hundred
 - a. Parenchymal cysts are usually 5–20 mm in diameter
 - b. Racemose cysts in the subarachnoid space may be as large as 6 cm
- c. There are intraventricular cysts
- d. Cysts are located:
 - i. Cortex
 - ii. Deep gray matter
 - iii. White matter
 - iv. Cerebellum
 - v. Meninges
 - vi. Ventricles
- e. Racemose cysts may occlude the internal carotid artery or burst within the ventricle, causing meningitis

Laboratory Evaluation

- 1. Antibodies to cysticerci are demonstrated by Enzyme Linked Immunoelctrotransfer Blot (serum)
- 2. ELISA for CSF samples

Neuroimaging

- 1. MRI:
 - a. Calcified and non-calcified cysts throughout the brain (dense in the cortex and basal ganglia)
 - b. Meningeal and ventricular involvement in some patients
 - c. Racemose cysts in the IVth ventricle

Chronic Infections Associated with Dementia

- 1. Tuberculosis
- 2. Neurosyphilis
- 3. Cryptococcus
- 4. Histoplasmosis
- 5. Coccidioidomycosis
- 6. Toxoplasmosis
- 7. Candida
- 8. HIV
- 9. Herpes zoster
- 10. CMV
- 11. Lyme's disease
- 12. Cysticercosis
- 13. SSPE (post-infection/measles)
- 14. Rubella panencephalitis (post-infection)
- 15. Herpes simplex

Further Reading

Further Reading on Dementia

Alzheimer's Disease

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