Handbook of Research on

Critical Examinations of Neurodegenerative Disorders

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Handbook of Research on Critical Examinations of Neurodegenerative Disorders

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Detailed Table of Contents

Neurons are the building units of the nervous system and are therefore critical units for the health of the brain and the spinal cord. This is necessitated by their inability to be either replaced or reproduced once lost. Their losses are implicated in a number of conditions which have been elaborated in this chapter. Oxidative stress has been strongly implicated in neurodegeneration through blockade of neuroprotection by a number of mechanisms including inhibitory effect on insulin-like growth factor I (IGF-1) via stimulation of the transcription factor, Forkhead box O3 (FOXO3). This chapter elaborates on these two phenomena which cannot be decoupled.

Free radicals are intricately woven into the fabric of oxidative stress and are significant in the development of neurodegenerative disorders (NDs). This chapter examines free radicals in the context of neurodegeneration and provides overview of the multiple roles they play in the pathophysiology and clinical progression of varying NDs including Pick's disease (PiD), Parkinson's disease (PD), Alzheimer's disease (AD), prion diseases (PrD), traumatic brain injury, and aging. The molecular mechanisms of degeneration in Huntington's disease (HD) are also examined with respect to free radicals. Different antioxidant systems and their mechanisms of action are briefly reviewed in addition to the role of diet in aging. The effectiveness of selected synthetic drugs and natural products used in oxidative stress is also reviewed. Lastly, the chapter examines challenges associated with the use of antioxidants and how promising future directions like the endocannabinoid system is being pursued in the race to effectively manage NDs.

Mitochondria are a dynamic organelle of the cell involved in the various biological processes. Mitochondria are the site of the adenosine triphosphate (ATP) production, electron transport chain (ETC), oxidation of fatty acids, tricarboxylic acid (TCA), and cellular apoptosis. Besides these, mitochondria are the site of production of reactive oxygen species (ROS), which further disrupts the normal functioning of this organelle also making mitochondria itself as an important target of oxidative stress. Thus, mitochondria serve as an important target in the process of neurodegeneration. In the present chapter, the authors describe mitochondria and its functioning, dynamics, and the mitochondrial dysfunction in aging and neurodegenerative disorders (NDs).

Alpha-synuclein is a protein that forms a major component of abnormal neuronal aggregates known as Lewy bodies. A particular group of neurodegenerative disorders (NDs) is characterized by the abnormal accumulation of α-synuclein; termed the α-synucleinopathies, this group includes Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). Lysosomal storage diseases have also been linked to α-synuclein toxicity. Several therapeutic targets have been chosen among steps of metabolism of α-synuclein. Reducing α-synuclein synthesis or expression and increasing the clearance can be achieved in many ways. The development of immunotherapeutic approaches targeting α-synuclein has received considerable attention in recent years. The aim of this chapter is to present the α-synucleinopathies, as well as to present the most recent researches about treatment of synucleinopathies based on knowledge of the pathophysiology of α-synuclein pathways.

Fritz Heinrich Lewy described the intracytoplasmic inclusions found in the neurons for the very first time. In 1919 these inclusions were termed as "LBs" by Tretiakoff. LBs were found in the brain of the patients suffering from Lewy body disease (LBD). LBD is characterized by the presence of Parkinsonian symptoms in the earlier stages and dementia in the later stages of the disease. LBs were classified on the basis of the region of the brain in which they are distributed and so is the case of the LBD means the type of the LBD depends on the anatomical areas of the brain involved. LBD is not a single disorder. It is a spectrum of disorders. This chapter addresses the entire profile of LBs, types, composition, formation, and various LB pathologies as well as diagnostic criteria and pharmacotherapy.

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder (ND) that primarily comprises the neurons responsible for controlling voluntary muscle movement. The unique neuropathologic findings include anterior horn cell degeneration producing muscle atrophy or amyotrophy, degeneration, and sclerosis of the corticospinal tracts. It is a common neuromuscular disease worldwide and has been

identified in people of all races. There seems to be neither identified risk factors nor family history associated with most of the documented ALS cases. There exists no treatment for ALS that can prevent neither its progression nor reverse its development. However, there are treatments available that can help control symptoms, prevent unnecessary complications, and make living with the disease easier. This chapter extensively discusses this neurodegenerative disorder based on the currently available knowledge on the condition.

Autism spectrum disorder (ASD) is neurodevelopmental disorder which is characterized by lack of social behaviors and impaired non-verbal interactions that start early in childhood. It can also lead to progressive neurodegeneration like schizophrenia disorder, Alzheimer's disease, Parkinson's disease, and dementia. Genetic studies of ASD have confirmed the mutations that interfere with neurodevelopment in mother's womb through childhood and these mutations are further involved in synaptogenesis and axon motility. Crucial role of amygdala is found to be deficit in ASD individuals whose association cognition with nucleus accumbens lead to impaired social behaviors and cognitive stimulus. Educational and behavioral treatments are considered the key steps used for its management along with pharmacological and interventional therapies. In this chapter, the author presents the etiology of ASD, proof of neurodegeneration in ASD, as well as the clinical feature and the management of ASD.

Creutzfeldt-Jakob disease (CJD) is a rare disease associated with neurodegeneration mostly characterized by damage to the neurons. CJD is caused by aggregation of misfolded proteins known as prions; thus, CJD is said to be a prion-related illness. CJD and other prion-related illnesses such as Kuru and Gerstmann-Sträussler-Scheinker disease (GSS) have been reported to have complex mechanisms due to their association with the brain and the nervous system in general. A lot of questions have been raised about the mechanism, diagnosis, and pathogenesis of this disease. The complexity of prion proteins themselves have contributed to more questions about the complications of CJD, whether misfolding of the prions are responsible for neurodegeneration or the misfolding are mere symptoms of the disease. This chapter attempts to explore some details about CJD and answers most related questions about the disease's mechanism. The author finally attempts to explore recent development in pathogenesis, diagnosis, and treatment of CJD.

Neurodegenerative disorders (NDs) are a group of disorders with the deterioration of attained skills often with no solutions, usually ending with death or crippling disabilities. This chapter contains a classification for childhood NDs as well as an algorithmic approach for easy management of these disorders. Genetic defects and pathophysiology of disorders like Canavan, Krabbe, subacute sclerosing panencephalitis (SSPE), etc. are written in detail. Suggestions regarding management of some of these conditions are

described as a lifecycle approach, from birth to death, to enable those who are taking care of such kids. Allogeneic hematopoietic stem cell transplantation (HSCT), gene therapy, combination therapy, and other experimental therapies have enlarged the scope of diagnosis and treatment options for these disorders. The author aims to brush up the existing and latest possibilities in NDs, including those at the experimental stage, for an easy understanding and for further research, especially as treatment options.

Section 3
Therapeutic Interventions for Neurodegenerative Disorders

Functional neurosurgery consists of procedures that either promotes judicious destruction or chronic stimulation of the nervous system in order to treat disordered behavior or aberrant function, as it is expected in neurodegenerative disorders ([NDs], e.g., movement disorders [Parkinson's disease, Tourette's syndrome, essential tremor, ballism, and dystonia]). Over the past 20 years, approximately 100,000 deep brain stimulation implant procedures have been performed worldwide. Neurosurgery is also a well-established therapeutic option for people with epilepsy whose seizures are not controlled by anti-epilepsy drugs. The most common pathological finding in patients with drug-resistant mesial temporal lobe epilepsy is hippocampal sclerosis. The aim of this chapter is to present the main NDs that can be treated through surgical procedures, and to describe the surgeries with a focus on the pathophysiology of diseases.

Preface

Neurodegenerative disorders have become one of the most exciting and glowing researched areas of neuroscience. The Handbook of Research on Critical Examinations of Neurodegenerative Disorders accentuate on the diverse genres of diseases, comprising Alzheimer's disease, Parkinson's disease, Huntington´s disease, Lewy body disease, amyotrophic lateral sclerosis, autism spectrum disorder, Creutzfeldt-Jakob disease, and multiple system atrophy. This book introduces various factors such as aging, oxidative stress, pathogenic protein, dysfunction of mitochondria and Golgi apparatus, alpha-synuclein, stroke, and zinc that serve as protagonist to neurodegeneration. Furthermore, this book provides a diaphanous explanation of various neurodegenerative disorders based on existing studies to clarify etiology, pathological mechanisms, diagnosis, therapeutic interventions, as well as current status and future opportunities and challenges. This book also focuses on numerous childhood neurodegenerative disorders and neurosurgical treatments.

This book represents the copious set of specific research updates. All over the world numerous erudite, experienced and eminent academicians, researchers and scientists had participated to write the texts of this book to give a concise thorough understanding of neurodegenerative disorders at a more advanced level with excellent presentation.

This book is suitable for professionals, academicians, students, researchers, scientists and industrialists around the world. Biomedical, health, and life science departments can use this book as a crucial textbook. Researchers and scientist from research institutes can use this book as efficient research info. Pharmacists, physicians, and other healthcare professionals can use this book as a complete reference book. Furthermore, for interested readers, this book is a storehouse of knowledge to comprehend neurodegenerative disorders complexity. The organizations of this book provided a profound knowledge and also maintain the reader's interest.

This book contains 19 chapters divided into 3 sections. The contents of the book cover the peril factors that are likely to the development and propagation of neurodegenerative disorders, and concise thorough understanding of these disorders as well as existing and forthcoming prevention and treatment strategy of neurodegenerative disorders.

Section 1 represents the spectrum of ample factors that can initiate and propagate chronic neuronal dysfunction that leads to neurodegenerative disorders. This section consists of eight chapters. A description of each chapter follows.

Chapter 1 is "The Aging Brain: From Physiology to Neurodegeneration". This chapter explores the physiological functioning of the brain. Further, it discusses the process, mechanism and various factors that cause aging. The pathway and mechanism of neurodegeneration are also introduced. Lastly, it highlights the functional and structural changes in the brain in aging and neurodegeneration.

Chapter 2 is "Oxidative Stress and Neurodegeneration". This chapter clarifies the precarious link between neurodegeneration and oxidative stress and how this could inform future research on the neurodegenerative disorders.

Chapter 3 is "Free Radicals in Oxidative Stress, Aging and Neurodegenerative Disorders". This chapter reviews the causes of susceptibility of the central nervous system to oxidative damage and the contribution of the aging in neurodegenerative disorders. Additionally, the role of free radicals in some neurodegenerative disorders as well as novel targets which are being explored to effectively manage these neurodegenerative disorders is presented.

Chapter 4 is "Mitochondrial Dysfunction in Aging and Neurodegeneration". This chapter explains the alteration in the mitochondrial dysfunction by aging and how this alteration is linked with the neuronal degeneration.

Chapter 5 is "Alternation of Mitochondrial and Golgi Apparatus in Neurodegenerative Disorders". This chapter focuses on that how mitochondria and Golgi apparatus get affected in neurodegenerative disorders. The target is to explain the factors that are mainly responsible for the morphological changes in these organelles.

Chapter 6 is "Neurodegenerative Disorders Progression: From Synaptic Dysfunction to Transmission Failure". This chapter describes the dynamics of neuronal dysfunction, the models that are used to study neurodegenerative disorders and the factors that cause the dysfunctioning. Further, it also highlights the progression of the pathological basis from synaptic deregulation to synaptic transmission deficits.

Chapter 7 is "Stroke: A Potential Risk Factor of Neurodegenerative Disorders". This chapter represents the relationship between stroke and neurodegenerative disorders, predominantly those related to cognitive impairment. Moreover, describes the pathophysiological mechanisms of vascular action on neurodegeneration reaching prevention and treatment suggestions.

Chapter 8 is "Zinc and Neurodegenerative Disorders". This chapter relates the significant role of zinc in relation to several biochemical and pathophysiologic activities in humans and its relation to neurological disarranges. The basic impact of zinc on homeostasis, oxidative stress, aging, and neurodegeneration is also stated.

Section 2 focuses on the clear explanation of the utmost imperative neurodegenerative disorders with a momentous impact on etiology, pathological mechanisms, disease management, current status, future opportunities, and challenges. This section consists of ten chapters. A description of each chapter follows.

Chapter 9 is "Neurodegenerative Disorders: An Introduction". This chapter portrays the causes and concepts of the classification of neurodegenerative disorders. Moreover, this chapter deals a concise depiction of the neuropathological features of numerous neurodegenerative disorders.

Chapter 10 is "Tau Pathology: A Step Towards Understanding Neurodegenerative Disorders Network Complexity". This chapter discusses various types of neurodegenerative disorders to understand the underlying mechanism of tauopathy. Additionally, presented a comprehensive study of biomarkers and pathways involved in pathological aggregation of tau protein in the human brain.

Chapter 11 is "Amyloid Beta: The Foremost Protagonist in Alzheimer's Disease". This chapter focuses on the amyloid beta hypothesis and the biomolecular targets, including the proteins and enzymes that contribute towards the development of Alzheimer's disease. A brief insight into the currently existing pipeline of potential drug candidates involving these targets has also been provided.

Chapter 12 is "Parkinson's Disease: A Progressive Disorder of the Nervous System that Affects Movement". This chapter provides a detailed overview of the Parkinson's disease from pathogenesis to therapeutics with existing challenges and the future directions.

Chapter 13 is "Alpha-Synucleinopathies: Parkinson's Disease, Dementia with Lewy Bodies, and Multiple System Atrophy". This chapter presents the alpha-synucleinopathies and the most recent researches about the treatment of alpha-synucleinopathies based on knowledge of the pathophysiology of alpha-synuclein pathways.

Chapter 14 is "Lewy Body Disease: Point Towards Progressive Dementia". This chapter represents the different pathologies, characterized by the presence of Lewy bodies in the different regions of the brain, which further form the basis of the progression of the Lewy pathology.

Chapter 15 is "Amyotrophic Lateral Sclerosis: A Predominant Form of Degenerative Disease of the Motor Neuron System". This chapter delves the mechanisms for motor neuron degeneration in amyotrophic lateral sclerosis as informed by up to date knowledge on this neurodegenerative disorder. In addition, diagnosis, pharmacotherapy, and forthcoming research tips are offered.

Chapter 16 is "Spectrum of Neurodegeneration in Autism Spectrum Disorder". This chapter expresses the effect of multi-factors such as oxidative stress, neuronal loss, microglia activation and proinflammatory cytokines that further lead to progressive neurodegeneration in autism spectrum disorder patients despite of showing its regression in neurodevelopmental practices.

Chapter 17 is "Creutzfeldt-Jakob Disease: A Prion Related Neurodegenerative Disorder". This chapter attempts to answer based on recent studies on the mechanisms and pathogenesis of Creutzfeldt-Jakob disease as well other details including epidemiology, diagnosis, and treatment of the disease. The chapter also highlights current and future perspectives in various studies aimed at finding the cure for the disease.

Chapter 18 is "Childhood Neurodegenerative Disorders". This chapter focuses on almost all details of neurodegenerative disorders of the children including epidemiology, pathophysiology, and management of these disorders. Moreover, the chapter gives an insight into the recent advances, experimental trials, and possible treatment and investigational options which may come up in the near future.

Section 3 offers the neurosurgical treatments strategy for the neurodegenerative disorders consistent with current studies, recent futuristic technologies, and techniques. This section consists of only one chapter. A description of this chapter follows.

Chapter 19 is "Neurosurgical Treatments of Neurodegenerative Disorders". This chapter presents the main neurodegenerative disorders that can be treated through surgical procedures, and to describe the surgeries with a focus on the pathophysiology of the disorders.

It is expected that readers shall find this book very informative and enormously useful. Since science is constantly changing readers are strongly recommended to check the recent update. The editors are ebulliently ready to accept any comment, suggestion, advice or critique.

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Section 1
Triggers of Neurodegeneration

Chapter 1
The Aging Brain:
From Physiology to Neurodegeneration

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ABSTRACT

Neurodegeneration is the progressive and gradual dysfunction and loss of axons in the central nervous system. It is the main pathological characteristic of chronic and acute neurodegenerative conditions like Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis (MS). The usual aspects of pathogenesis of disease can be abridged with regards to the downstream implications of uncontrollable protein oligomerization and aggregation from postmitotic cells. The brain structure constantly changes in normal aging without any dysfunction accompanying the structural changes in brain. The decline in cognitive capabilities, for example, processing speed, memory, and functions related to decision making are the sign of healthy aging. The reduction in brain volume in healthy aging is possibly related to neuronal loss at some marginal extent. The following chapter discusses the structural and functional alterations in the brain in ageing and neurodegeneration.

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INTRODUCTION

Aging of the brain is described through various anatomical, molecular and functional changes directing to enhance susceptibility to numerous diseases (Glorioso, Oh, Douillard, & Sibille, 2011). During aging, structural brain changes include volumetric shrinkage of brain and change in specific brain morphology in some region (Peters, 2006). Apart from the damage in structural integrity and neural plasticity, progressive declining in reserves of cellular homeostatic and variation in the mechanism of calcium dependent signaling has been recommended as the significant events associated in brain aging (Cai & Tammineni, 2017). Brain aging is also associated with some chemical and molecular alteration such as changes in hormones and neurotransmitter levels, accelerated formation of reactive oxygen species (ROS), dysfunctioning of mitochondria, accretion of nuclear and mitochondrial DNA damage convoyed by age related failure in DNA repairing and aggregation of intracellular and extracellular proteins (Wallace, 2010). Such severe changes in cellular and molecular levels cause difficulties in regular activities like attention, sleep, language, speech, decision making and cognitive abilities like work memory and long term memory (Alhola & Polo-Kantola, 2007). Higher-order brain system breakdown in aging is associated partially to myelinated fibres disruption which connects neurons to various cortical regions. Though the minimal neuronal loss in most of the cortical region is a part of normal brain aging, variation in synaptic physiology of neurons aging may participate in alteration of connectivity and higher order integration (Bishop, Lu, & Yankner, 2010). Significantly, these changes reduced down the coordination of brain activity which leads to weak performance in numerous cognitive domains.

Neurodegeneration is continuous loss of structural and functional properties of neurons corresponds to some pathological conditions which including neurons death (Gorman, 2008). In manner, neurodegenerative disorders (NDs) signify a huge assembly of neurological disorders with varied pathological and clinical expressions disturbing particular neuronal sets in detailed functional anatomic systems that progress in a persistent manner (Lin & Beal, 2006). Different NDs like PD, AD, Huntington disease (HD) and amyotrophic lateral sclerosis (ALS) are common in therapeutic research studies. NDs are mostly characterized through the factors like genetic risk factors, certain age ranges, courses of progression, clinical symptoms, dysfunctioning and neuronal death particular biochemical abnormalities, and presence of extracellular and intracellular protein (Kovacs, 2016). In the advance study, the beginning of NDs are instigated by the protein aggregation which are called proteinopathies (Shelkovnikova, Kulikova, Tsvetkov, Peters, Bachurin, Bukhman, et al., 2012). In this case, the aggregation of soluble monomers or oligomers cause toxic conditions subjected to consideration like some slight variations in the synthesis of α-synuclein and tau protein cause the occurrence of certain stressful condition which lead to PD and frontotemporal dementia respectively (Wang & Roberts, 2010). For these proteins, it is common that the holoprotein comparatively or entirely benign and with a series of cleavage of these protein lead to the production of toxic species or fragments. Likely, the rate of full length protein production is not a significant issue with respect to the rate of cleavage level of that protein. The example of ongoing studies on this fact is the cleavage of full-length amyloid precursor protein (APP) resulted to the production of toxic product called amyloid β (Aβ) peptide which get aggregated onto the neurons and cause AD (O'Brien & Wong, 2011). Similarly, this toxic-fragment model appears to be appropriate to some polyglutamine diseases like spinocerebellar ataxia type 3 and HD (Shao & Diamond, 2007). This notion also proves to be helpful in therapeutically tracing of NDs. The chapter highlights the physiological functioning of brain, structural and functional brain changes in ageing and neurodegeneration. The chapter also focusses on the factors which are responsible for aging and neurodegeneration.

BACKGROUND

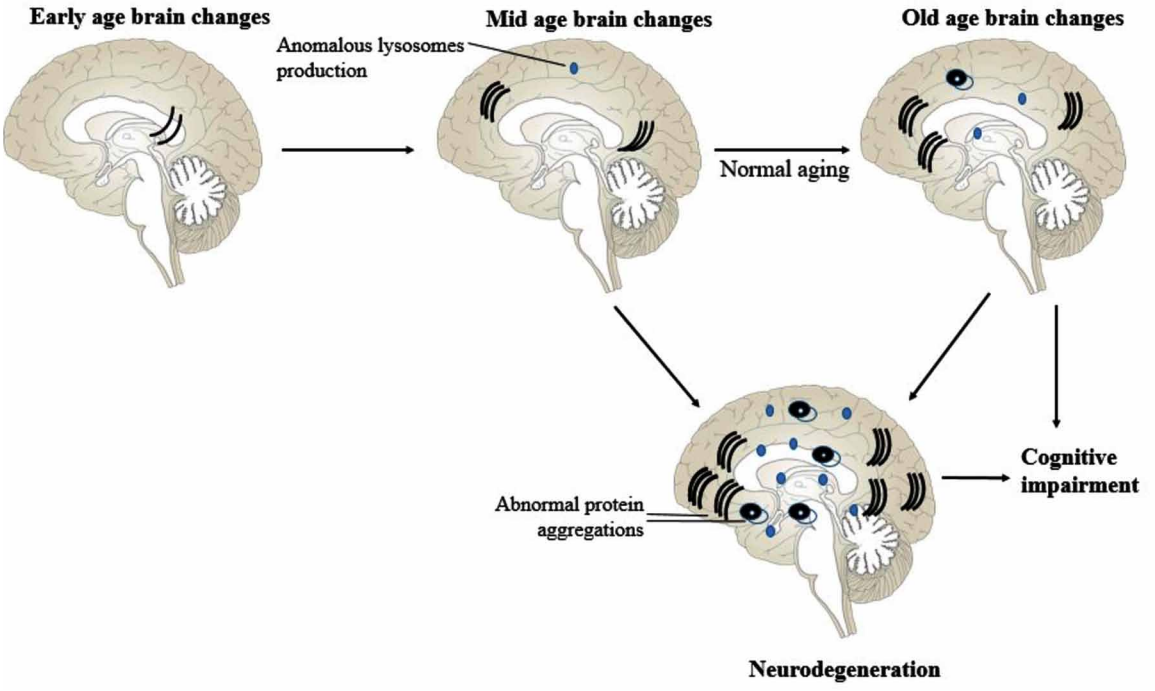
Relatively, neurons shrinkage, synaptic spines reduction and decrease in amount of synapses expected to justify the reductions in gray issue (Zhou, Homma, & Poo, 2004). Additionally, the length of axons covered with myelin sheath is significantly reduced, nearly 50%. In neurodegeneration, major signs of alteration are structural, however far not functional and consistently found to be associated with clinical phenotype and disease severity which further inspected for its connectivity correlation of molecular pathology (Alexander, 2004) (Figure 1). Gradual change in neural cells cannot trigger these variations instead differences in the action of neural networks and, possibly, chronic intoxication by irregular proteins that can be overcome by the brain and help in the concept of therapeutic implications. ND, for example HD and PD, are linked with the intracellular aggregation of toxic proteins and some are produced by aggregate prone proteins (Gorman, 2008). These diseases are called proteinopathies that depends on the conditions wherein the proteins are predominantly cytosolic in HD and PD, mostly intranuclear (like spinocerebellar ataxia type 1), aggregation of endoplasmic reticulum (like mutations in neuroserpin causes familial encephalopathy with neuroserpin inclusion bodies) and extracellular secretion (for example amyloid-β aggregation cause AD) (Shelkovnikova, Kulikova, Tsvetkov, Peters, Bachurin, Buchman, et al., 2012). Study of transgenic and genetic data indicate that numerous mutations accountable for proteinopathies cause illness by conferring a toxicity amplification of function on the relevant proteins (Sweeney et al., 2017). For example, some minor mutations in α-synuclein and tau protein can be the major cause for types of PD and frontotemporal dementia respectively that promptly aggregate as compared to wild type proteins (Recasens & Dehay, 2014; Schulz-Schaeffer, 2010). Similarly, in case of HD, mutation in polyglutamine expansion cause increased tendency of their aggregation with polyglutamine tract length (Daldin et al., 2017). Consequently, there is a need to understand their levels of regulation in cellular processes, rates of synthesis and degradation.

PHYSIOLOGICAL FUNCTIONING OF BRAIN

Brain is the most integral and perhaps highly intricate organ of the human body. It is the powerhouse which controls all physiological and psychological functioning of the body. There are the three major parts of the brain called forebrain, midbrain and hindbrain which are further classified into smaller division with their specific functionality. Forebrain is accountable for processing of sensory information gathered from five sensory organs i.e. skin, nose, eyes, tongue and ears (Posner & Rothbart, 2007).

Forebrain is further divided into diencephalon and telencephalon. Diencephalon included thalamus and hypothalamus region which coordinately manage the sensory and autonomic processes whereas telencephalon comprise of the biggest part of the brain known as cerebrum. The outermost surface of the neuronal tissues in cerebrum is called cerebral cortex. The medial longitudinal fissure of the cortex divides it into two main sections called right cerebral hemisphere and left cerebral hemisphere. The basic functioning of cerebral cortex comprises of motor areas, sensory areas, and association areas. The motor areas positioned in both the hemispheres have its major concern with the regulation of voluntary movement. With the significance of the name, sensory areas are connected with the processing of the data collected from the senses. The association areas are primarily assist the abstract thinking and language and also support in producing expressive perceptual experience of the surrounding world (Bailey, 2017).

Figure 1. Schematic diagram representing structural brain changes in neurodegeneration



Midbrain is situated between the forebrain and hindbrain like a bridge which transmit the signals form hindbrain to forebrain coming from touch and hearing senses, gathered by sense organs i.e. skin and ears respectively. Optic tectum is the upper region of the midbrain that helps in combining visionary and auditory records (Bailey, 2017).

The main function of hindbrain is to regulate specific visceral functions in human body like heartbeat, blood pressure and breathing. Hindbrain is also divided into three parts namely medulla oblongata, pons and cerebellum. Pons are assigned with task of monitoring the waking and sleep functions in harmonization to the other parts of nervous system whereas the cerebellum synchronizes the association of arms and legs and also manage the processing of information of sensory which is received from visual and auditory systems (Tyler, Danilov, Bach-y-Rita, & Bach-y-Rita, 2007).

NDs in central nervous systems are grouped in diseases on the basis of the region of occurrence like basal ganglia, cerebral cortex, cerebellum and brainstem and further classification is done based on their major characteristics and properties. For example, the disorders that mainly concern the cerebral cortex are segregated to nondementing and dementing conditions. Notably, while AD is probably the most often mentioned source of dementing cortex pathology, dementia can seemingly be detected in no less than 50 various disorders. Furthermore, dementia is witnessed in NDs and various toxic, metabolic, ischemic, traumatic and infectious insults of the brain. However, on the basis of abnormal movement phenomena, the basal ganglia diseases are categorized as hyperkinetic or hypokinetic. Hypokinetic disorders of the basal ganglia are characterized by PD, where the speed and amplitude of actions are reduced and in severe situations, even nonexistent, subject suffocates like a prisoner in its own body (Purves et al., 2001). On the other end, hyperkinetic basal ganglion disorders that are exemplified by essential tremor and HD (Magrinelli et al., 2016). In mentioned circumstances, extreme abnormal movements like tremor or

chorea are overlaid onto and restrict the normal voluntary movements. Whereas, division of NDs of the cerebellum and its associated networks is mostly demanding due to the noticeable connection amongst the several pathological conditions. Certainly, diseases related to cerebellum are classified into three foremost neuropathological categories: pontocerebellar atrophy (lesion altering some brain structures and cerebellar) (Namavar, Barth, & Baas, 2011), friedreich ataxia (lesion influencing the spinal cord at the posterior column, heart and peripheral nerves) (Bidichandani & Delatycki, 2017) and cerebellar cortical atrophy (injuries constricted to the inferior olives and purkinje cells) (MacKenzie-Graham et al., 2006). There are some diseases of cerebellum which can't be grouped in mentioned classifications like dentatorubral degeneration, where the most pronounced injuries are located in the red nuclei and dentate. Machado Joseph disease, where degeneration includes the upper and lower motor neurons, dentate system and substantia nigra (Paulson et al., 1997).

PROCESS AND MECHANISM OF AGING

With the time passes, brain displays several anatomical, molecular, and functional variations and leads to escalated frequency of neurological disorders and traumatic brain lesions (McKee & Daneshvar, 2015). Aging of brain comprises of depletion of brain structural integrity, changes in the levels of hormones, enzymes, deregulated metabolism, elevated oxidative stress, genetic and epigenetic modulation, varied protein processing and synaptic function and together these alterations directed to disability in physiological and cognitive functions (Chakrabarti et al., 2011). Initially in brain aging, prevalent volumetric brain damage is observed in frontal cortex, temporal cortex, putamen, thalamus, and nucleus accumbens. Also in MRI analysis, it was observed that there is a reduction in grey matter volume whereas the white matter volume increases in frontal, parietal and temporal cortices, insula and superior parietal gyri in both males and females (Terribilli et al., 2011). The reductions in the brain volume cause because of neuronal shrinkage, deduction in synaptic spines, dropped level of synapses and length shortening of myelinated axons. With the aging progression cerebral ventricles enlarge, this phenomenon is called ventriculomegaly and further was studied biomechanically in depth with significant applications to hydrocephalus by Wilkie et al. 2012 (Wilkie et al., 2012). Also, permeability through blood brain barrier (BBB) increases with aging (Rosenberg, 2014). Incorporating neuroanatomical changes during aging with molecular variation comprising alteration in neurochemicals, genetic and epigenetic factors.

Chemical Changes

Aging of brain includes noted variation in the levels of neurotransmitters, hormones, enzymes and other metabolites. In the study conducted by Ota et al. 2006, the level of dopamine reduce down by 10% per decade from initial adulthood as a result of dopaminergic neurons damaging present in between frontal cortex and striatum and due to the reduction in binding affinity and amount of dopamine receptors (Ota et al., 2006). Loss in dopamine level is related with the decline in motor and cognitive performance due to progression of aging. The level of serotonin (Meltzer et al., 1998) and glutamate (McEntee & Crook, 1993) also goes down with aging which is responsible for synaptic plasticity loss in old brain. Activities of neurotransmitters regulated by enzymes such as monoamine oxidase enhance with aging and cause the release of free radicals from reactions which reserve the inherent antioxidants (Kumar et al., 2012).

Other important elements that affect the brain aging and cognitive performance are hormones such as growth hormones, melatonin, thyroxine and sex hormones involving testosterone, estrogen, progesterone and DHEA (dehydroepiandrosterone). During brain aging, these hormones declines and the stress hormones cortisol increases significantly (Sorwell & Urbanski, 2013) which is believed to be a severe risk factor for cardiovascular disorders, instant brain aging and obesity. Functional and structural changes during aging are credited largely to modulate the level of estrogen that primarily acts through its estrogen receptor (ERα and ERβ) and intracellular receptors. The expression of those receptors is controlled by various factors comprising of their very own ligand estrogen, and others like thyroid hormone and growth bodily hormone and. The amounts of these factors reduce with aging that signaling resulting in alterations in brain functions (Näntö-Salonen, Muller, Hoffman, Vu, & Rosenfeld, 1993). Recent report which ER 13 interacts with casein kinase2. Phosphokinase N and C - myristoylation, present in mitochondrial and nuclear proteins may be useful to regulate gene regulation in mind for therapeutics (Giorgi, De Stefani, Bononi, Rizzuto, & Pinton, 2009).

Insulin and Insulin-like growth factors (IGFs) have been progressively recorded as molecules that are significant in regulating the speed of aging in humans (Hammerman, 1987). Increased insulin levels and immunity with advancing age influences integrity, brain blood vessel function and energy metabolic process and imposes the chance of developing dementia in late life. The brain aging may suffer from impaired glucose metabolic process or an input of sugar due to collapse of cerebrovascular efficiency. Recent studies show that lactate level in the brain produced by a change from the lactate dehydrogenase (Bergersen, 2015).

Genetic Changes

Expansion in gene expression studies like microarray analysis of genes has helped to comprehend the molecular mechanisms underlying the changes which occur during brain aging. Most of gene expression studies in human brain across the lifetime show changes in molecules associated with anxiety, inflammation, immune response, mitochondrial function, expansion factors, neuronal survival, synaptic plasticity and calcium homeostasis. Evaluation of phylogenetically distant organisms has shown some widely conserved functional classes genes with expression changes which are age-dependent (Gout, Kahn, Duret, & Paramecium Post-Genomics, 2010). While enzymes associated with stress response, inflammation and DNA repair are up regulated. Mitochondrial genes are repressed in process of aging in all the individuals studied. As purposed by Bishop et al. (2010), in analysis of transcriptional profiling of the aging process of cortex in rhesus macaques, humans and mice, the biggest conserved shift was age-dependent increased regulation of apolipoprotein D which functions as a lipid anti-oxidant conferring immunity and is induced in the brain of organisms with AD (Bishop et al., 2010). Different areas of the forebrain exhibit gene profile vary with age. For example, superior frontal gyrus shows a remarkable alteration in expression of gene although changes in the entorhinal cortex are mild. Changes happening in 60-70 years old individuals across the whole cortical region indicate it to be a transition point in aging of brain.

In hippocampus, CA1 (cornu ammonis 1) region is more vulnerable to aging and exhibits a higher number of changed genes relative to dentate gyms (DO) and the CA3 and an increase in expression of genes linked to the apoptosis and immune response (Shah & Zeier, 2013). Male brain is illustrated by global decrease in anabolic and catabolic capacity with aging, and down-regulating genes which are involved in protein transport/synthesis and energy production. Improved immune activity is a leading feature of aging in both genders, with correspondingly greater female brain activation. Besides regional

and gender differences, gene expression has also been shown to be specific for neurons and glia. It is suggested that glial-enrich genes is largely correlated with immune system and complement activation is up regulated, whereas neuronal enriched genes related to synaptic structure and function, calcium regulation, signal transduction and transmembrane receptors, are largely down-regulated with age. Even among glial genes, astrocyte markers are up -regulated while oligodendrocytic genes are repressed during aging (Loerch et al., 2008).

Epigenetic Changes

Besides genetic alterations, the emerging field of epigenetics indicates that building-up of abnormal epigenetic marks comprising histone and DNA modifications can be a driver of aging-related physiological and cellular alterations. Study of Zeng et al. (2011) reveal that age-reliant shortfalls in long-term loss of hippocampal dendritic spines and synaptic plasticity in the aged Fischer 344 rats are closely related with upregulation of histone deacetylase (HDAC2), reduction in histone acetylation, and decrease in expression of histone acetyltransferase (Zheng, Seabold, Horak, & Petralia, 2011). Further examination discloses brain-derived neurotrophic factor (BDNE) as one of the crucial genes affected by such changes. Age-dependent reductions in 113 and 114 acetylation are noticed in multiple promoter regions of the *BUM* gene indicating the impairment of downstream signaling in the aged hippocampus and a substantial reduction in BDNE expression. These discrepancies could be salvaged by enhancing the expression of trk13 and 13DNI by inhibition of FIDAC or via directly activating trkB receptors with 7,8-dihydroxyflavone which is a newly recognized, selective agonist for trkB. Epigenetic changes in genes like *Arc* and *zif268* in vulnerable brain regions of hippocampus and prefrontal cortex are also related with age-associated cognitive deficits (Penner, Blair, Albrecht, & Dovidio, 2014). Dynamic alterations in the structure of chromatin across the lifetime could potentially either contribute to enhanced aging and age-related dysfunctions in other cases, or counter aging and age -linked disorders in some cases. Despite the identification of several genes influencing brain aging and overall lifespan, an important question still remains unanswered if age-associated cognitive alterations are facilitated by any of the chief regulators of aging and lifespan identified in model organisms.

NEUROBIOLOGICAL MECHANISMS ASSOCIATED WITH AGE-RELATED COGNITIVE DECLINE IN HUMANS

Memory processes are strongly affected by experiences of life. Among life experiences, stress is proved to modulate memory function (Sandi, 2004). Stress is one of the major factors involved in cognitive decline in humans. Stress is a condition that varies as per the situation. There are circumstances that require moderately acquired adaptations from the individual and there are situations that may be tremendously persistent and adverse. But it is an inevitable entity since life constantly deals with challenges and changes. Since the concept of stress varies from person to person, the impacts of stressful experiences on cognitive functions vary. Stress within limits can facilitate information storage, which is helpful while learning and retaining things but experiencing excessive stress can be highly harmful to the memory function (de Kloet, Oitzl, & Joëls, 1999; Roozendaal, 2002; Sandi, 1998).

Stress

Stress is a biologically substantial factor and has a profound effect on the functioning of the brain. It can amend the properties of brain cell and is also able to interrupt cognitive processes, subsequently limiting human life quality. Increasing stress increases the glucocorticoid hormone in the body (Rajeswaran & Bennett, 2013). The stimuli that exert harmful impacts on individual fall under the category of stressors. The way in which an individual interprets a situation and responds to it plays a crucial role in determining whether a stimulus is a stressor or not. Usually, these responses work in accordance with the previous experiences of individuals (Council, 2001; Hibberd, Yau, & Seckl, 2000; McEwen, 2002). Lifetime exposure to anxiety and the consistent upsurges in glucocorticoid hormones are suggested to be crucial factors leading to the acceleration of cognitive decline in the aging individuals. Therefore, in addition to increasing the extent of cognitive disturbances detected in aged individuals, stress can also increase their appearance. Aging is related with decreased feedback sensitivity of the HPA (hypothalamic-pituitary-adrenal) axis to pharmacological challenges and higher basal cortisol levels and (Wilkinson, Peskind, & Raskind, 1997; Wolf, Convit, de Leon, Caraos, & Qadri, 2002). Studies have shown that increasing stress with increasing age leads to inferior learning abilities. Middle age is more susceptible to younger age to stress-induced cognitive disturbances.

FUNCTIONAL CHANGES IN AGING

Aging impacts a variety of brain functions including attention, speech, sleep, decision making, working and long term memory (Hedden & Gabrieli, 2004). Experiments with rodent models show that old age exhibits decline in cognition and motivation, decreased interest in novel tasks, motor disabilities and increased anxiety. These changes show corresponding pattern in primates and humans.

Sleep

Sleep dysregulation is a usual ailment amongst the elder people. Sleep alteration which are related to age include sleep fragmentation, insomnia, circadian advance, and loss of slow, deep wave sleep whereas daytime indicator consists drowsiness, increase in napping and breakthrough sleep (Blalock, Buechel, Popovic, Geddes, & Landfield, 2011). Also, healthy younger adults subjected to experimentally induced selective deficiency of night time (stationary phase) deep sleep demonstrates some aging- for example phenotypes, including daytime sleepiness, biochemical and metabolic dysfunctions and cognitive deficits. Recent studies propose that slow, deep wave sleep during the inactive period promotes memory, possibly through localized synaptic protein synthesis effects (Buechel et al., 2011). Therefore, the impaired slow wave sleep seen with age might contribute to cognitive deficits. Inspite the apparently alike effects of sleep dysregulation and age on cognition, and high incidence of sleep variations with age, relatively few studies have examined probable mechanistic relations between sleep architecture changes and cognitive decline which is related to age.

Working Memory

Older adults exhibit significant deficits in working memory (Schulze et al., 2017). Whilst, the mechanisms of these ages-associated deficits are still obscure, decline in the activity of prefrontal cortex has been attributed to age dependent deficits in working memory.

Episodic memory is principally affected by ageing. It stands for the memory for specific experiences or events that occurred in the lifespan (Fjell & Walhovd, 2010). A great problem for elderly is the recollection of context or remembering of source information; when or where something was heard or read, or even whether something actually occurred or was just thought about, what has been known as "reality monitoring". Although semantic memory is principally conserved during aging, older people provide general information rather than specific details.

Attention

Older adults show significant impairment in attention. Frontal lobe that requires switching or dividing of concentration among various tasks or inputs, plays an integral role in conduct of cognitive functioning of attention (Fjell & Walhovd, 2010). Prominently, these types of tasks appear to be responsive to training and show benefits of cardiovascular fitness. Attention deficits can have a noteworthy effect on old person's ability to function properly and independently in day to day life. One vital aspect of the day to day functioning affected by attention problem is driving. Driving is an activity that is essential to independence for many old people. Driving necessitates a constant switching of attention in response to surrounding eventualities. Attention must be distributed between observing the surroundings, driving, and selecting relevant from irrelevant stimuli in a jumbled visual array. Research has shown that increased automobile accidents in older adults result from divided attention impairments (Owsley & McGwin, 2010).

Decision Making

Comparatively little research has been done on the effect of aging on decision-making. It has been noticed that while making decision, old people tend to rely more on previous information about the problem and less on new information however young people probably have less knowledge about the prior information and incline to sample and assess more recent information and ponder upon more alternatives before making their decisions (Miller, 2010).

FACTORS AFFECTING BRAIN AGING

Multiple factors affect the rate of brain aging, while some of them accelerate, others slow down age-related worsening and slow down the completion of pathological levels. Recognizing such factors is crucial to design therapeutic strategies. Some of the factors that modify brain aging are discussed below:

Hypertension

Hypertension is a chronic age-linked illness which is related to numerous changes in the vascular system (Cabeza, Nyberg, & Park, 2016). Chronic raise of blood pressure affects structure of brain and people with medically controlled hypertension are at lower threat for cognitive decline than those who are undiagnosed or untreated. Hypertension accelerates age-related shrinkage of the hippocampus (Raz, Rodrigue, & Haacke, 2007). Individuals with vascular disease factors like hypertension display longitudinal decline in the regions that are generally stable in normal aging, for instance the primary visual cortex. Indeed, in contrary to the hale and hearty adults, individuals with vascular risk factors and vascular disease show rapid expansion in parietal areas and this increase in the pace of expansion is connected with higher systolic blood pressure. Unfortunately, the knowledge of neuroanatomical correlates of hypertension in standard animal models is scarce. Though, selective susceptibility of the prefrontal regions to hypertension is observed in impulsively hypertensive rats, and treatment with antihypertensive agents displays remarkable neuroprotective effect in the prefrontal cortex (Raz & Rodrigue, 2006).

In addition to hypertension, metabolic markers of cardiovascular risk may be linked with structural differences in the brain usually credited to aging. Homocysteine (Hey), an amino acid produced with involvement of vitamins of the 13 group as co-factors, is one such marker. In healthy adults, Hey escalation is connected with deterioration of the hippocampus, reduced total Grey matter volume and ventriculomegaly. Increased plasma Hey levels predict cognitive decline in nondemented elder individuals, and is related to poor performance on a wide variety of neuropsychological tests, exclusively those measuring delayed executive control and recall (Raz & Rodrigue, 2006).

Stress and Depression

Another cause backing to variable changes in brain function associated with age is individual differences in the stress system arising either due to natural genetic variation or through exposure to a variety of stress causing elements over the lifespan of the individual. Stress has an important influence on the brain throughout the lifespan. Early life stressful experiences initially impair learning and memory processes but enhances emotional memory formation later in life (Shors, 2006). Recent research has reported that people who are exposed to chronic stress or who have shown recurring depression exhibit accelerated brain aging. With growing age, telomeres become short, and studies have shown that this shortening is accelerated by oxidative stress and inflammation (Kordinas, Ioannidis, & Chatzipanagiotou, 2016). On this basis, length of telomere has been linked to age -related diseases and, unhealthy lifestyle and longevity. Also, it has been proposed that telomere length is a determinant of biological aging. Recent research demonstrates that tinier telomere length is linked with both cortisol levels revealing the exposure to prolonged stress and repeated depression (Wikgren et al., 2012).

Vascular Factors and Dementia

White matter lesions (WML), small vessel disease, strokes and dementia increase with growing age and all of them are the damages linked to vascular factors and blood pressure and. Increased cardiovascular risk, decrease in cerebral blood flow, vascular density and cerebral reactivity are associated with WML or hyperintensities (Artero et al., 2004; Kuo & Lipsitz, 2004) (Marstrand et al., 2002). It is yet vague if the

WML causes the vessel loss or vice versa. (Moody et al., 2004).WML are more prominent in frontal than posterior regions of the brain and is related to reduced cognition (Artero et al., 2004; Petkov et al., 2004).

Along with contributing to the cognitive complications in ageing, vascular factors also give rise to the two most common dementias. The incidence of dementia increases exponentially with the increase in age. It is around 20% of those aged 80 and rising to 40% of those aged 90 (Lobo et al., 2000). The two types of dementia seen most frequently in the elder people are Alzheimer's disease (AD) and vascular dementia (VaD) which account for around 40%–70% and 15%–30%. of dementias respectively (Fratiglioni et al., 2000; Lobo et al., 2000). There is an intersection between these two dementias and studies have exposed that AD falls under the category of vascular disorders. A postmortem study found that 77% of VaD cases showed AD pathology (Barker et al., 2002) and high blood pressure has been associated with increased neurofibrilliary tangles characteristic of AD (Sparks et al., 1995). Multiple types of vascular pathology have been associated with AD including microvascular degeneration, disorders of the blood-brain barrier, WML, microinfarctions, and cerebral haemorrhages (K. Jellinger, 2002). It has been suggested that large vessel factors, for example, atherosclerosis, increase the risk of AD and may play a part in cerebral vessel amyloid deposition (Ellis et al., 1996). AD patients do show significantly higher levels of cerebrovascular pathology when compared with controls at postmortem examination (K. A. Jellinger & Mitter-Ferstl, 2003) although this did not correlate with severity of cognitive decline. The characteristic neurofibrillary tangles and plaques found in AD are also evident to some degree in most elderly brains at postmortem examination even those without symptoms, as are white matter lesions (Wen & Sachdev, 2004).

Ageing and development of dementia has shown to be related to occurrence of diabetes, hyperhomocysteinaemia, hypertension, and a high cholesterol even though the proof for all but hypertension is far from clear (Areosa & Grimley, 2002; Budge et al., 2000; Fontbonne, Berr, Ducimetière, & Alpérovitch, 2001; Joosten, 2001; Shepherd et al., 2002). This could be avoided by incorporating changes in diet, reduction/avoidance of alcohol, and by doing regular exercise.

NEURODEGENERATION: PATHWAY AND MECHANISM

The specific conformational changes in proteins happen during neurodegeneration and these transformed proteins intrude the homeostasis of major ions and mitochondrial energetics of the cell (Ward, Zucca, Duyn, Crichton, & Zecca, 2014). These protein alterations are intermingled with multiple domains of cell dysfunction, including: genetic composition; epigenetic modification of genes; post-translational alterations in RNA; endoplasmic reticulum-related protein modifications, including phosphorylation and ubiquitination; cofactors of proteins like metal ions, chaperones; endosomal and lysosomal clearance. These altered proteins lead to the death of neurons by eliciting downstream microglial responses and neuroinflammation. The cell to cell transfer of these altered proteins leads to progression of neurodegeneration across the brain (Prusiner, 2013). The culprit proteins are specific for each ND. In AD, aggregation of amyloid, tau and TDP-43 proteins happen. In the case of PD, neuronal α-synuclein gets deposited. Generally, in all the NDs, monomers are generated and then they aggregate to give rise to oligomers and eventually they turn into insoluble form of the protein. The major abnormalities present in these disorders are unregulated autophagy and poor protein processing. These abnormalities hinder the protein disposal and proteostasis biogenesis, folding, trafficking and degradation of proteins. As stated above, these abnormal proteins lead to mitochondrial dysfunction and disrupted cellular energet-

ics (Guo, Sun, Chen, & Zhang, 2013). These abnormalities result in disturbed oxidative mechanism and increased free radical production.

STRUCTURAL BRAIN CHANGES IN NEURODEGENERATION

Progressive cerebral atrophy is a peculiar attribute of neurodegeneration. The dendritic and neuronal losses are the major causatives of atrophy (Johnson, Fox, Sperling, & Klunk, 2012). In neurodegeneration, volume of the grey matter (GM) and microstructural wholeness of the white matter (WM) tracts gets changed. The white matter consists of inferior longitudinal fasciculus (ILF) and inferior fronto-occipital fasciculus (IFOF). IFOF touches the superior frontal cortex rostrally and dorsal parietal and occipital cortex caudally. ILF connects the anterior temporal and the occipital cortices. IFOF is involved in visuospatial function, while ILF plays a role in visual memory. The pattern of loss differs between diseases reflecting regional disease expression and/or selective neuronal vulnerability. Studies have revealed that in individuals with Parkinson's disease with dementia have dispersed prefrontal cortex and parietal–temporal atrophy (Burton, McKeith, Burn, Williams, & O'Brien, 2004; Camicioli et al., 2003; Junqué et al., 2005; Kenny, Burton, & O'Brien, 2008; Tam, Burton, McKeith, Burn, & O'brien, 2005). The individuals distressed with Parkinson's disease with non-demented or have minor cognitive impairment have displayed varying degrees of atrophy for the amygdala, hippocampus, parietal–temporal cortex and prefrontal cortex (Beyer, Janvin, Larsen, & Aarsland, 2007). In Primary open angle glaucoma (POAG) patients, GM atrophy was observed in the lateral region, medial region, most anterior, and most posterior parts of the visual cortex (Boucard et al., 2009). Some studies have revealed that the thickness in cortical region in primary and secondary visual cortex gets reduced in POAG patients (Yu et al., 2013). Additionally, individuals suffering from POAG exhibited GM atrophy in regions involved in processing of cognitive functions such as the fronto-orbital cortex (decision-making), hippocampus (memory) and superior parietal lobule (spatial orientation). Remarkably, several of these structures are significantly involved in the tau pathology of AD (Frisoni, Fox, Jack, Scheltens, & Thompson, 2010). Studies reported that AD is identified by a sneaky start and unstoppable progression of atrophy that is manifested firstly in the medial temporal lobe (Scahill, Schott, Stevens, Rossor, & Fox, 2002). Usually, the earliest site of atrophy is the entorhinal cortex, shadowed by the hippocampus, amygdala, and parahippocampus (Chan et al., 2001; Dickerson et al., 2001; Killiany et al., 2002; Lehericy et al., 1994). Other structures like posterior cingulate are also affected earlier. These neural damages then binge on spreading to include the temporal neocortex and then all neocortical association zones.

TECHNIQUES AND ADVANCE IMAGING TO IDENTIFY THE PROGRESSION OF NEURODEGNERATION

Usually, NDs have a long latency period, during which pathological changes happen, followed by the inevitable neuronal damage. This period is known as pre-symptomatic period. There are certain biomarkers and advance imaging techniques which helps in identifying pre-symptomatic individuals with indication of neurodegenerative change. They are also used assess the stage of their disease.

Biomarkers

A biomarker could be a naturally occurring molecule or gene or a characteristic that plays a key role as an indicator of usual biological developments, pharmacological reactions, or pathogenic processes to a therapeutic intervention. Brain imaging or patient-derived fluids (CSF, blood, urine, saliva) may provide the relevant information about the biomarker (Gonzalez-Cuyar, Sonnen, Montine, Keene, & Montine, 2011). Biomarkers for NDs are less well developed and explored, but the discovery of useful biomarkers across NDs is anticipated. But in the AD, amyloid protein is measured by CSF biomarker and provides total insight into disease pathophysiology and progression. Fluid biomarkers include both trait (e.g., genetic) and state (e.g., CSF markers) measures. Genetic biomarkers are used to detect individuals who are at risk b identifying mutation carriers, risk polymorphisms etc. State biomarkers are used in the identification of pre-symptomatic individuals and to support the accuracy of disease diagnosis. Genetic biomarkers are used to detect individuals who are at risk. State biomarkers are used in identification of pre-symptomatic individuals and to support diagnostic accuracy of disease diagnosis.

Brain Imaging Techniques

The most extensively used neuroimaging technique for examination of neurodegeneration in vivo is structural MRI. It has the ability to do both local and global assessment of atrophic brain changes. It can also be used for assessing function of brain. Magnetic resonance spectroscopy [MRS], diffusion tensor and diffusion weighted imaging [DTI/DWI], and perfusion imaging are more advanced structural MRI techniques and are used in investigation of dementia (Risacher & Saykin, 2013). DTI/DWI techniques quantify the wholeness of tissue using mean diffusivity (MD) or apparent diffusion coefficient (ADC) and fractional anisotropy (FA) (Huisman, 2010). Decreased FA and elevated MD/ADC are considered to be indicators of reduced gray matter and white matter integrity and neuronal fiber loss. Biological metabolites in target tissue can be quantified by MRS. Two major metabolites that leads to alterations are myoinositol (mIns) and N-acetylaspartate (NAA). Former is a measure of glial cell production and neuronal destruction while later is a marker of neuronal integrity.

Along with other imaging techniques, cerebral perfusion is also usually measured in studies of neurodegeneration (Risacher & Saykin, 2013). It is done by using techniques like PET and SPECT, which incorporate the use radiolabeled ligands to measure perfusion, neurochemical, and metabolic processes in vivo. In studies of neurodegeneration, SPECT is used to estimate brain perfusion while PET (positron emission tomography) is used to evaluate the functional changes in the neurotransmitter, metabolism of brain, and the level of other proteins. This assessment can deliver significant information about degenerative alterations occurring in the brains of diseased individuals.

Functional MRI (fMRI) is used for measuring the activity of brain during a sensory, cognitive, or motor task or at rest by quantifying blood oxygen levels and blood flow. The primary outcome measured in most fMRI studies is blood oxygenation level dependent (BOLD) contrast signal in which regional brain activity is measured via changes in local blood flow and oxygenation (Ogawa et al., 1992). The BOLD signal is a useful measure for brain activation (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). The altered neuronal metabolism and blood flow due to brain atrophy may cause alterations in the BOLD signal. fMRI studies often evaluate brain activity during cognitive or functional motor tests. In addition to estimates of regional task-related brain activity, quantification of brain networks can provide a unique measure of brain activity (Greicius, Krasnow, Reiss, & Menon, 2003).

FUTURE RESEARCH DIRECTIONS

One of the major hurdles of forthcoming research will be the identification of significant factors that govern individual differences in susceptibility to stress, hypertension, and aging.

The biomarkers for NDs are less well developed and explored, so future studies will focus on the discovery of useful biomarkers across NDs. It will help in detection of disease prior to its onset and thus could help in treating it effectively. Future studies will be focusing on utilization of novel techniques for understanding the pathology of NDs, unveiling of disease at initial stage, and the development of targeted therapeutics. The advances in neuroimaging will help in improving the clinical diagnosis by detecting the disease even prior to its commencement, and its early intervention by embracing the potential therapeutics (Risacher & Saykin, 2013). It is anticipated that advanced neuroimaging techniques for diagnostics will significantly enhance the specificity, sensitivity and accuracy of diagnosis. The framework for development of preventive therapies is also expected. Future studies may also include developing a probable and multicentre design of novel tools meant for the purpose of diagnosis; assessment of various potential biomarkers and conduct of a clinical trial (till death as end-point) that can assess both clinical features and determine the biological diagnostics and ultimately neuropathological confirmation by inspecting the brains of patients at death (Agrawal & Biswas, 2015). However, pre-symptomatic detection and preventive treatment management of neurodegeneration and age-related cognitive decline will be the greatest future impacts of existing techniques and those under development (Small et al., 2008).

CONCLUSION

Stress and hypertension are the most common factors associated with nearly all NDs, resulting in neurofibrillary tangles, Aβ plaques and brain atrophy which lead to modulation of structure and functions of the brain. The increasing incidence of hypertension due to the aging population worldwide and rising occurrence of stress can also escalate the count of people suffering from ND, since midlife hypertension nearly doubles the possibility of developing diseases like AD in later life. These factors lead to the decline in cognition and memory function. Unnecessary and enormous stress experienced at difficult time windows of life can intensely affect cognitive function at later stages, with a particular effect on cognitive aging. There are certain biomarkers both genetic and state which are helpful in pre-determination of disease. They can be observed by neuroimaging or by analyzing patient-derived fluids. Imaging studies of NDs are extremely enlightening regarding structural, functional, and molecular changes in brain. Neuroimaging techniques cannot be taken into account for differential diagnosis of various diseases, but they have proved to be helpful. Further studies with advanced MRI techniques and future PET tracers for proteinopathies beyond amyloid (i.e., tau, α-synuclein, and TDP-43) will probably provide even more data about pathology associated with the various degenerative and dementing syndromes. Additionally, neuroimaging techniques may prove to be useful in conduct of clinical trials of novel therapeutics intended to treat these disorders for both monitoring changes related to disease or as end-points to complement present clinical outcome measures.

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Chapter 2
Oxidative Stress and Neurodegeneration

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ABSTRACT

Neurons are the building units of the nervous system and are therefore critical units for the health of the brain and the spinal cord. This is necessitated by their inability to be either replaced or reproduced once lost. Their losses are implicated in a number of conditions which have been elaborated in this chapter. Oxidative stress has been strongly implicated in neurodegeneration through blockade of neuroprotection by a number of mechanisms including inhibitory effect on insulin-like growth factor I (IGF-1) via stimulation of the transcription factor, Forkhead box O3 (FOXO3). This chapter elaborates on these two phenomena which cannot be decoupled.

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INTRODUCTION

Neurodegenerative disorders (NDs) are a group of pathological disorders that primarily affect neurons and are associated with progressive loss of neuronal structure and function, and death (Khan et al, 2016). Neurodegeneration is manifested in a number of disorders including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), prion disease, ophthalmological diseases, etc (Khan et al, 2016; Tezel, 2006).

Neuronal loss is triggered by a number of mechanisms which include inflammation and oxidative stress (Harris, 2014; Barreto et al, 2011; Cabezas et al, 2012). Protein misfolding, compromised chronic oxidative stress response, excitotoxicity, altered calcium homeostasis, reduced cerebral blood flow and supply, impaired phosphorylation, loss of gene expression regulating ability, changes in proteases/inhibitors and environmental factors also play a role in neuronal loss (Khan et al, 2016; Sayre et al, 2001; Leszek et al, 2016).

Oxidative stress has also been implicated aetiologically in the development of neurodegeneration in other conditions such as HD, a trinucleotide CAG repeat expansion polyglutamate toxicity disorder (Hensley et al, 2006), and ALS (Polidori et al, 1999). Despite the huge hereditary and biochemical confirmation of increased oxidative stress in NDs, and also the established therapeutic benefits of antioxidants in animal models, there is no success with clinical use of antioxidants in human subjects. Accordingly, the role of oxidative stress in the pathogenesis of NDs stays disputable.

A number of causalities have been attributed to the development of neurodegeneration. Such factors include environmental and genetic causes; however, oxidative stress continues to be ascribed to play a focal pathogenic role in their development (Mark, 2004). Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are generated in vivo as a result of oxidative stress and free radical generation. These two groups of reactive metabolites are believed to play a significant role in neurodegeneration (Emerit & Edeas, 2004). ROS are known to have significant impact on the neuronal biochemical composition. This is due to the high levels of unsaturated lipids in these neuronal biochemical molecules and their susceptibility to peroxidation and oxidative alterations (Uttara et al, 2009). Butterfield et al (2002) has also reported on the susceptibility of the double bonds in unsaturated fatty acids to free radical attack. This triggers a cascade of events that ultimately lead to the damage of neighbouring unsaturated fatty acids. Also, the brain tends not to have high levels of antioxidants to mop up free radicals when compared to other internal organs such as the liver (Uttara et al, 2009). Marklund et al (1982) has reported on the brain's reduced levels of catalase. This, coupled with the fact that the substantia nigra (SN) is enriched with iron and dopamine, both pro-oxidants, tend to increase the levels of reactive species in the brain (Zaleska et al, 1989). This chapter therefore discusses the relationship between oxidative stress and the development of NDs.

BACKGROUND

The pathological signature of NDs is the gradual, progressive and selective loss of anatomically or physiologically related neural systems (Leszek et al, 2016). With the loss of neuronal architecture in these multiple circuits comes the altered integrity of neuronal tissues and irreversible loss of brain function. This is mostly seen as cognitive deficits, dementia, dyskinesia, behaviour deviations and psychological

disorders (Garcia et al, 2017). Research has suggested the significant relation of these disorders at the subcellular level. This is encouraging finding which would help with the discovery of novel diagnostic and therapeutic potentials for NDs. Some established parallel pathways between various NDs include atypical protein assemblage and induced apoptosis; and these span from systemic to molecular levels. This points to the multi-level nature of neurodegeneration in neuronal circuits (Bredesen et al, 2006).

AD and PD are neuropathologically characterized by abundant insoluble protein deposits e.g., amyoid β peptides (Aβ [1-40/42]) and hyperphosphorylated tau in AD (Jimenez-Del-Rio & Velez-Pardo, 2012) α- Synuclein in PD (Forno, 1996), specific neuronal and synaptic loss of the hippocampal pyramidal neurons (AD), and substantia nigra dopaminergic neurons (PD), probably via oxidative stress (Wang & Michaelis, 2010). There are over 200 known pathogenic mutations among the three genes that encode for the proteins: Aβ amyloid precursor protein (APP), presenilin-1 (PSEN1), presenilin-2 (PSEN2), and the six genes that encode for the proteins: α-synuclein (*SNCA*), Leucine-rich repeat kinase 2 (*LRRK2*), *Parkin*, PTEN-induced putative kinase 1 (*PINK1*), *DJ-1*, and P-type ATPase 13A2 (*ATP13A2*). Both Bekris et al (2010a) and Bekris et al (2010b) have reported on the fact that these mutations have been established to play a significant role in the development of familial Alzheimer and Parkinsonism. Interestingly, these mutations are directly related to oxidative stress and mitochondrial dysfuntion (McCoy & Cookson, 2012). In AD, the conformational changes in Aβ leads to the accumulation of toxic fibrillary Aβ aggregates. Oxidative stress also causes tau hyperphosphorylation and aggregation (Van Raamsdonk et al, 2017).

There is an increased oxidative stress via mitochondrial dysfunction and this is accounted for by multiple genetic risk factors for AD. These genetic factors include apolipoprotein E allele APOE Ɛ4, CD2-associated protein (*CD2AP*), translocase of outer mitochondrial membrane 40 (*TOMM40*) and translocator protein (*TSPO*). Again, Van Raamsdonk et al (2017) identified other risk factors for AD which were the variant genes that should play protective roles against oxidative stress such as clusterin (*CLU*), glutathione S-transferase omega 2 (*GSTO2*), mitochondrial fission regulator 1 (*MTFR1*) and methionine sulfoxide reductase B3 (*MSRB3*). Neuropathological findings identify the involvement of SN depletion of dopaminergic neurons, with an associated decrease in striatal dopamine and formation of intraneuronal alpha-synuclein aggregates in most parts of the brain, to be a major contributing factor to the late-stage PD (Sanders et al, 2014). Although several studies point to the possible therapeutic benefits of antioxidant therapies in improving the pathogenic mechanism of PD, these therapies are yet to be translated into slowing of neurodegeneration in PD clinically (Van Raamsdonk et al, 2017).

OXIDATIVE STRESS AND INFLAMMATION IN THE BRAIN

Molecular damages arise from increased biochemical imbalances that result in enhanced oxidative stress. These molecular alterations can lead to significant failure in biological responses of cells and culminate in cell death (Burxer, 1974; Golikov, 1985). ROS are generated from imbalances in biochemical processes in almost all cellular components which include the cytoplasm, endoplasmic reticulum, lysosomes, nucleus, plasma membrane, peroxisomes, and mitochondria by the actions of enzymes like oxidases, peroxidases, dehydrogenases, lipoxygenases, and cyclooxygenases (Drose et al, 2014). Through the electron carriers of the respiratory chain, the mitochondria tend to play a significant role in the production of ROS hence its importance in neurodegeneration (Lenaz, 1998).

Mitochondrial oxidative damage has been described as crucial in the pathogenesis of AD as evidenced by reduced brain metabolism preceding the development of abnormalities in neuropsychological testing, thus suggesting a casual role of impaired brain metabolism in Alzheimer's pathogenesis (Meraz-Rios et al, 2014; de la Monte et al, 2014). Aluminium neurotoxicity has been attributed to its interaction with peroxisome proliferator activated receptor gamma co-activator-1α (PGC- 1α) hence a potential target in the prevention of mitochondrial-dependent neurodegeneration observed in NDs (Sharma et al, 2013). Some neurotoxic agents also cause damage to mitochondria via their ability to damage dopamine-producing cells found in the SN (Schuler & Casida, 2001).

Mitochondria is a target of most of the disease specific pathogenic mutant proteins and therefore account for the promotion of oxidative stress and the mitochondrial apoptotic pathway (Ferreiro et al, 2012). The prevalence of NDs increases with aging and aging is now considered as one of the strongest risk factors for PD (Collier et al, 2011). Although de Oliveira et al (2012) and Rikans & Hornbrook (1997) have identified the neuroprotective effect of low levels of ROS, oxidative stress has an important relation with NDs. Nitric oxide, in the presence of superoxide, forms a reactive peroxynitrite which causes cellular and tissue damage which implicates it in several diseases, including atherosclerosis, stroke, and AD (Mao & Reddy, 2010; Shin et al, 2005).

In the pathology of neurodegenerative disorders, the generation of free radicals are quite harmful as they affect nucleic acids, lipids, and proteins (Valco et al, 2006). Studies increasingly point to the involvement of oxidative stress in the development of prion diseases; these are fatal NDs. Henceforth, oxidative stress-induced mitochondrial and neuronal cell damages are suggestive of mitochondrial damage and dysfunction associated with prion disease progression. Acquatella-Tran et al (2013) attribute this to the initial prion disease development.

Although inflammation and oxidative stress are distinct biochemical processes, there is a close relation between them and they function in parallel in the brain due to its high susceptibility to oxidative stress (Leszek et al, 2016). Despite the fact that studies on the linkage between inflammation and oxidative stress are not conclusive, their interaction which explains their tendency to occur together and enhance each other is known. Inflammation activates and triggers oxidative stress and also activated microglia produce ROS as defense mechanism against pathogens or their markers (Barreto et al, 2014) which when exceeds levels that can be contained by the cell's antioxidant capacity may lead to cellular and tissue damage (Lau et al, 2007). Oxidative stress can also enhance inflammation via the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), a transcription factor which controls the expression of many genes including those involved in both acute and chronic inflammatory response (Avila et al, 2014).

GLUTAMATERGIC AND MITOCHONDRIAL INHIBITION IN OXIDATIVE STRESS-INDUCED NEURODEGENERATION

There is a linkage between the glutamatergic mechanisms and the mitochondrial function. There is a close association between glutamatergic alterations and mitochondrial impairment with each feeding the other in a vicious cycle where they tend to strengthen each other in their induction of the onset and progression of NDs as reported by Cassano et al (2016).

Mitochondria

Mitochondria, which are the power house of cells, play integral roles in apoptotic mechanism, lipolysis, regulation of cells redox potential, free radical scavenging and cellular calcium and iron homeostasis under the tight regulation of nuclear and mitochondrial DNA (mtDNA), and associated proteins (Correia-Melo & Passos, 2015). The multiple cellular and metabolic activities they undertake make the mitochondria very susceptible. There is continual generation of ROS within the mitochondria as a result of oxidative phosphorylation occurring within them and can in turn damage their structure and functions as well as those of other organelles within the cell (Camara et al, 2010).

Brain hypoperfusion has been attributed to oxidative stress and mitochondrial failure while coenzyme Q and creatine have also been reported by Aliev et al (2011) to account for the protective effect on metabolism of energy in cerebral hypoperfusion. The mitochondrial dysfunction is particularly problematic in excitable cells, which have exceptional energy requirements, because there is an increase in ROS production, and oxidative damage is responsible for NDs (Chauhan et al, 2012). Mitochondrial dysfunction can be attributed to strenuous exercise, stress, environment toxicants, injury, aging and cancer (Hassan et al, 2013). Intrinsic mitochondrial apoptotic process is the most common form of cell death observed in neurodegeneration (Elmore, 2007). The functionality of the mitochondria is tightly linked with cell biology and this is because the mtDNA of mitochondria is replicated and stabilized by nuclear encoded proteins, as reported by de Moura et al (2010). Chatterjee et al (2011) also observed that ROS can cause direct mutation in mtDNA or can indirectly affect nuclear DNA upon its leakage from organelles.

A number of factors account for the effectiveness of the mitochondria and cell although they have high levels of antioxidant enzymes. These factors include age, stress, nutritional status and the level of immunity the individual possesses (Rahman, 2007). This makes mitochondrial dysfunction a contributing factor to the development of NDs. Sporadic AD has been ascribed to mitochondrial dysfunction (Garc et al, 2013) with amyloid accumulation associated with inherited AD (Tang & Gershon, 2003). Mutation in nuclear gene coding and dysfunction in electron transport chain (ETC) complex I are factors implicated in PD development (Winklhofer & Haass, 2010).

There is an indirect correlation between the increased numbers in CAG trinucleotide repeats (CAG repeats) and the dysfunction in the complex II which arises as a result of mtDNA damage by ROS (Damiano et al, 2010). Reddy & Reddy (2011) also reported that accumulation of mtDNa, perturbation in oxidative phosphorylation and a host of other mitochondrial abnormalities are hallmark of early and late onset NDs. Also histopathological findings establishing mitochondrial damage have also been realized in NDs (Kolesnikova, 2013). It is however worth noting that there has been new body of knowledge on the mechanistic capabilities of mitochondria which has opened alternative avenues of study in this regard (Solis-Herrera et al, 2015; Herrera et al, 2015)

Disordered functioning of the mitochondrial chaperones such as the heat shock protein (Hsp) 60/Hsp10 complex accounts for the changes in the mitochondrial complexes seen in nervous system diseases such as AD and PD (Macario et al, 2010; Walls et al, 2012). There is a functional relationship between glutamate and the mitochondria (see Figure 1). Mitochondria play a significant role in regulating Ca^{2+} concentration and when there is impaired mitochondrial function, there is an increased cell death (Green & Kroemer, 2004). The uptake of Ca^{2+} by the mitochondria is of importance in the regulation of adenosine triphosphate (ATP) synthesis, the amplitude and spatiotemporal patterns of intracellular Ca^{2+} transients, the mitochondrial fission-fusion, dynamics the opening of mitochondrial permeability transition pores (mPTPs), and the generation of ROS (Gunter & Sheu, 2009; Drago et al, 2011). The

knowledge of mitochondrial Ca^{2+} uptake has long been known but the nature of the transporters involved in the uptake were known relatively recently (Baughman et al, 2011). The mitochondrial Ca^{2+} uniporter (MCU) is believed to shuttle Ca^{2+} into the inner membranes of the mitochondria (Cassano et al, 2016)

During resting conditions, the mitochondrial Ca^{2+} content is low, but when a cell is stimulated with a cytosolic Ca^{2+}-increasing agonist (e.g., glutamate, histamine, ATP), the mitochondria accumulate high amounts of Ca^{2+} via the MCU complex (De Stefani et al, 2011; Somlyo et al, 1985). Other findings point to the fact that MCU controls excitotoxicity and is transcriptionally repressed by neuroprotective nuclear Ca^{2+} signals (Qui et al, 2013). In particular, MCU increases mitochondrial Ca^{2+} levels following N-methyl-D-aspartate (NMDA) receptor activation, with a resultant increase in membrane depolarization within the mitochondria which culminates and cell death. There is a reduction in the NMDA-induced increases in mitochondrial Ca^{2+} when the MCU expression is reduced endogenously with resultant decrease and mitochondrial depolarization and resistance to excitotoxicity.

Qiu et al (2013) has reported on the role of MCU on activity-dependent adaptive mechanism that limits mitochondrial Ca^{2+} overload when cytoplasmic Ca^{2+} levels are high. The mechanism entails the transcriptionally repressing MCU via synaptic activity involving Ca^{2+} and Ca^{2+}/calmodulin-dependent protein (CaM) kinase-mediated induction of neuronal PAS domain protein 4 (Npas4). This leads to inhibition of NMDA receptor-induced mitochondrial Ca^{2+} uptake and eventually cell death due to excitotoxicity (Qui et al, 2013). Npas4 can promote negative gene regulation in neurons, and it is an immediate-early gene (Lin et al, 2008).

Several key pro-death pathways are activated in parallel in response to an excitotoxic insult, including NO and ROS production, oxidative stress, *c*-Jun N-terminal kinase (JNK) and poly (ADP-ribose) polymerase- 1 (PARP-1) activation, and cAMP response element-binding protein (CREB) shut-off (Lau & Tymianski, 2010; Borsello et al, 2003). How significant these are hinders on the cell type, stage of development and severity of cell damage. Hopefully, further findings on the MCU-driven Ca^{2+} uptake will elaborate on the number of excitotoxic pathways. There have been reported role of other mitochondrial Ca^{2+} uptake mechanisms although their molecular identities and specific roles in the Ca^{2+} transport cannot be ascertained. Among these, two other Ca^{2+}-transporting proteins, mitochondrial ryanodine receptor type 1 and leucine-zipper-EF-hand–containing transmembrane protein 1, have been investigated although further studies on them need to be done (O-Uchi et al, 2012).

Glutamate

As the most common excitatory neurotransmitter, glutamate plays important roles both in physiological and pathological brain function including the regulation of neurogenesis, neurite outgrowth, synaptogenesis, and programmed cell death (apoptosis) (Mattson, 2008; Shepherd & Huganir, 2007; Martin et al, 2000). There are both ionotropic and metabotropic glutamate receptors (Stayte & Vissel, 2014). The ligand-gated ionotropic glutamate receptors (iGluRs) permit the flow of ions through its Na^{+} and/or Ca^{2+} membranes once they are activated. NMDA, alpha-amino-3-hydroxyl-4-isoxazolepropionic acid (AMPA) and Kainate subtypes belong to this family of iGluRs (Hollmann & Heinemann, 1994; Wright & Vissel, 2012; Wiltgen et al, 2010).

However, metabotropic glutamate receptors (mGluRs) are G-protein coupled receptors. Upon ligand binding to these receptors, there is an initiation of a series of second messenger mediated intracellular reactions, which are involved in the signal transduction (Conn et al, 2005; Kuwajima et al, 2007). Brain levels of glutamate are very high, about 10 mM, but in the extracellular spaces of the brain the concen-

trations of glutamate are almost ten thousand times lower (1-5 μM), due to the role of the excitatory amino acid carrier 1 (EAAC1), glutamate transporter 1 (GLT1) and glutamate/aspartate transporter (GLAST). EAAC1 is present in the brain and works as a neuronal glutamate reuptake. GLT1, which is mainly expressed in astrocytes, is the most important carrier when it comes to keeping glutamate levels low in the extracellular spaces. GLAST is mainly activated when there is high glutamate levels and they are mainly expressed in glial cells (Niciu et al, 2012).

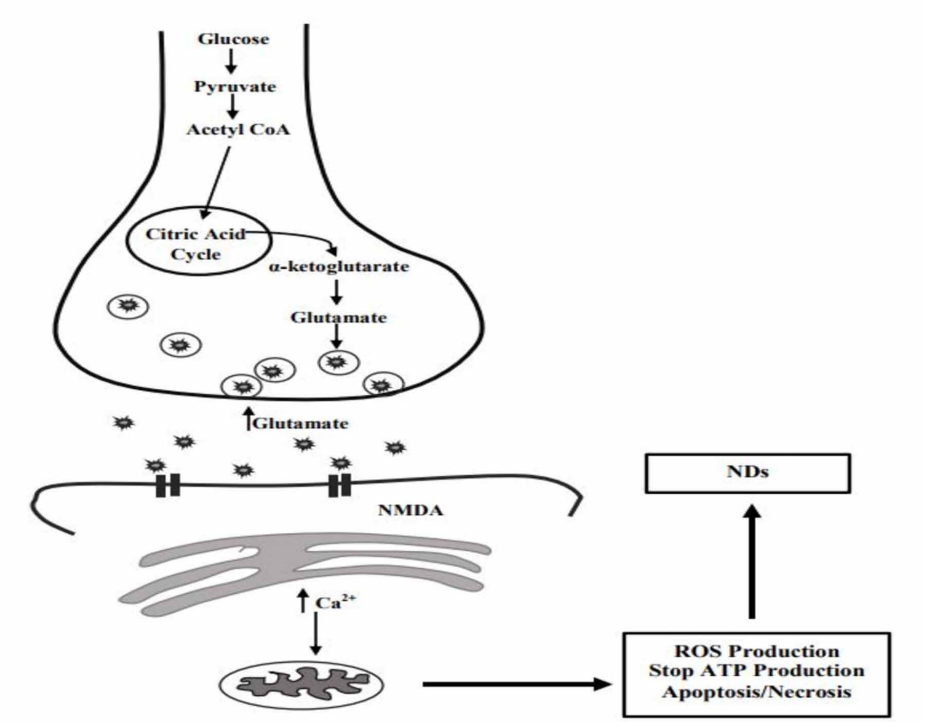
The metabolic relationship between astrocytes and neurons is critical for energy metabolism as well as for the synthesis of neurotransmitters. During the glutamatergic transmission, the arrival of an action potential causes a depolarization of the membrane, with consequent opening of Ca^{2+} channels and glutamate release into the synaptic cleft. Thereafter, the glutamate binds to its receptors and it is transported into the astrocytes through the GLT1, where it is amidated to glutamine in the glutamine synthetase pathway. Glutamine is metabolized to glutamate, indirectly generating gamma-aminobutyric acid (GABA) as well as the tricarboxylic acid (TCA) cycle intermediate, alpha-ketoglutarate (α-KG) in the neurons (Dienel, 2013; Cooper, 2012). Elevated extracellular glutamate levels can cause neuronal death in a phenomenon called "excitotoxicity" and it is involved in many neurological diseases in the CNS (Atlante et al, 2001; Yang et al, 2011).

Calcium ion overload accounts for the glutamate-induced excitoxicity. This is attributed to glutamate binding to NMDA receptors (NMDARs), and to a minor extent binding to other receptor subtypes (Yang et al, 2011; Nicholls & Budd, 2000). Other studies also link glutamate overstimulation to the excitotoxicity. Changes in the activation pattern of NMDARs at different subcellular locations have been proposed as critical in activating pathways leading to neuroprotection versus neurodestruction (Hardingham & Bading, 2010). NMDARs are also found at extrasynaptic sites (Clark et al, 1997), raising the possibility that the synaptic and extrasynaptic subsets of NMDARs play different physiological and pathological roles in the cell (Figure 1). In line with this, there is available evidence the role of differential activation of extrasynaptic relative to synaptic NMDARs in the development of glutamatergic neurotoxicity (Leveille et al, 2008; Xu et al, 2009).

There is activation of glutamate receptors (mainly NMDA) when there is increased concentration of glutamate. This leads to elevated Ca^{2+} levels within the mitochondria. Increased Ca^{2+} concentration contributes to impaired mitochondrial function, which triggers excitotoxic cell death via a number of connected pathways. Changes in the mitochondria such as increase in ROS, ATP synthesis failure contribute significantly to cellular disruption (Adapted from Cassano et al, 2016)

Extreme actuation of extrasynaptic pathways particularly initiates apoptotic signal transduction cascade advancing neuronal cell death, while activation of synaptic NMDARs has a neuroprotective part by means of Ca^{2+}-mediated signal transduction pathways advancing neuronal survival. The dichotomous neuroprotective and neurotoxic effects induced by initiation of the synaptic and extrasynaptic NMDARs, respectively, are mediated by complex regulatory activities on protective (anti-apoptotic, pro-survival and anti-oxidant) and pro-apoptotic genes (Papadia et al, 2008). Strangely, the noncompetitive NMDAR antagonist, memantine, shows differential consequences for synaptic and extrasynaptic NMDARs (Chen and Lipton, 2006). At low concentrations, memantine does not concentrate in the synaptic cleft to antagonize synaptic NMDRs; rather, it antagonizes extrasynaptic NMDARs, which spare their exposure to high levels of extracellular glutamate in pathological states like neurodegenerative processes (Xia et al, 2010).

Figure 1. Role of Ca^{2+} in the glutamatergic transmission



OXIDATIVE STRESS AND ALZHEIMER'S DISEASE

Oxidative Stress and Amyloid Beta Accumulation in Alzheimer's Disease

There is a convincing proof of oxidative damage in AD brain after death, with critical collection of markers of lipid, protein and DNA oxidation, and transition metals which include copper and zinc within the sight of impaired antioxidant defense (Butterfield et al, 2013). Redox proteomics investigation of after death AD brain shows oxidative harm to key proteins associated with energy metabolism, neurotransmitter-related proteins, mitochondrial proteins and proteasomal components (Butterfield et al, 2014). The cross talk between oxidative stress and Aβ proteinopathy may happen by means of numerous ways influencing transcription of the *APP* gene or translation of APP messenger RNA (mRNA), processing and degradation of APP and Aβ peptides and also associations of APP with transition metals. The promoter locales of the *APP* gene have been mapped in various species, and a few translation factors, for example, heat shock factor 1 (HSF-1) and NF-κB, which are receptive to ROS, can bind and play a role in *APP* gene induction (Theuns and Van Broeckhoven, 2014). APP mRNA contains a 5′-untranslated district (UTR) stem–loop order of the iron-responsive element (IRE), where the IRE-binding protein (IREBP) downregulates translation. There is a reported elevation of iron levels in AD brains which points to a link between oxidative stress and APP production (Huang et al, 2004).

The major processing enzymes of APP in the amyloidogenic pathway are β-secretase (BACE1) and γ-secretase (Dong et al, 2012). The effect on gene expression of BACE1 by the transcription factors

specificity protein 1 (Sp1), NF-κB, and hypoxia-inducible factor 1-alpha (HIF-1α), is often very complex, and may result in both up- and downregulation of *BACE1* gene depending on the cell types and the physiological or experimental conditions of the cells (Chen et al, 2013). A number of factors account for the varied response post transcription factors binding. Example, NF-κB's interaction with ROS is complex and could result in either activation or enhanced nuclear translocation under specific experimental conditions or decreased nuclear binding in others. In the same way, the nature of the subunits binding to the NF-κB binding sites may determine whether up- or downregulation of *BACE1* gene occurs (Kaur et al, 2015). Then again, there is evidence of an increase in the enzyme activity through stress-activated protein kinase from 4-hydroxynonenal (4-HNE) or oxidants (such as H_2O_2 and iron–ascorbate mixture, which are products of oxidative damage (Ganguly et al, 2017).

Also Ganguly et al (2017) has reported on the ability of oxidative stress to upregulate BACE1 activity at the translational level involving double-stranded RNA-dependent protein kinase (PKR) and eukaryotic initiation factor-2 (eIF2) phosphorylation. These findings give credence to the role of oxidative stree in increasing the activity of BACE1 in AD (Ganguly et al, 2017). From a study which elaborated on this, it was realized that oxidative stress-induced increase in BACE1 activity both in cultured cells and in experimental animals requires the involvement of γ-secretase and activation of the JNK/c-jun pathway. The γ-secretase enzyme complex, which is made up of presenilin1 (PS1), nicastrin, PEN2 and APH1, is also essential for the release of Aβ42 from APP, and its activity is heightened by oxidative stress through upregulation of PS1 (Tamagno et al, 2008).

The elevated levels of Aβ42 have been linked with oxidative stress in some studies and this happening is attributed to the expression and processing of APP (Misonou et al, 2000). Also, low-density lipoproteins receptor-related protein 1 (LRP1) and the receptor for advanced glycation end products (RAGE) are believed to inhibit the clearance of Aβ in AD due to the effect of oxidative stress (Ramanathan et al, 2015). There are two forms of LRP1; the membrane-bound form is responsible for the removal of cerebral amyloid beta to the circulation across the blood–brain barrier and is expressed in neurons, astrocytes, vascular endothelial cells and smooth muscle cells, while the soluble form binds the Aβ in the peripheral circulation while RAGE is found in the blood-brain barrier and functions to permit reentry of Aβ from the peripheral circulation (Deane et al, 2009). Ramanathan et al (2015) reports that there are changes in the membrane-bound LRP1 when there is oxidative stress and this goes a long way to impair the clearance of Aβ from the brain. Again, failure to properly bind to circulating Aβ, will lead to reentry into the brain.

Aβ is known to also increase the intracellular production of ROS and also contribute to neuronal death via its involvement with ASK 1 (Kadowaki et al, 2005). This Aβ-induced ROS production is believed to be due to its activation of reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. However, with mitochondrial production of oxygen radicals, mitochondria-targeted antioxidants have been shown to curtail their production (Hu & Li, 2016). An alternate mechanism of Aβ-induced ROS production is via activation and priming of microglial by soluble and fibrillary forms of the peptide. This is mainly seen in primary and co-culture of microglia and neurones (Qin et al, 2006).

With Aβ acting via a number of receptors, there is activation of microglial cells which leads to the production of ROS and proinflammatory cytokines such as interleukin (IL)-6, IL-1β, tumor necrosis factor alpha (TNF-α) which triggers an inflammatory response in AD brain. This means that the microglia contain a B-type of scavenger receptor, called CD36 with studies showing that it acts as a receptor for fibrillar Aβ. The peptide-mediated activation of this receptor results in an increased microglial ROS production, cytokine expression and phagocytosis (Doens & Fernández, 2014). MAC-1 receptor and

phosphoinositide 3-kinase (PI3K) also regulate Aβ-induced microglial activation and ROS production. Ganguly et al (2017) has reported on their ability to activate NADPH oxidase which functions mainly as a regulator of microglial-mediated ROS production.

Oxidative Stress and Tau Phosphorylation in Alzheimer's Disease

The development of neurofibrillary tangles from intracellular amassing of hyperphosphorylated tau protein is another trademark highlight of AD pathogenesis, which accounts for the axonal degeneration and synaptic dysfunction related with neurodegenerative disorder (Alavi Naini and Soussi-yanicostas, 2015). The microtubule-related tau protein has various phosphorylation sites in the proline-rich and in the C-terminal locales of the protein, and various kinases – particularly glycogen synthase kinase 3 beta (GSK3β) and cyclin-subordinate kinase 5 (CDK5) – can phosphorylate the previous. Tau can be dephosphorylated by a few phosphatases, dominatingly protein phosphate 2A (PP2A), protein phosphate 1 (PP1) and protein phosphate 2B (PP2B) (Alavi Naini and Soussi-yanicostas, 2015). In AD, the expanded phosphorylation of tau protein is the aftereffect of expanded activities of GSK3β and CDK5, and a related diminishing in PP2A function (Ganguly et al, 2017). Then again, explanations for such changes in the kinase functions and that of phosphatases in these disorders are not clear.

Chronic oxidative stress as glutathione depletion has appeared to build tau phosphorylation in cultured M17 neuroblastoma cells through JNK and p38 activation and in addition decreased phosphatase function (i.e. PP2A) (Su et al, 2010). Notwithstanding, there have been reports of dephosphorylation of tau under oxidative stress in various models of study through kinases modulation, (for example, GSK3 or CDK5) or phosphatases, (for example, PP1), making the relationship between oxidative stress and tau phosphorylation difficult to ascertain (Zambrano et al, 2004). Figure 2 outlines the different conceivable mechanisms through which oxidative stress prompts a gathering of amyloid β42, which thus impedes mitochondrial work and interfaces with metal ions in microglia in an AD brain.

Aβ42 accumulates as a result of increased expression of APP and BACE1 when there is increased oxidative stress. The clearance of Aβ42 from the brain is also retarded by oxidative stress. On the other hand, the multiple interactions of Aβ42 with mitochondria, microglia and metal ions lead to further oxidative stress. Arrows suggest interactions; a line with an end bar indicates retardation (Adapted from Ganguly et al, 2017).

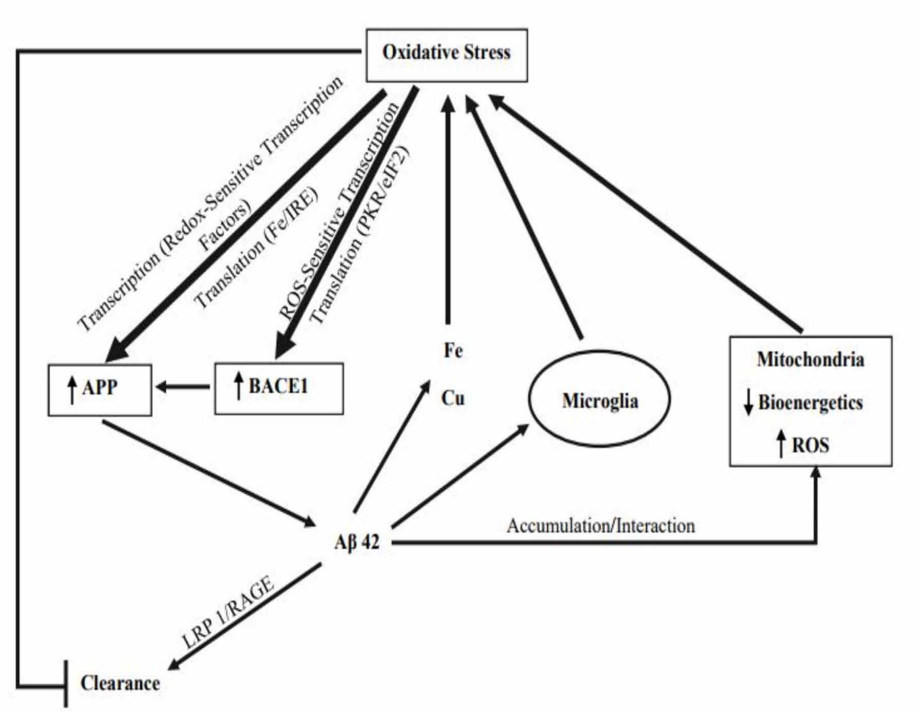
Abbreviations: Aβ42: Amyloid beta peptide 1–42; APP: Amyloid precursor protein; BACE1: β-Secretase; eIF2: Eukaryotic initiation factor-2; IRE: Iron-responsive element; LRP1: Low-density lipoprotein receptor-related protein 1; PKR: Double-stranded RNA-dependent protein kinase.

OXIDATIVE STRESS AND PARKINSON'S DISEASE

α-Synuclein and Oxidative Stress in Parkinson's Disease Pathogenesis

α-Synuclein is an unfolded protein that can connect with vesicular and membranous structures and assumes a part in synaptic vesicle reusing, stockpiling and compartmentalization of neurotransmitters (Yavich et al, 2006). Fibrils of α-synuclein, residing in Lewy bodies, are related with expanded oxidative or nitrosative stress, hence keeping up physiologic levels of α-synuclein in neurons is important for neuronal survival (Paxinou et al, 2001). Chaperone-mediated autophagy (CMA) rids the cells off

Figure 2. Oxidative stress-mediated amyloid beta proteinopathy in Alzheimer's brain



α-synuclein and prevents its build up. Be that as it may, its debasement by CMA is impeded by post-translational alterations (Cuervo and Wong, 2013). Over accumulation and post-translational alteration of α-synuclein result in death of DAergic neurons (Zhou et al, 2013). Oxidative stress effectively controls protein accumulation in PD as seen in the analyses of the brain after death, demonstrating expanded levels of post-translational alterations of the α-synuclein by oxidative stress, including those by 4-hydroxy-2-nonenal (HNE-α-synuclein), nitration (n-α-synuclein), and oxidation (o-α-synuclein), which have been ensnared in advancement of oligomerization of α-synuclein (Alam et al, 1997). Among them, HNE-α-synuclein and n-α-synuclein are more inclined to framing oligomers than unmodified α-synuclein.

The cellular toxicity of HNE-α-synuclein is significantly higher than other post-translationally modified species (Xiang et al, 2013). Mitochondrial dysfunction caused by α-synuclein and overexpression of wild or mutant α-synuclein in SH-SY5Y has been shown to increase the intracellular level of ROS (Di Mario et al, 2016). On the other hand, iron which facilitates ROS production and catalyzes peroxidative damage to biomolecules, accumulates in the SN of PD brains in excess amounts and causes translational upregulation of α-synuclein (Febbraro et al, 2012). Furthermore, the binding of transition metals such as iron and copper to α-synuclein has been studied with a variety of biophysical techniques in different studies, and apparently, such binding may lead to enhanced cytotoxicity of α-synuclein through multiple mechanisms. One of such mechanisms is iron-mediated formation of large sodium dodecyl sulfate (SDS)-resistant oligomers of α-synuclein capable of forming membrane-spanning channels, which may partly explain the toxicity of α-synuclein on intracellular organelles (Carboni & Lingor, 2015). Since DAergic neurons are particularly affected in PD, it has been suggested that DA oxidation products such as ROS and toxic quinones could contribute to PD pathology (Ganguly et al, 2017). In this context, it

is interesting to note that the interaction of α-synuclein with DA has been studied by several groups, indicating a modulatory role of DA oxidation products on α-synuclein oligomerization and cytotoxicity (Leong et al, 2009). In a very elaborate study, it has been shown that in human DAergic neurons and rat DAergic cell lines exposed to paraquat, increased accumulation and aggregation of α-synuclein occurs, which is crucially dependent upon the activity of NADPH oxidase, implicating the role of ROS in the process. This study has further shown that the systemic injection of paraquat in rats causes increased protein expression of α-synuclein and NADPH oxidase, along with the accumulation of oxidative damage markers in the SN, which can be abolished by knocking down NADPH oxidase (*NOX1*) gene by adeno-associated virus-mediated overexpression of a specific short hairpin RNA (shRNA) (Cristóvão et al, 2010).

The knockdown of *NOX1* likewise keeps the nigral DAergic neuronal misfortune after paraquat treatment of rodent. Another intriguing cross talk between oxidative stress and α-synuclein is likely when oxidatively changed protein turns out to be incompletely impervious to metabolism by the ubiquitin-proteasome framework (UPS) or chaperone-intervened autophagy, prompting collection of the misfolded protein (Ganguly et al, 2017). A few sort of oxidative changes of α-synuclein have been illustrated, for example, nitration of tyrosine deposits, oxidation of methionine buildups and covalent adduct synthesis with 4-HNE. Such oxidatively adjusted α-synuclein proteins, when all is said and done, repress oligomerization and fibril formation by the native monomer, and rather may offer ascent to "off-pathway" oligomers, however the unwanted outcome of this has not been certain (Schildknecht et al, 2013). The different mechanistic approaches prompting the aggregation of α-synuclein in the PD mind and the harmfulness of this protein in monomeric or oligomeric structure in the mitochondria are featured in Figure 3.

Increase in *SNCA* and iron/IRE-regulated posttranscriptional mechanism accounts fot the increased expression of α-synuclein in the brains of people with PD. α-Synuclein (monomers and oligomers) have multiple interactions with mitochondria, causing dysfunction of the organelle and increasing ROS production while iron and DA-oxidation products also account for increased oxidative stress in PD brain. The arrows indicate interactions, but arrows with end bars suggest inhibition (Adapted from Ganguly et al, 2017).

Iron-Mediated Oxidative Stress in Parkinson's Disease

In neurodegenerative disorders such as PD and multiple system atrophy, there are aberrantly high levels of iron and oxidative stress (Repetto et al, 2012). Oxidative stress is normally accompanied by increased free iron. Experimentally identifying high intracellular iron does not essentially signal an increased oxidative stress if there are associated increases in proteins that store iron in redox inert forms such as the ferrihydrate core of ferritin (Perry et al, 2002). The entry and release of iron from ferritin occurs via its more coordinately labile ferrous state, active in Fenton generation of hydroxyl radical. Microglia, a major site of ferritin-bound iron, is one source of iron and might contribute to oxidative damage in PD and other neurodegenerative disorders through superoxide-dependent reductive release of ferritin iron, leading to lipid peroxidation, which might be due to Fenton chemistry (Sayre et al, 2001). Besides superoxide, ferritin iron can be released by 6-hydroxydopamine, a neurotoxin implicated in PD, and by other easily oxidized catechols (Sayre et al, 2001).

Figure 3. Accumulation of α-synuclein and its toxic role in the development of Parkinson's disease

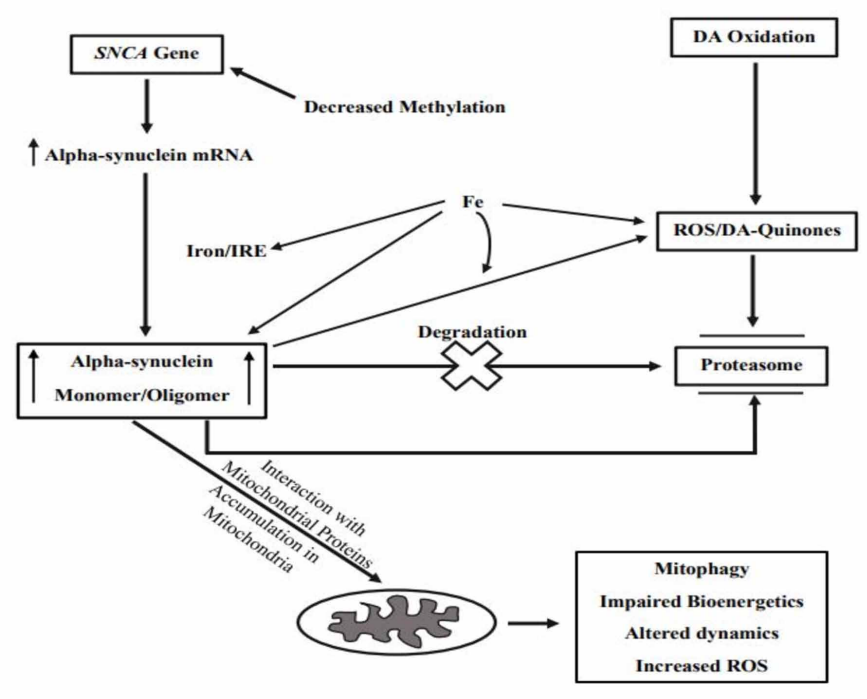
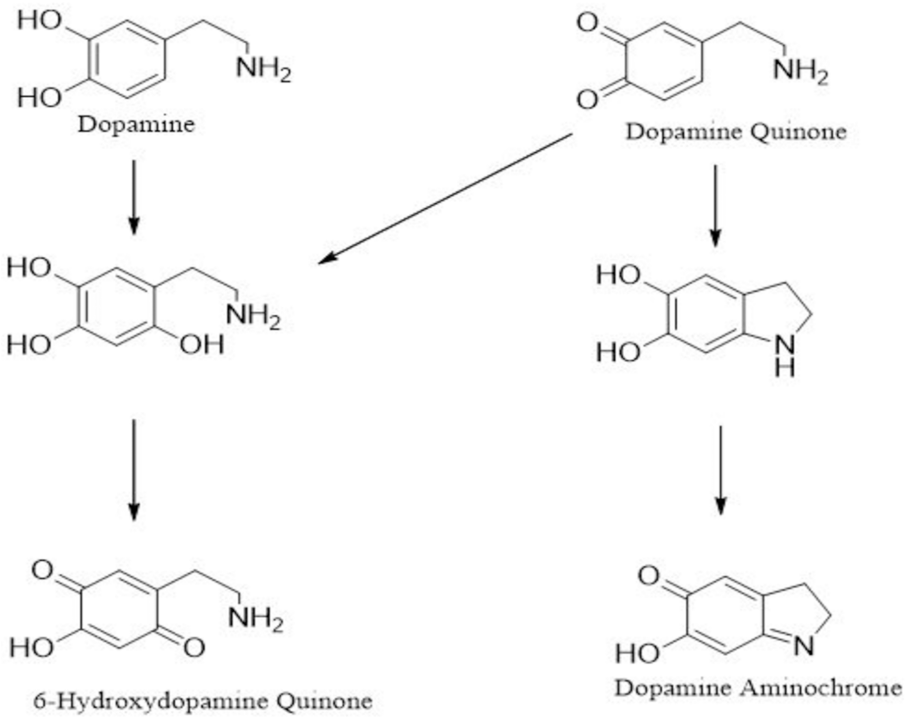


Figure 4. Oxidation chemistry of dopamine showing the competition between aminochrome and 6-hydroxydopamine formation (Adapted from Sayre et al, 2001)



Sayre et al (2001) reports that sequestration of redox-active iron in the mitochondria of aging nigral astroglia may account for the iron buildup in astrocytes in SN old rats. This may predispose the senescent nervous system to PD (Sayre et al, 2001). Also, anomalous oxidation of dopamine (Figure 4) to 6-hydroxydopamine accounts for redox imbalances, and this will eventually result in autoxidation to its corresponding quinone with the generation of superoxide. In the presence of Fe^{2+} and either H_2O_2 or alkyl peroxide, dopamine is converted to 6-hydroxydopamine and 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinolone, a neurotoxic alkaloid. These reaction pathways may become operative under conditions relevant to neurodegeneration (Sayre et al, 2001).

CONCLUSION

Neuronal proteins and structural components are modified due to oxidative stress in the different neurodegenerative disorders which culminates in neuroinflammation and loss of cognitive function as seen in the above discussed neurodegenerative disorders. As has been enshrined in this chapter, oxidative stress plays a key role in the pathological cause of neurodegeneration. Henceforth, antioxidants may play a significant role in therapeutic management of neurodegeneration upstream. This chapter has clearly discussed the link between neurodegeneration and oxidative stress and should inform future studies on the pathology as well as management of NDs.

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Chapter 3
Free Radicals in Oxidative Stress, Aging, and Neurodegenerative Disorders

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ABSTRACT

Free radicals are intricately woven into the fabric of oxidative stress and are significant in the development of neurodegenerative disorders (NDs). This chapter examines free radicals in the context of neurodegeneration and provides overview of the multiple roles they play in the pathophysiology and clinical progression of varying NDs including Pick's disease (PiD), Parkinson's disease (PD), Alzheimer's disease (AD), prion diseases (PrD), traumatic brain injury, and aging. The molecular mechanisms of degeneration in Huntington's disease (HD) are also examined with respect to free radicals. Different antioxidant systems and their mechanisms of action are briefly reviewed in addition to the role of diet in aging. The effectiveness of selected synthetic drugs and natural products used in oxidative stress is also reviewed. Lastly, the chapter examines challenges associated with the use of antioxidants and how promising future directions like the endocannabinoid system is being pursued in the race to effectively manage NDs.

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INTRODUCTION

Since Moses Gomberg's first description of triphenylmethyl radical in literature in 1900, free radicals have remained an important subject of discussion owing to their numerous physiological effects (Gomberg, 1900). Initially they were not believed to be present in biological systems due its excessive reactivity. However, by the end of the second half of the 20th century, the scientific world had come to terms with the fact that free radicals are found in biological systems and contribute to several pathologies as well as aging (Lushchak, 2014). Today it is recognized that free radicals instigate oxidative stress and propagate neuronal injury thus playing a major role in NDs like AD, PD, amyotrophic disorders, PrD and several others (Khan et al., 2016). It is important to note that free radicals are not always deleterious such as the generation of nitric oxide in neurotransmission and the production of superoxide anion ($O_2^{\bullet}$) by activated microglia. There is a focus on free radicals in the central nervous system (CNS) and mechanisms involving free radicals in selected NDs. Free radicals are reviewed as potential targets of drug action in the management of NDs. Thus this chapter will evaluate what free radicals are and review their contribution to oxidative stress induced neurodegenerative disorders as well as aging. It is expected that at the end of this chapter further knowledge on the mechanisms of free-radical induced neurodegeneration in some NDs would have been gained in addition to an understanding of the prospects of novel therapeutic approaches. Overall, this chapter examines the interplay of free radicals and oxidative stress in the development and progression of several NDs.

BACKGROUND

Free radicals are exceptionally reactive atoms or molecules with one or more unpaired electrons and capable of independent existence (Halliwell, 1992). In some instances, free radicals have been used interchangeably with reactive oxygen species (ROS). While this may be correct sometimes, not all ROS are free radicals. Although both generate oxidative stress, ROS are chemically reactive species that contain oxygen and may or may not necessarily be a radical. For example, whereas hydrogen peroxide (H_2O_2) is a reactive oxygen species, it is not a free radical. Other examples include lipid, protein and nucleic acid peroxides. There are also reactive species that are not oxygen species such as reactive species of nitrogen (peroxynitrite ($ONOO^{\bullet}$) and nitric oxide ($^{\bullet}NO$)), carbon and sulfur.

However, the common denominator in all these terminologies is oxidative stress. Oxidative stress is a chemical process resulting from excessive free radical production due to an insufficiency of the counteracting antioxidant response system (Birben, Sahiner, Sackesen, Erzurum, & Kalayci, 2012). Free radicals and reactive species of oxygen or otherwise participate in chain reactions that culminate in oxidative stress. Normally in aerobic organisms, molecular oxygen is reduced to water via intermediate steps of oxygen reduction that forms $O_2^{\bullet}$, $H_2O_2$and the hydroxyl radical ($^{\bullet}OH$) (Halliwell & Gutteridge, 1990). Free radicals and other reactive species' production in the body is approximately balanced by antioxidant mechanisms needed to mop up these reactive species. However NDs as well as aging, the production of free radical is higher than antioxidant defense. Antioxidants are molecules which at minimal concentrations compared with that of an oxidizable substrate, appreciably slows or stops oxidation of that substrate (Halliwell & Gutteridge, 1990). These enzymatic or non-enzymatic antioxidants, reduce the potential damage of the reactive species thus only minor reactive species induced-damage occurs. Therefore, oxidative stress arises in the event of a significant disparity between the production of free

radicals and other ROS and antioxidants production (Halliwell, 2007). In other words, it is a disturbance in the oxidant–antioxidant balance in favor of oxidant mechanisms with a resulting potential tissue damage regarded as oxidative damage (Sies, 1997).

CENTRAL NERVOUS SYSTEM, FREE RADICALS AND NEURODEGENERATIVE DISORDERS

During normal physiological processes, the brain utilizes about 20% of the total oxygen in the body which leads to the generation of more free radicals than in any other tissue (Joshi & Praticò, 2014; Smith, Cappai, & Barnham, 2007). Reactive oxygen species (ROS) are important in numerous cellular and signaling pathways at physiological concentrations such as cell cycle regulation and enzyme activation (Dröge, 2002; Zorov, Juhaszova, & Sollott, 2014). When in excess, they are however scavenged by defense mechanisms which may be enzymatic and non-enzymatic antioxidants. Overproduction of ROS leads to generation of oxidative stress, which has been shown to cause several harmful effects including Deoxyribonucleic acid (DNA), lipid and protein damage (Ohta, Yashiro, Ohashi, & Imai, 2012). Oxidative stress remains a major feature contributing to cerebral biochemical impairment seen in some NDs (Huang, Zhang, & Chen, 2016).

The brain, in comparison to other body organs, has been shown to be predominantly exposed to oxidative damage. This is due to its high metabolic rate, due to a highly active mitochondria metabolism. Additionally, the brain vulnerability to oxidative damage is because a huge proportion of it is made of lipids (Birben et al., 2012. Also, another important factor is the fact that the brain contains low antioxidant defense mechanisms (Birben et al., 2012). Furthermore, neurons have a longer life span than other cells and so are exposed to accumulated oxidative damage over time (Magrassi, Leto, & Rossi, 2013). These among others make the neurodegeneration due to oxidative damage more significant in the brain and spinal cord.

Neurodegeneration is characterized by the progressive loss of specific neuronal cells with an accompanying protein aggregation leading to disorders such as AD, PD and amyotrophic lateral sclerosis (ALS). The genesis of these disorders is attributed to a myriad of factors which are yet not completely understood (Khan et al., 2016). Among these factors include: a genetic basis and familial inheritance, exposure to environmental risk factors, altered immune and inflammatory responses, idiopathic protein aggregation, ageing and of course, the ubiquitous oxidative stress, and its attendant damage (Khan et al., 2016).

Another conceivable mechanism of oxidative stress-induced pathology implicates a dysfunction of ROS-mediated cell-cell communication. Excessive $O_2^{\bullet}$, $OH^{\bullet}$ production by NADPH oxidases (NOXs) and the free radical peroxynitrite ($ONOO^-$) by nitric oxide synthase cause massive cell damage through endoplasmic reticulum (ER) stress, impaired calcium handling, and nitration of tyrosine residue of several proteins. NOX is a multi-subunit enzyme which is composed of membrane and cytosolic components including NOX (NOX1-5) and phox subunits. NADPH produces $O_2^{\bullet}$ by transporting an electron from NADPH to oxygen (Ma et al., 2017). The enzyme has been implicated in diverse roles including host defense and cellular signaling (Panday, Sahoo, Osorio, & Batra, 2015). This cell damage perturbs the structure of proteins and alters the catalytic action of enzymes thus, impairing cell signaling pathways which depends on such proteins and enzymes. Additionally, several cell signaling cascades require ROS

as messengers therefore a constant rise in concentrations of ROS can cause an over-activation of such pathways, with several damaging consequences (Freixes, Rodríguez, Dalfó, & Ferrer, 2006).

The high oxygen demands of the brain yet with limited defense strategies against oxidative stress increases its susceptibility to oxidative damage and makes oxidative damage a significant causative effect of neurodegeneration. Evidence to this is led by the several observations of markers of oxidative damage in the brain, spinal fluid and plasma of AD (Arlt, Beisiegel, & Kontush, 2002; Butterfield, Castegna, Lauderback, & Drake, 2002; Selley, Close, & Stern, 2002), PD (Dexter et al., 1989) and ALS (Pedersen et al., 1998; Sayre, Smith, & Perry, 2001) patients. Additionally, DNA damage due to oxidative stress is observed as DNA nitration and hydroxylation in AD brains and increased 8-hydroxy-2-deoxyguanosine and 8-hydroxyguanine levels in PD brains (Alam et al., 1997; Gabbita, Lovell, & Markesbery, 1998). Furthermore, the brain is rich in oxidizable catecholamines such as noradrenaline and dopamine that can undergo auto-oxidation to generate free radicals in the presence of metal ions and propagate neuronal damage (Gerlach, Ben-Shachar, Riederer, & Youdim, 1994; Halliwell & Gutteridge, 1990).

Antioxidant Response System and Biomarkers of Oxidative Stress

The antioxidant defense system is an endogenous enzymatic and non-enzymatic system in place to protect the body from oxidative damage (Ohta et al., 2012). It comprises of enzymatic (superoxide dismutase, glutathione peroxidase and catalase) and non-enzymatic low molecular weight reductants (glutathione, α-tocopherol, and ascorbic acid). The antioxidant defense system prevents free radical mediated damage of cells by converting the overproduced free radicals to non-destructive cellular molecules. Astrocytes also important in maintaining high intracellular concentrations of some antioxidants, making them resistant to oxidative damage by elevating expression of some antioxidant enzymes; increasing glucose metabolism and transport; increasing manufacturing of glutathione; and salvaging ascorbic acid (Cabezas et al., 2014). Ascorbic acid is very important for sustaining oxidative balance as it acts a cofactor for antioxidant enzymes. Studies have shown that ascorbic acid deficiency plays acute role in oxidative damage seen in AD and normal aging (Dixit et al., 2015). Glutathione (GSH) is the main brain antioxidant molecule (Johnson *et al*., 2012). A progressive diminution of GSH concentration during aging as well as age-associated diseases like has been suggested is some studies (Carvalho, Lim, Nijland, Witte, & Van Horssen, 2014; Johnson, Wilson-Delfosse, & Mieyal, 2012). GSH protects neurons from oxidative damage, primarily by serving as a redox regulator and hence crucial for the detoxification of ROS in neurons (Johnson et al., 2012).

Several markers of oxidative stress have been measured in peripheral blood; these include lipid peroxides, GSH, ascorbic acid and α-tocopherol (Sinclair et al., 1998). Lipid peroxidation is a central feature of oxidative stress (Lushchak, 2014). Oxidative stress-mediated membrane lipids peroxidation is detrimental as it results in modifications in the biological properties of the membrane i.e.the magnitude of membrane fluidity (Lushchak, 2014). This leads to inactivation of membrane-bound receptors and that may ruin cellular functioning and disrupt tissue permeability. Products of lipid peroxidation such as malondialdehyde (MDA), have been used as possible markers of oxidative stress (Sultana et al., 2013).

Measurement of the plasma antioxidants provides an indication of the level of oxidative stress and is routinely used as biomarker of oxidative stress in NDs. This was shown by previous studies that demonstrated a decrease in peripheral levels of retinol, ascorbic acid and α- tocopherol along as well as a diminished activity of SOD and glutathione peroxidase in AD patients (Sinclair et al., 1998; Ferreira

et al., 2015). Other works also correlated the increase in oxidative stress with a decreased GSH activity (Sinclair et al., 1998).

Role of Diet in Oxidative Stress and Neurodegeneration

Diet may play a huge role in providing supplementary antioxidants. A typical meal possibly contains several naturally occurring antioxidant molecules (Bayram et al., 2012). These antioxidant compounds are found in different concentrations in vegetables, legumes, fruits, cereals, olive oil, wine, cocoa, and tea (Bayram et al., 2012; Coelho, Hermsdorff, & Bressan, 2013). Studies have shown that an antioxidant-rich diet potentially averts oxidative damage and cognitive decline due to its free radical or active oxygen scavenging properties (Coelho, Hermsdorff, & Bressan, 2013). This has led to a great need to search for nontoxic active ingredients of natural resources that could reverse the biochemical imbalances that occur in NDs.

Oxidative Stress-Induced Mitochondrial Dysfunction in Neurodegeneration

In the brain, the primary sites of ROS generation include mitochondria in the neurons and glia. The production of free radicals in these areas is exacerbated in disorders like PD due to inflammation, dopamine degradation, mitochondrial dysfunction, aging, GSH depletion, and high levels of iron (Dias, Junn, & Mouradian, 2013). Mitochondrial dysfunction, increased apoptosis together with low antioxidant levels are also evident in the development of AD (Birben et al., 2012). In addition, neurodegeneration-induced ROS causes damage in key cellular proteins and disrupt lipid membranes thus promoting oxidative stress (Dias et al., 2013; Birben et al., 2012). Mitochondrial dysfunction leads to increased free radical production in the respiratory chain (Dias et al., 2013; Huang et al., 2016). Particularly, mitochondrial complex I deficiency has been identified to be strongly associated with PD. Indeed, a large amount of the unfavorable neural apoptosis observed in PD can be attributed to the complex I defect (Huang et al., 2016).

Aging and Oxidative Stress

Aging has been shown to be a major risk factor for ND (Moll, El-Ami & Cohen, 2014; Bickford, Flowers & Grimmig, 2017). Aging is a complex phenomenon that results in reduced organ functioning, decline in cognition and overall decline in the organism's homeostasis. As stated already, the brain is prone to oxidative stress however an aging brain is highly susceptible to a greater extent as a result of a loss of resilience associated with aging (Bickford et al., 2017). This leads to a decreased resistance to various forms of stress as well as an increased susceptibility to oxidative stress and thus several diseases. Even though, aging is poorly understood, one of the most widely accepted theories is the 'Free Radical Theory' which attributes aging to the deleterious effects of free radicals on cell components (Harman, 1956).

The environment of the aged brain has been associated with two main biological processes; oxidative stress and inflammation with microglia being one of the major cell types implicated in both processes (Bickford et al., 2017). In the healthy, young brain, microglia (known as the resident tissue macrophages in the CNS) perform housekeeping duties and constantly assess the microenvironment thereby effectively protecting the CNS from invading pathogens amid other attacks (Koellhoffer, McCullough & Ritzel, 2017). Thus, microglia in the CNS induce an innate immune response and once activated can perform several functions including phagocytosis (Fenn, Henry, Huang, Dugan & Godbout, 2012). It

has been shown that there is an increase in reactive microglia in aged brains with an associated increase in inflammatory markers (Fenn et al., 2012). Aged microglia is also identified in the pathophysiology of Traumatic Brain Injury, AD, and worsening outcomes in stroke (Koellhoffer et al., 2017).

Some agents with anti-oxidant activity such as polyphenols have been shown to be potent modulators of neuroinflammation. This effect may be due to the stimulation of the transcription factor, nuclear factor erythroid related factor 2 (Nrf2)-antioxidant response element (ARE) pathway thereby reducing the production of pro-inflammatory cytokines and modulating glial function (Bickford et al., 2017). The Nrf2-ARE pathway is very vital for the proper functioning of microglia. Polyphenols may therefore be very important in neuroprotection as shown by a study by Bickford et al., 2017 where NT-020, a polyphenolic rich mixture, was able to improve the aging environment as well as cognition with minimal side effects. In fact, when NT-020 was administered to aged human participants (65-85 years) for two months, it was noted that there was an increase in processing speed (according to memory tests) suggesting the important role that antioxidants play in neurodegeneration (Bickford et al., 2017).

MOLECULAR MECHANISMS OF FREE RADICAL-INDUCED DEGENERATION IN NEURODEGENERATIVE DISORDERS

Alzheimer's Disease and Other Dementias

Dementia is a syndrome caused by several disorders which negatively influence cerebral structures and functions, to cause deterioration of memory functions and behavior (Sosa-Ortiz, Acosta-Castillo, & Prince, 2012). Most common causes of dementia include AD, frontotemporal lobar degeneration (FTLD), vascular dementia, Creutzfeldt-Jakob disease (CJD), PD, and Lewy Body dementia (LBD). There is a very strong association age with the prevalence of dementia, so there is an expected increase in the number of people living with dementia as the aging population increases (Sosa-Ortiz et al., 2012).

AD is a very common ND which affect around 16 million of the elderly population worldwide and is the leading cause of dementia (Butterfield & Boyd-Kimball, 2004). It accounts for 60-80% of dementia in the elderly population (Sosa-Ortiz et al., 2012; Huang et al., 2016). AD is characterized by neurofibrillary tangles composed of hyperphosphorylated tau protein and amyloid-beta (Aβ)-containing plaques in addition to cognitive impairment and progressive neurodegeneration. The neocortex and hippocampus are the main affected brain areas. AD symptoms usually start with minor amnesic episodes and progress toward a vivid change in personality (Sosa-Ortiz et al., 2012). The etiology of AD is multifaceted including major environmental and genetic risk factors (Huang et al., 2016). Increased lipid peroxidation and inadequate antioxidants were shown in the peripheral tissues of AD patients. Similar to most NDs, the specific biochemical mechanism of the pathogenesis of AD remains unknown although evidence suggests a massive loss of acetylcholine and a possible role of oxidative stress (Butterfield et al., 2001). Oxidative damage plays an important part in Aβ deposition in AD. Lushchak (2014) reviews complex relationships between excitotoxicity and Aβ deposition, as well as production of ROS in AD.

FTLD, example PiD, are diseases which degeneration primarily affect the frontal (front) and temporal (side) regions of the brain (Diehl et al., 2004). PiD is characterized by the presence of abnormal bodies also known as Pick's bodies in affected neurons (Rademakers, Neumann, & Mackenzie, 2012). Though the symptoms appear similar to those seen in AD, PiD is unique in that it progresses very rap-

idly. Symptoms include inability to recognize people as well as deterioration of skilled movement and language abilities, (Mendez & Shapira, 2011).

Lewy Body dementia (LBD) is characterized by the deposition of abnormal proteins called Lewy bodies in affected brain regions (Diehl et al., 2004). Dementia with Lewy bodies and Parkinson's disease dementia (Lewy body dementia), are ranked second among the commonest types of degenerative dementia in patients older than 65 years (Gomperts et al., 2012). LBD patients present with symptoms similar to AD. During early stages, symptoms of LBD may be mild but ultimately result in significant impairment of cognitive function (Postuma, Gagnon, Pelletier, & Montplaisir, 2013).

Motor Neuron Disorders

Motor neuron disorders (MND) are group of progressive conditions in which lower and upper motor neurons degenerate and result in decreasing strength in limb, abdominal, thoracic and bulbar muscles without affecting oculomotor and sphincter muscles (Wijesekera & Leigh, 2009). The term generically applies to a complete spectrum of the diseases including progressive bulbar palsy, amyotrophic lateral sclerosis (ALS) and progressive muscular atrophy and of which ALS is the most common and devastating. It is characterized by progressive injury and cell death of motor neurons in the motor cortex, brain stem and spinal cord. This results in the progressive muscle weakness, wasting upper and lower motor neurons with pathologically brisk reflexes of the limb and bulbar muscles (Bäumer, Talbot, & Turner, 2014; Leigh & Ray-Chaudhuri, 1994). It is now recognized that extra motor parts of the CNS are also involved in MND and thus MND can be regarded as a multisystem disease whereby motor neurons are affected quickest and harshest (Wijesekera & Leigh, 2009).

The disorders occur in about one to two individuals per 100 000 and predominantly in middle aged and elderly patients (Shaw, 1999). Men have a relatively higher prevalence of the disease than women (1.5:1) although this seems to be turning towards a balanced prevalence in recent years (Logroscino et al., 2008). In most instances, onset is sporadic (90%) while heredity has also been reported (10%). MND patients have dire prognoses with median survival of approximately 3.5 years after onset of symptoms as a result of death due to paralysis of respiratory muscles (Leigh & Ray-Chaudhuri, 1994; Shaw, 1999).

Several hypotheses have been postulated as to the pathophysiology of MND including genetic predisposition, increased glutamatergic excitotoxicity, failure of axonal transport, mitochondrial dysfunction and oxidative stress (Turner et al., 2013).

Free Radicals and Oxidative Stress in Motor Neuron Disorders

Free radical-instigated oxidative stress is a significant portion of the already understood aspects of the pathophysiology of MND. Although familial MND is not fully understood, several point mutations in chromosome 21 gene product coding for the enzyme, copper-zinc superoxide dismutase (*SOD 1*), is responsible for 20% in different pedigrees of familial cases and 2% of all cases of MND (Rosen et al., 1993; Shaw, 1999). This ubiquitous antioxidant enzyme converts the superoxide free radical into less harmful hydrogen peroxide (H_2O_2) before it is taken care of by other antioxidant enzymes. Evidence suggest that the mutant enzyme exerts its damaging by an abnormal handling of hydrogen peroxide and peroxynitrite which cases elevated production of hydroxyl radicals and nitrotyrosine residues (Carrì, Valle, Bozzo, & Cozzolino, 2015; Cookson & Shaw, 1999; Shaw, 1999; Shibata, Hirano, Yamamoto, Kato, & Kobayashi, 2000). The mutated Cu/Zn SOD may also form neurotoxic intracellular aggregates

or release cytosolic Cu or Zn which then becomes neurotoxic (Shaw, 1999). The increased expression of Cu/Zn SOD in both axons and cell bodies of motor neurons in comparison to all other cells of the nervous system increases their susceptibility to damage by such genetic alterations. In addition, alterations in apurinic/apyramidinic (AP) endonuclease, an important enzyme for repairing oxidative damage to DNA and forming abasic sites, is also associated with ALS (Olkowski, 1998). Other genes have also been identified that increase the susceptibility to MND to various degrees aside SOD and AP endonuclease.

Neuronal injury instigated by free radicals is a key cause of several age-related neurodegenerative diseases because the effects of oxidative stress in neurons, which naturally are non-replicating, is cumulative. Given the effects of mutations in antioxidant enzyme SOD on the development of certain familial ALS, interest in free radicals and for that matter oxidative stress in MND has been high for a long time. Cultured fibroblasts of skin samples of both familial and sporadic motor neuron patients indicate an amplified sensitivity to oxidative insults (Aguirre et al., 1998; Wijesekera & Leigh, 2009). Also, post-mortem results points towards a change in expression of parts of the intracellular antioxidant defense mechanism. This has been recorded in ALS patients and signifies an attempted compensatory response to the increased oxidative stress (Shaw, Chinnery, Thagesen, Borthwick, & Ince, 1997).

The evidence to support an involvement of an aberrant oxidative damage management is also due to the observation that antioxidant molecule vitamin E exhibits beneficial effects in Cu/Zn *SOD1* mutated transgenics by delaying the onset of MND. Ghadge and colleagues (Ghadge et al., 1997) report that free radicals especially O_2^- are implicated in the mutant SOD-mediated cell death, owing to the fact that SOD and glutathione mimetics reversed this mortality. Their data also show that expression of mutant SOD escalates the vulnerability to oxidative stress and increases rate of accumulation of O_2^-. Cell death regulatory protein B-cell lymphoma 2 (BCl-2), which affects free radical production and for that matter cell survival, also protects the cells against mutant SOD-induced apoptosis (Hockenbery, Oltvai, Yin, Milliman, & Korsmeyer, 1993). These seem to explain an important involvement of free radicals and oxidative stress in ALS and MND in general.

Nonetheless, clinical trials involving potent antioxidant n-acetylcysteine showed non-significant correlates suggesting that the situation is not completely clear.

Huntington's Disease

HD is a devastating autosomal dominant ND with abnormal trinucleotide (CAG) expansion in the *huntingtin* (*HTT*) gene (Velusamy et al., 2017) which is characterized by impaired cognition, movement and psychiatric disorders (Ma et al., 2017). Usually, healthy individuals have 5-6 CAG repeats in exon 1 of the *HTT* gene but affected individuals have more than 36 repeats (Manoharan et al., 2016). The associated neuronal death has been attributed to the accumulation of mutant Huntingtin proteins as there is abnormal folding and protein function (Velusamy et al., 2017).

Oxidative stress is hypothesized as significant mechanism in the progression of this disorder with several studies confirming this hypothesis. For instance, the activity of the mitochondrial complexes II, III and IV have been found to be reduced in the striatum of HD patients' post-mortem (Lee, Gold, & Linker, 2012). It has been shown that in HD patients, there is elevation of biomarkers for oxidative stress such as malondialdehyde in the striatum, cortex and serum. The expansion of the CAG triplets has been shown to induce oxidative stress which causes damage to the cell membrane, DNA and other enzymes involved in adenosine triphosphate (ATP) production (Velusamy et al., 2017). This mitochondrial damage therefore provides a strong mechanism for initiating apoptosis in HD brains (Velusamy et al., 2017).

This is because under oxidative stress, there is the activation of glutamate receptors which leads to an increase in the influx of calcium ions. This increase leads to the translocation of proapoptotic Bcl-2 proteins to the mitochondrial membrane as well as the activation of caspase 8 thus initiating apoptosis (Bansal & Singh, 2017). Manoharan et al. (2016) hypothesized that, the causes of oxidative stress in HD include imbalance in oxidant-antioxidant status, higher lipid concentration and high energy requirement as well as poor antioxidant status. This has been supported by a reduced superoxide dismutase activity in the cortex and cerebellum in HD patients (Ma et al., 2017).

NADPH oxidase (NOX2) enzyme has been proposed to be involved in the increase in ROS in the progression of HD. For instance, elevated ROS levels in PC12 cells expressing huntingtin proteins are lowered by treatment with NOX inhibitors (Valencia et al., 2012). Again, higher levels of NOX activity was found in the brain of HD patients as compared to controls (Valencia et al., 2012).

Elevated 4-hydroxy-2-nonenal (4-HNE) adducts levels have been found in both clinical and preclinical models of HD (striatum of both human and mice HD brains) (Lee et al., 2011). Thus, 4-HNE is proposed to be a relevant marker for determining oxidative damage in HD. Data from this study revealed that 4-HNE immunoreactivity was co-localized with mutant huntingtin (mtHtt) inclusions in the striatal neurons of R6/2 HD mice suggesting the importance of 4-HNE as a possible target for therapeutic intervention (Lee et al., 2011).

Parkinson's Disease

PD is a ND which affects over 10 million people above the age of 65 worldwide (Schneider & Obeso, 2014). In PD there is degeneration of dopaminergic neurons in the substantia nigra pas compacta of the basal ganglia which control motor functions. PD exhibits both motor and non-motor symptoms including resting rigidity and postural instability, tremor, bradykinesia, and akinesia (Schneider & Obeso, 2014). Non-motor symptoms observed in PD include cognitive, mood, autonomic and sleep disturbances (Schneider & Obeso, 2014). James Parkinson and Charcot among others had reported several non-motor symptoms in their classic literature that include delusion, pain, fatigue, dysfunction of the bladder and cognitive deterioration (Garcia-Ruiz, Chaudhuri, & Martinez-Martin, 2014).

The etiology of PD remains unclear, but oxidative stress has been considered as one of the major pathophysiological mechanisms involved (Dias et al, 2013). The main mechanism identified leading to oxidative stress in PD include the dopamine oxidation which produces toxic semiquinones. Secondly, the enhanced catabolism of dopamine by monoamine oxidase B (MAO-B) may instigate increased production of hydrogen peroxide, superoxide anions, and-hydroxyl radicals and the accumulation of alpha-synuclein aggregates (Hwang, 2013). These free radicals reduce the activity of mitochondrial complex I, this in turn contributes to the production of more reactive oxygen species which leads to apoptotic cell death (Dias et al, 2013; Blesa et al., 2015).

Prion's Disease

PrD also referred to collectively as transmissible spongiform encephalopathies (TSEs) are uncommon fatal NDs that are acquired either by direct transmission, inheritance of dominant prion protein gene mutations and in about 85% of cases through idiopathic sporadic causes (Brown, 2005; Prusiner, 1991). A prion is a novel pathogenic particle made up of a self-propagating misfolded protein with an abnormal conformation (Sarnataro, Pepe, & Zurzolo, 2017). It is a cell surface glycosylphosphatidylinositol (GPI)-

anchored glycoprotein expressed by neurons, glial cells and several other cells in the body. Human TSEs include: CJD), Gerstmann-Sträussler-Scheinker (GSS) syndrome, kuru and fatal familial insomnia. TSEs are characterized by neuroamyloid formation and dementia and neuropathological changes including spongiform degeneration in the brain (Brown, 2005; Wong, Wang, Brown, & Jones, 1999).

CJD is an unusual but deadly disorder that causes swift-developing and progressive (Iwasaki, Mori, & Ito, 2012). CJD is caused by the transmissible proteinaceous infectious particle called "prion". This pathogen consists of a protein which transforms normal protein molecules into infectious molecules. CJD signs include rapidly declining memory, behavioral changes and ataxia (Iwasaki et al., 2012).

Similar to several NDs, the footprints of oxidative damage are readily identified throughout the brain of the affected patients (Brown, 2005; Elmallah, Borgmeyer, Betzel, & Redecke, 2013; Pamplona et al., 2008; Yun, Gerlach, Riederer, & Klein, 2006).

Methionine Oxidation of Prion Protein

The succinct underlying mechanisms in TSEs are unclear; however the footprints of oxidative stress exist in the aspect of pathophysiology of the disease that is understood. The chief event in the pathophysiology of TSEs is post-translational alteration of normal cellular prion protein (PrP^{C}) into an abnormal infectious and misfolded isoform known as scrapie (PrP^{Sc}) (Elmallah et al., 2013). Scrapie is protease resistance and can be passed between individuals (Brown, 2005; Elmallah et al., 2013). In sporadic TSEs, PrP^{C} is converted to the abnormal misfolded infectious isoform (scrapie) via a mechanism triggered by methionine oxidation (Elmallah et al., 2013; Younan, Nadal, Davies, Brown, & Viles, 2012).

Human PrP^{C} is soluble and has significant susceptibility to proteinase K (PK) digestion whereas PrP^{Sc} is an insoluble aggregated protein multimer with an enhanced PK resistance (Brown, 20050. Proteins with cysteine and methionine residues are the most vulnerable to oxidation by free radicals. This makes the mammalian PrP^{C} exceptionally prone to oxidation as a result of its high number of Met residues (Canello et al., 2008). Met-sulfoxide, the product of methionine oxidation, is often identified in brain deposited PrP^{Sc} isoforms and is deemed to be a specific marker for pathogenic prion proteins (Canello et al., 2008). Little alterations PrP polypeptide can initiate a misfolding cascade of PrP^{C} into scrapie. Methionine oxidation into methionine sulfoxide is a trigger that begins a series of events leading to PrP misfolding. In TSEs methionine oxidation is seen as the initial trigger signal in the conversion of PrP^{C} into scrapie and formation of toxic species—the main pathophysiology of sporadic TSEs. Oxidation of methionine within PrPC disturbs its hydrophobic core and leads to the formation of monomeric molton-like species with high aggregation capabilities (Colombo, Meli, Morra, Gabizon, & Gasset, 2009)

Loss of Antioxidant Defense in Transmissible Spongiform Encephalopathies

Oxidative damage accounts for a majority of the prion diseases which arises sporadically (Elmallah et al., 2013). Markers of oxidative stress are even observed in early preclinical stages of scrapie infection (Yun et al., 2006). In prion diseases, there is a significant loss of antioxidant defense. As PrP^{Sc} accumulates in the brain, an increase in oxidative damage end-products and a reduction in antioxidant defense is observed. Conversion of the normal cellular prion protein which has antioxidant properties to its protease resistant isoform leads to a loss of this antioxidant activity. This process is facilitated by oxidation of methionine by H_2O_2 to methionine sulphoxide (Younan et al., 2012).

There is now a preponderance of evidence that suggests that normal cellular prion protein (PrP^C) is associated with cellular response to oxidative stress and that oxidative, glycoxidative, lipoxidative and nitrative protein damage to it is observed in PrD (Brazier, Doctrow, Masters, & Collins, 2008; Brown, Schmidt, & Kretzschmar, 1998; Freixes et al., 2006; Pamplona et al., 2008; Wong et al., 1999). PrP^C itself exerts anti-oxidant properties by undergoing β-cleavage (cleavage of copper-binding octapeptide repeats in PrP^C by reactive oxygen species) to protect the cell from damage from free radicals (Wong et al., 1999). Therefore β-cleavage of PrP^C is an important step in the mechanisms by which PrP defends cells from oxidative stress (Watt et al., 2005). Antioxidant capacity of purified prion protein diminishes by up to 85% in the most common human prion disease, sporadic CJD (sCJD), and correlates to elevated of markers oxidative stress in the brains of sCJD patients. Cultured astrocytes and neurons from PrP^C-deficient mice are very vulnerable to oxidative damage (Brown, Schulz-Schaeffer, Schmidt, & Kretzschmar, 1997). Immunohistochemical studies of brain tissues of prion-infected mice indicate an extensive increase in neuronal markers for lipid oxidation and other neuronal oxidative stress indicators such heme oxygenase-1 and nitrotyrosine (Guentchev, Voigtländer, Haberler, Groschup, & Budka, 2000). This supports the assertion that, ROS-mediated neuronal damage is present in the neurodegeneration observed in TSEs (Rizzardini et al., 1997; Wong et al., 2001).

The exposure to neurotoxic peptide derivatives of prion protein induced elevation of oxidative stress markers cultured astrocytes (Rizzardini et al., 1997). In a human TSE experiment, nitrotyrosine positive neurons were found throughout the brain signifying that the occurrence of oxidative stress is widespread in TSEs and also affects most neurons in the CNS (Guentchev, Groschup, Kordek, Liberski, & Budka, 1998). Free radicals-instigated oxidative stress is linked to iron accumulation and both total iron and Fe^{3+} are substantially elevated in the cerebral cortex, striatum, and brainstem of PrP^{Sc} -infected mice in a scrapie model in addition to elevated malondialdehyde concentrations (Kim et al., 2000), thus implicating free radicals in TSEs.

Even though the *in vivo* function of normal prion protein still remains unknown (Sarnataro et al., 2017), it is now accepted that normal (PrP^C) has SOD-like activity when bound to Copper ions (Cu^{2+}) and thus may even be a marker of brain oxidative stress as it has significant antioxidant activity (Brown et al., 1999; Milhavet & Lehmann, 2002). That is why oxidative stress, due to impaired Cu^{2+} homeostasis may be a risk factor in the development of sporadic prion diseases (Requena et al., 2001). The conversion of PrP^C to PrP^{Sc} leads to a loss of this SOD-like activity and an accumulation of products of oxidative damage. PrP^C knock-out mice also show diminutive SOD activity (Brown, Schmidt, & Kretzschmar, 1997). These evidences augment the suggestion that oxidative stress is a significant contributor of neurodegeneration in prion diseases.

Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) is a common neuromuscular disorder characterized by muscle weakness and paralysis. It is caused by a deficiency in the survival of the neuron gene (*SMN1*) that leads to a reduction in the levels of functional SMN proteins (Wan, Ottinger, Cho, & Dreyfuss, 2008). The SMN complex consists of SMN and other proteins called Germins (Wan et al., 2008; Zhang et al., 2008) required for the biosynthesis of small nuclear ribonucleoprotein particles (SnRNPs) (Fischer, Liu, & Dreyfuss, 1997; Yong, Wan, & Dreyfuss, 2004). SnRNPs play essential roles in processing pre-mRNA to mRNA (Yong et al., 2004). Even though the disease has been mainly classified as a motor neuron

disease, the SMN complex plays a key role in splicing regulation and thus making SMA splicing disease (Zhang et al., 2008).

ROS have been shown to inhibit the SMN complex (Wan et al., 2008). β-lapachone, a potent producer of ROS, along with other agents such as hydrogen peroxide, cumene hydroperoxide and environmental toxins which produce free radicals inhibit the effects of the SMN complex. This inhibition was shown to be dose dependent and the effect of the inhibition was shown to be of a functional deficiency equivalent to what happens in SMN protein deficiency. Thus, the SMN complex is very vulnerable to ROS (Wan et al., 2008).

Even though the direct role of mitochondria in the pathogenesis of SMA has not been fully elucidated, it has been shown in pre-clinical studies that, free radicals generation increases after SMN knockdown (Acsadi et al., 2009). SMN small interfering Ribonucleic acid (siRNA) transfection led to an increase in free radical production as compared to control at both 48 h and 72 h after SMN knockdown. This increase in free radicals may lead to mitochondrial DNA mutations and deletions (Acsadi et al., 2009). It was also realized that changes in mitochondrial function (which were observed as activity of caspase-3 and ATP levels) were observed before cell injury after SMN knockdown (Acsadi et al., 2009).

Traumatic Brain Injury

Traumatic brain injury (TBI) has been shown to be a major cause of death in young adults with one of its major causes being road traffic accidents (Ma et al., 2017). It has been projected by the World Health Organization that by 2020, road traffic accidents will be the third leading cause of death and disability worldwide (Finfer & Cohen, 2001) suggesting the concurrent increase in the incidence of TBI which will occur. However, in countries where there are low incidences of road traffic accidents due to safer roads and strict traffic regulations, TBIs are still reported due to falls (in the elderly) and violence suggesting that safer roads are not the only way to combat TBI (Maas, Stocchetti, & Bullock, 2008).

TBI refers to brain damage from a mechanical force (Choi et al., 2012; Maas et al., 2008) which can occur with or without loss of consciousness. Even though, some of the earlier manifestations of TBI have been managed effectively (thereby improving survival rate), most patients suffer from delayed neuronal death and cognitive impairment (Choi et al., 2012).

The initial damage from TBI is as a result of the mechanical injury which occurs at the time of impact; however secondary changes also develop later (Zhang et al., 2012). The initial injury results in skull fracture, cerebral contusions and epidural or subdural hematomas (Chakraborty, Skolnick, & Narayan, 2016). It has been shown that oxidative stress is important in the development of cerebral edema which is associated with TBI, the disruption of the blood brain barrier (BBB) and the resulting neuronal damage which occurs post-TBI (Ma et al., 2017). O_2^-, produced when an oxygen molecule obtains an electron from another molecule is the most common cellular free radical and the source of other ROS that leads to lipid peroxidation (Dohi et al., 2010). Excess O_2^-, causes tissue damage primarily through the formation of hydroxyl radical and peroxynitrite (Zhang et al., 2012). The reaction to form peroxynitrite is a diffusion-limited reaction with no requirements for enzymes. Both the $^{\bullet}OH$ and $ONOO^{\bullet}$ are powerful oxidants but with different biological implications as the hydroxyl radical is more promiscuous than the peroxynitrite in terms of substrate specificity (Pacher, Beckman, & Liaudet, 2007). These ROS can cause DNA damage and lipid peroxidation which could lead to inflammation in nearby tissues thus promoting apoptosis (Chakraborty et al., 2016). These reactive species can also oxidize polyunsaturated fatty acids in the cell membrane which leads to the formation of various reactive molecules including

HNE. HNE is very reactive and an increase in its levels is used as a specific marker of oxidative stress (Romano et al., 2017).

The mitochondria have been known to be the major source of superoxide anion after brain injury, however it has been recently shown that NOX also plays a role. NOX usually refers to the NOX2 isoform which was characterized first. NOX2 has been shown to be highly co-localized in neurons at 1 h after TBI suggesting its significance in this disorder (Zhang et al., 2012). NOX2 has been shown to be localized in the cerebral cortex and hippocampal CA1 region and its activation has been shown to be dependent upon formation of an active complex with several phox subunits (p47phox, p67phox, p40phox) and activated Rac1, which activated and translocated to the cytoplasm from the membrane to form an active enzyme complex (Zhang et al., 2012). NOX2 has also been found to be localized in microglia and hence can contribute to neuroinflammation (Zhang et al., 2012).

FREE RADICALS AND OXIDATIVE STRESS AS TARGETS OF DRUG THERAPY IN NEURODEGENERATIVE DISORDERS

Mechanism of Synthetic Drugs and Natural Products in Reducing Free Radicals and Combating Oxidative Stress

Neurodegenerative disorders are different in their manifestations but a single common underlying factor is the induction of oxidative stress by free radicals. Different therapies have been postulated to manage these disorders including the use of agents which scavenge free radicals in an attempt to rid the body of such chemicals. To slow the progression of neurodegenerative disorders, approaches utilized include preventive therapy, disease modifying therapy and hormone therapy. Preventive therapy aims at improving the redox status (in order to ensure homeostasis) as well as preventing the resulting sequelae from the primary insult (Losada-Barreiro & Bravo-Díaz, 2017). However, most of these remedies have been shown to be ineffective in clinical trials even though positive results were obtained in pre-clinical trials (Ma et al., 2017). Mechanisms which have been exploited as potential targets to combat the various neurodegenerative disorders are elaborated on below.

NADPH Oxidase Inhibition in Traumatic Brain Injury

Because initial injury cannot be reversed in traumatic brain injury, significant research targets preventing or minimizing secondary injury (Chakraborty et al., 2016). ROS generation has been implicated in impairment brain functioning neuronal death after TBI. Both prophylactic and curative treatment with apocynin, a NADPH oxidase (NOX) inhibitor, originally isolated from the roots of *Picrorhiza kurroa* (Maraldi, 2013), significantly decreased oxidative damage in the cortex and the hippocampus in rodents (Zhang et al., 2012). Pretreatment with a specific NOX2 inhibitor, *gp91ds-tat,* also greatly reduced the neuronal damage and edema after TBI (Zhang et al., 2012). Further evidence that NADPH oxidase is an important target to combat neurodegeneration by reducing oxidative stress is adduced by the observation that *gp91phos* (NOX2) gene deficient-mice exhibited reduced primary cortical damage and ROS levels at the site injury (Dohi et al., 2010). Also, pretreatment with intraperitoneal injection of apocynin led to reduced TBI-initiated oxidative produced neuroprotective effects as observed by decreased atrophy and neuronal loss in the CA3 region of the hippocampus in rats (Choi et al., 2012). The neuroprotective

plant extract, *Ginkgo biloba,* has also been shown to be an NADPH oxidase inhibitor which was able to reduce the activity of neutrophil-containing myeloperoxidase (Maraldi, 2013).

Oxygen Free Radical Scavengers as Neuroprotective Agents

Antioxidants produce their effects by donating their own electrons in order to counteract their effects of ROS. Generally their effects as classified by Losada-Barreiro & Bravo-Díaz (2017) may be to maintain the production of ROS to the minimum, scavenge produced ROS or restore damage ROS-target molecules.

Transcranial injection of the antioxidant glutathione, the powerful tripeptide antioxidant that efficiently scavenges the hydroxyl radicals as well as detoxifies H_2O_2, after head injury significantly reduced inflammation and meningeal cell death (Danta & Piplani, 2014). Also, administration of N-acetylcysteine (precursor to glutathione) both in patients and rodents have shown positive outcomes in mild and moderate traumatic brain injury (Corps, Roth, & McGavern, 2015). This is one of the few successful clinical trials involving antioxidants as therapy for a neurodegenerative disorder. It is important however to note that, the likely key in using antioxidants to management TBI is to initiate therapy as soon as possible so as to avoid lesion expansion and the subsequent sequelae which results (Corps, Roth, & McGavern, 2015).

Another antioxidant with positive outcomes in both pre-clinical and clinical trials is the potent antioxidant, vitamin E. In randomized controlled, double-blind clinical trials with vitamin E in moderately impaired AD patients, the progression of functional impairment was delayed. α-Tochopherol also slows the advancement of PD in both clinical and preclinical trials (Danta & Piplani, 2014). Natural products such as *Gingko biloba*, flavonoids, soybean isoflavones and nicotine have been shown to reduce the neurotoxicity that is predominant in Alzheimer's disease by reducing oxidative stress (Velusamy et al., 2017). Other natural products including luteolin derivatives, *Calendula officinalis* flowers, olive oil and melatonin have shown possible neuroprotective effects in Huntington disease (HD) models all due to their antioxidant properties (Velusamy et al., 2017). For example, *Ginkgo biloba* has been shown to reduce the rate of 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP)-induced neurodegeneration of dopaminergic neurons (Wąsik & Antkiewicz-Michaluk, 2017). This beneficial effect is due to its ability to scavenge superoxide free radicals. Additionally, *Ginkgo biloba* regulate glutathione reductase and other antioxidant systems, superoxide dismutase activity as well as its neurotrophic effects (Rojas et al., 2004). All these antioxidant therapies however are not effective as sole treatment but are effective against oxidative stress and slows the progression of HD (Manoharan et al., 2016)

Neuroprotective Steroids

Neuroprotective steroids are either synthetic or natural steroids that mainly protect the CNS or peripheral nervous system (PNS) from neurodegeneration. They include dehydroepiandrosterone, testosterone, estradiol, pregnenolone and progesterone. These agents act by mainly protecting neurons from oxidative stress, excitotoxicity and inflammation while promoting repair processes such as neurogenesis among others (Bansal & Singh, 2017). In AD, estradiol is known to regulate Aβ accumulation in the brain as well as protect neuronal cells from the resulting damage. It is also able to prevent the hyperphosphorylation of tau protein which is a hallmark of AD (Bansal & Singh, 2017).

Efficacy of Combatting Free Radicals in the Management of Neurodegenerative Disorders

The effectiveness of free radical scavenging agents as therapeutic agents is fraught with challenges. Thus the efficacy of some of these agents including apocynin in pre-clinical trials have not been translated in most clinical trials. Generally, this may be due to the inability of the agents to permeate the BBB or the fact that most of these agents do not target a specific oxidative mechanism (Ma et al., 2017).

One of the main challenges is the burden of off-target effects. For instance, diphenyliodonium (DPI) a very potent NOX inhibitor also has effects on cholinesterases, xanthine oxidase and calcium pump which may account for some of its adverse effects (Maraldi, 2013). Also, it has been shown that the use of NOX inhibitors targets both physiological and pathological effects of NOX and might lead to undesirable side effects. This will require the use of specific inhibitors which will help to reduce off-target effects as well as the need to selectively target only pathological NOX signaling (Ma et al., 2017).

Popular antioxidants like ascorbic acid and flavonoids as monotherapy or in combination have also not shown very positive results in human studies for the treatment of all neurodegenerative disorders (Ma et al., 2017). In certain conditions, where they prove to be beneficial, the nature of the formulation becomes a hindrance to their effective use. A perfect example is that of flavonoids which are highly polar molecules and hence are unable to cross the blood brain barrier effectively. Thus, for an antioxidant to be efficacious in ND management, it should have the following basic characteristics as classified by (Danta & Piplani, 2014):

1. The molecule must be able to accept electrons from reactive molecules and remain stable upon receipt of the electron
2. Be fairly lipophilic to facilitate crossing of the blood brain barrier and
3. Be fairly selective in order to prevent off-target effects

Future Research Directions Towards a Holistic Treatment of Neurodegenerative Disorders

Setbacks

There are currently no treatments for the complete amelioration of neurodegenerative diseases even though symptoms of some NDs can be partially assuaged using antioxidants. Positive results obtained in pre-clinical trials have not always been successfully replicated in humans during clinical trials (Ma et al., 2017). Oxygen-free radical scavengers have been used in clinical trials to manage several neurodegenerative disorders but mostly with no positive outcomes (Ma et al., 2017).

With the important role played by SOD in the pathology of several neurodegenerative disorders it was expected that SOD would ameliorate several neurodegenerative disorders (Chakraborty et al., 2016). However, upon administering pegorgotein, a conjugated form of superoxide dismutase with reduced antigenicity and prolonged half-life, there was no statistically significant difference in neurologic outcome or mortality between pegorgotein and placebo-treated groups in a traumatic brain injury clinical trials (Young et al., 1996). The effects of tirilazad, an amino steroid with antioxidant and lipid peroxidation inhibition properties was also studied in clinical trials and it was observed that there was no difference in favorable outcomes or mortality between treatment and placebo groups (Chakraborty et al., 2016).

Prospects

It has become imperative to look at other approaches for mitigating oxidative stress beyond the routine antioxidant approach recognizing the various failures to translate observations in preclinical data to clinical trials.

The Endocannabinoid System

It is now believed that targeting the endocannabinoid system to regulate oxidative stress-induced cell death may hold therapeutic potential in NDs from traumatic brain injury through AD and PD to amyotrophic disorders and HD. This is backed by the evidence from effects of interaction at both cannabinoid receptors (CB1 and CB2) (Paloczi, Varga, Hasko, & Pacher, 2017). CB2 expression in microglia appears upregulated in oxidative stress related NDs, such as AD, MS, or PD although how free radicals induce CB2 receptor expression is still elusive while CB2 agonists have exerted neuroprotective effects and attenuated of neuronal cell damage (Paloczi, Varga, Hasko, & Pacher, 2017).

Additionally, the neuroprotective role of CB1 nonselective receptor agonists (WIN55, 212-2 and HU210) has been reported in a murine PD model. Interrupting CB1 signaling led to reduced ROS production and suppression of NOX which culminated in increased survival of nigrostriatal dopaminergic neurons in the striatum (Chung et al., 2011). It has also be shown that the activation of CB1 receptor by anandamide protects hippocampal neurons from oxidative injury by decreasing intracellular ROS and lowering the expression of type 2 NADPH oxidase —effects that are abolished in the presence of CB1 antagonist AM251 or CB1-siRNA (Jia et al., 2014). Moreover, the non-psychoactive phytocannabinoid, cannabidiol, shows neuroprotection by diminishing ROS levels and lipid peroxidation products in vitro and in vivo in Alzheimer's disease models (Iuvone et al., 2004). With regard to traumatic brain injury, a positive correlation occurs between tetrahydrocannabinol intake and decreased mortality in adult TBI patients (Nguyen et al., 2014) while anandamide-CB1 receptor signaling reduces the progression of clinical symptoms in G93A-SOD1 transgenic mice model of ALS (Bilsland et al., 2006).

On the contrary, other studies have also demonstrated that CB1 receptor activation may promote ROS generation in other body systems and therefore the contribution of CB1 signaling may be cell-type dependent or an indirect consequence of various processes (Steffens & Pacher, 2015). This situation warrants further studies to evaluate the interaction of cannabinoids and ROS production in the disease progression of the various neurodegenerative disorders in order to understand the complex interactions and ultimately provide more efficacious cannabinoid-based therapies with minimal offset effects for neurodegenerative disorders in future

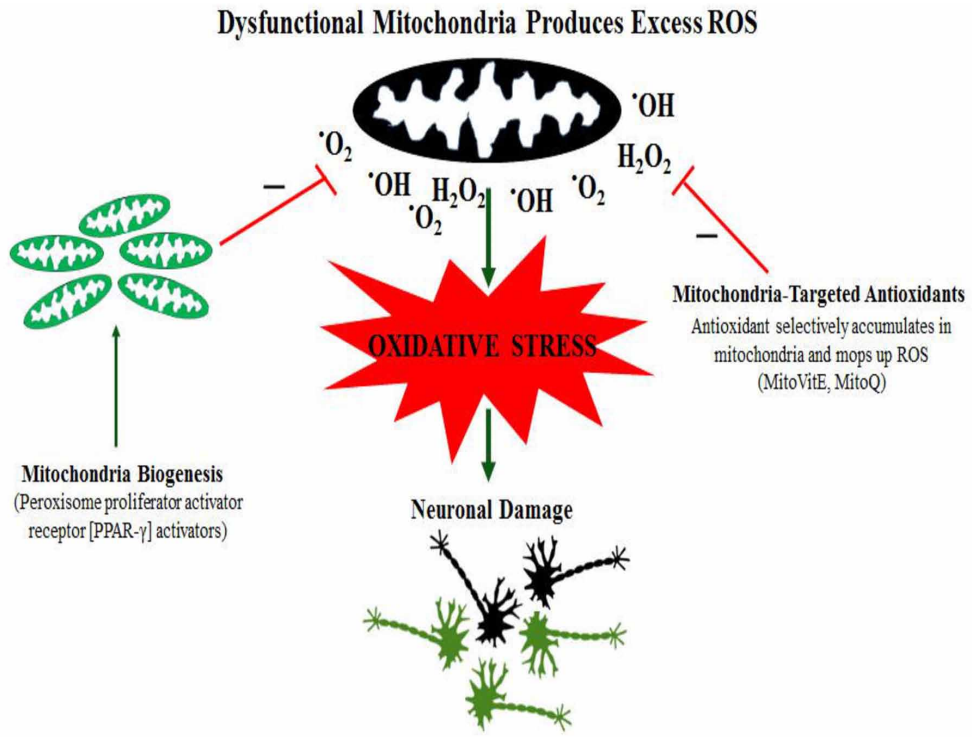
Mitochondria Targeted Antioxidant Therapy

The mitochondria's physiological actions include a variety of important cellular regulatory processes including ROS generation and detoxification. With the failure to translate pre-clinical success in antioxidant therapies to clinical trials, interest in mitochondria-targeted antioxidants therapy is increasing as a potential option to circumvent this challenge. The mitochondrion is an attractive target for drug-delivery strategies it is an important source of ROS.

This has led to the development of several investigational agents such as MitoVitE and MitoQ which are vitamins E and ubiquinone moiety of coenzyme Q10 derivative conjugated to the lipophilic cation triphylphosphonium respectively with the ability to cross the mitochondrial phospholipid bilayer, selectively accumulate in the mictochondria and mop up free radicals at their site of generation (Oyewole & Birch-Machin, 2015). The efficacy and toxicity of MitoQ have been evaluated in both pre-clinical and clinical trial for Parkinson's disease (Snow et al., 2010). MitoQ shows protection from MPTP-induced loss of behavioural activities and degeneration of dopaminergic neurons and terminals and demonstrated appreciable effects in phase I and II clinical trials (Jin et al., 2014; Snow et al., 2010). It has also been effective in mice models of Alzheimer's disease on mouse neuroblastoma (N2a) cells cultured with amyloid-β (Aβ) peptide (Manczak et al., 2010)

Another strategy of new interest is increasing mitochondria biogenesis. It is acknowledged that increases in neuronal mitochondrial numbers could compensate for bioenergetic dysfunction in neurodegeneration (Figure 1). Therefore, there is currently significant increase interest in peroxisome proliferator activator receptor (PPAR-γ) activators such as resveratrol, pioglitazone and rosiglitazone and the potential use to upregulate mitochondrial biogenesis and mitigate the increased oxidative burden seen in neurodegenerative disorders (Schapira, Olanow, Greenamyre, & Bezard, 2014).

Figure 1. Methods for mediating oxidative stress via reducing excess production of reactive oxygen species by dysfunctional mitochondria



CONCLUSION

In the battle to effectively manage NDs, it has been shown that free radical-induced oxidative stress is a major player hence this chapter provides an overview of the multiple roles played by ROS in different NDs. The various mechanisms which target the generation or end effects of ROS and are being used to alleviate the sequelae resulting from these diseases have been discussed. Antioxidant systems such as the enzymes and low molecular weight reductants are reviewed with their possible mechanisms of action in certain NDs highlighted. The interplay of diet in aging and oxidative stress is also highlighted. Mechanisms of synthetic drugs and natural products in combatting ROS are reviewed with emphasis on their effectiveness in clinical trials and associated challenges. Lastly, the chapter examines novel targets requiring further research such as the endocannabinoid pathway and the mitochondria-targeted antioxidants. These have been outlined to stimulate research into novel management strategies of NDs. Great strides have been made in understanding the mechanisms of NDs, however, there is still a knowledge void that needs to be filled. Current therapeutic agents cannot adequately to provide the desired therapeutic effect, hence additional research is required to deliver efficacious therapeutic agents with minimal off-target effects.

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Chapter 4
Mitochondrial Dysfunction in Aging and Neurodegeneration

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ABSTRACT

Mitochondria are a dynamic organelle of the cell involved in the various biological processes. Mitochondria are the site of the adenosine triphosphate (ATP) production, electron transport chain (ETC), oxidation of fatty acids, tricarboxylic acid (TCA), and cellular apoptosis. Besides these, mitochondria are the site of production of reactive oxygen species (ROS), which further disrupts the normal functioning of this organelle also making mitochondria itself as an important target of oxidative stress. Thus, mitochondria serve as an important target in the process of neurodegeneration. In the present chapter, the authors describe mitochondria and its functioning, dynamics, and the mitochondrial dysfunction in aging and neurodegenerative disorders (NDs).

INTRODUCTION

Mitochondria are the main organelle of the cell which plays key role in the various processes including oxidative phosphorylation, calcium signaling (Rizzuto et al, 2012), stress responses (Pellegrino & Haynes, 2015) and cellular apoptosis (Bratic & Larsson, 2013). The primary role of mitochondria is the production of ATP by the process of oxidative phosphorylation. During this process some of the electrons eventually leaks and this results in the generation of free radicals or reactive oxygen species (ROS) (Payne & Chinnery, 2015). The production of ROS is known to cause the oxidative damage to various components of mitochondrial electron transport chain (ETC) resulting in the mitochondrial dysfunction. Mitochondria dysfunctional is further characterized by decreased activity of ETC complexes, decreased rate of electron transport in complex-I and IV, reduced capacity of oxidative phosphorylation, decreased ATP production, increased water permeability in brain mitochondria, decreased ATP-synthase activity, increased accumulation of oxidative products, decreased mitochondrial membrane potential, increased

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mitochondrial size and fragility. Further all these factors are the determining factors of brain aging (Navarro & Boveris, 2010). Further inactivation of complex-1 has been recognized as characteristic of aging and neurodegeneration in brain. Mitochondrial dysfunction is more prominent in the areas of brain including hippocampus, frontal cortex and substantia nigra (Navarro & Boveris, 2010). In the present work author discuss different causes and features of mitochondrial dysfunction and demonstrate the role of mitochondrial dysfunction in the neurodegenerative pathologies.

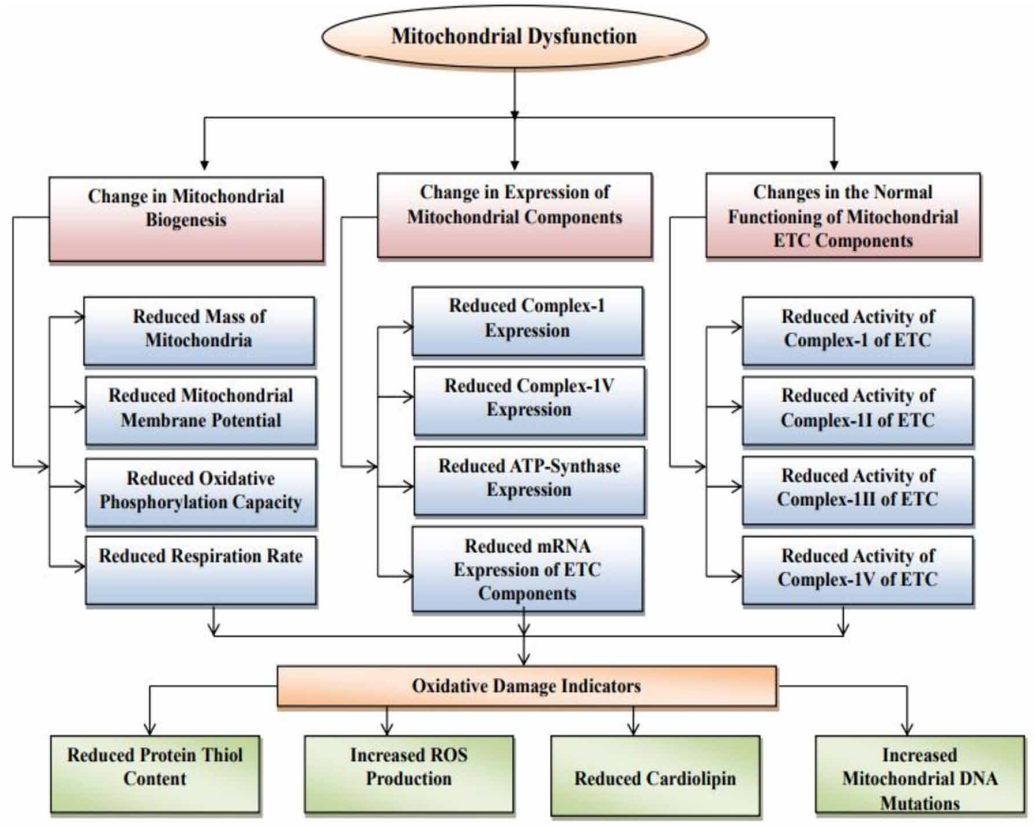
BACKGROUND

Mitochondria are the organelle linked with the production of ATP and dysfunction of this organelle thus led to ATP deficit. Besides the synthesis or production of ATP, mitochondria are the important site of various other physiological processes including sequestration of calcium within neurons (Trevelyan et al, 2010), misfolded/altered/damaged protein clearance pathways (Emmanouilidou et al, 2010; Jana, 2012; Li & Li, 2011; Rubinsztein et al, 2011), site of ROS production (Cui et al, 2012) and production of apoptogenic factors involved in the process of cellular apoptosis (Tsujimoto, 2000). The production of ROS increases with the increase in the age and aging is characterized by the increased generation of ROS which evokes oxidative stress and affects normal functioning of various cellular molecules (Gerschaman et al, 1954; Harman, 1956). Mitochondrial ROS production mediated damaged to cellular molecules led to the accumulation of oxidative and damaged products (Beckman &Ames, 1998; Harman, 2006; Vina et el, 2003). Further mitochondria derived from the brain of aged individual showed increased membrane permeability (Navarro & Boveris, 2004); reduced membrane potential and increased degradation (Beckman & Ames, 1998; Navarro & Boveris, 2004, 2007b) and decreased ATP-synthase activity (Lam et el, 2009). Dysfunctional mitochondria results in the prolonged elevation of intracellular calcium that results in the neuronal dysfunction observed in PD patients (Trevelyan et al, 2010). Reduced activities of mitochondrial protein clearance pathways including UPS system and autophagy (Emmanouilidou et al, 2010; Jana, 2012; Li & Li, 2011; Rubinsztein et al, 2011) has been observed in the brain of the PD patients SN region (Bedford et al, 2008; McNaught et al, 2003; McNaught & Jenner, 2001). Also the activities of these pathways declines with the increase in the age (Emmanouilidou et al, 2010; Jana, 2012; Li & Li, 2011; McNaught et al, 2003; McNaught & Jenner, 2001; Rubinsztein et al, 2011) suggesting aging increased the risk of PD onset. Also it has been reported that the risk of developing PD increases after the age of 65 years and the PD generally affects the individuals in the later stages of life (de Lau & Breteler, 2006; Fearnley & Lees, 1991; Ma et al, 1999b; Nussbaum & Ellis, 2003; Wood-Kaczmar et al, 2006). The different events that evolved in context of mitochondrial dysfunction have been shown in Figure 1.

MITOCHONDRIA AND AGING

Mitochondria consist of 2 membranes; outer membrane is porous while the inner membrane is impermeable. It is suggested that Bcl-2 class proteins (including proapoptotic proteins i.e. Bax, Bak, Bok, Bid, Bad, and Puma and antiapoptotic proteins i.e. Bcl-2, Bcl-x_L, and Mcl-1) (Adams & Cory, 1998) maintains the integrity of the outer membrane of the mitochondria (Chipuk et al, 2010). The space between the 2 membranes is called inter membranous pace in which cytochrome c (cyt-c) is present (Tait & Green,

Figure 1. Mitochondrial dysfunction and the events involved. Mitochondrial dysfunction mainly arises due to impaired mitochondrial biogenesis, impaired expression of the mitochondrial components and the impaired functioning of the mitochondrial components. These events results in the oxidative damages which is further characterized by the increased ROS production, reduced protein thiol content, reduced cardiolipin and increased mitochondrial DNA mutation. These events further results in the neurodegeneration (Balaban et al, 2005; Hu & Wang, 2016).



2010). Bcl-2-family proteins possess ion channel activity and render membranes permeable to cyt-c (Korsmeyer et al, 2000, Kuwana et al, 2002). The genetic material present inside the mitochondria are double stranded circular DNA (Taylor & Turnbull, 2005) known as mitochondrial DNA (mit-DNA). mit-DNA is not protected by histone proteins therefore highly mutagenic in nature (Cheng et al, 1992; Kuchino et al, 1987; Yakes & Van Houten, 1997); lack DNA repair mechanisms (Stuart & Brown, 2006) and containing oxidized bases (Ames 1989; Richter et al, 1988) making it prone to oxidative damage (Mecocci et al, 1997). mit-DNA encodes for the several components of ETC, thus any damage to mit-DNA affects the functioning of ETC (Alexeyev et al, 2004) which further affects the production of ATP and ROS (Indo et al, 2007). mit-DNA mutations arise due to the consequence of unrepaired DNA damage (Larsson, 2010) and its frequency increases during aging (Corral-Debrinski et al, 1992; Fayet et al, 2002; Yen et al, 1991) resulting in increased ROS production, reduced oxidative phosphorylation, and increased cell death (Allen & Coombs, 1980; Niranjan et al, 1982; Rossi et al, 1988; Wunderlich et al, 1970). mit-DNA deletion also increases with the increase in age and their levels were found highest in

the including basal ganglia, substantia nigra (SN) and cortex of the brain (Corral-Debrinski et al, 1992; Soong et al, 1992). Aging is characterized by the increased generation of ROS (Gerschaman et al, 1954; Harman, 1956) and mitochondria are the site of ROS production, therefore the theory of aging centers around the mitochondria (Beckman & Ames, 1998; Harman, 2006; Vina et el, 2003). Further mitochondrial ROS production is considered as a main characteristic of aging (Beckman &Ames, 1998; Harman, 2006; Vina et el, 2003) and age related neuronal degeneration (Harman, 1972). Aging is also accompanied by the reduction in DNA repair mechanism (Imam et al, 2006) suggesting age related deficits in mit-DNA repair enzymes potentiate the process of neurodegeneration (Jeppesen et al, 2011; Zhang et al, 2010). Aging brain is characterized by the accumulation of defective or dysfunctional mitochondria (Boveris & Navarro, 2008; Navarro & Boveris, 2007a, b) suggesting age-related mitochondrial dysfunction contributes to neuronal degeneration (Balaban et al, 2005). Different features of mitochondrial dysfunction are shown in Table 1.

MITOCHONDRIA AS A SITE OF REACTIVE OXYGEN SPECIES PRODUCTION

Mitochondria are a major site of ROS production and the production of ROS increases with the increase in the age of the individual (Sohal et al, 1994; Sohal & Sohal, 1991). ROS are produced by the mitochondria due to the defects in the oxidative phosphorylation mechanism (Murphy, 2009). ROS also produced in the body during normal conditions (Wei et al, 2001) and their production requires the molecular oxygen (Smith et al, 2007). The leakage of the electron from the ETC combines with the molecular oxygen to form the superoxide radical ($O_2^{\bullet}$) (Finkel & Holbrook, 2000) which is highly toxic in nature and therefore converted by the enzyme superoxide dismutase into hydrogen peroxides (H_2O_2) which is further toxic in nature and in the presence of Fe^{2+}, H_2O_2 is further converted into hydroxyl radical ($OH^{\bullet}$) (Valko et al,

Table 1. Different features of the mitochondrial dysfunction in age related neurodegeneration.

S. No.	Parameters	Levels/Activity/Expression
1.	Oxidative parameters [thiobarbituric acid reactive substances (TBARS) or *malondialdehyde (MDA)]*	Increased levels of TBARS or MDA.
2.	Mitochondrial enzymes	Decreased activity of enzymes such as ATP synthase, DNA glycosylase
3.	Mitochondrial proteins	Decreased expression and levels of mitochondrial proteins (such as cardiolipin)
4.	Mitochondrial DNA	Increased number and rate of mutations and deletion of mitochondrial DNA
5.	Mitochondrial mRNA	Decreased mitochondrial mRNA expression
6.	Mitochondrial mass	Decreased mitochondrial mass
7.	Mitochondrial oxidative phosphorylation	Decreased mitochondrial oxidative phosphorylation
8.	Mitochondrial membrane potential	Decreased mitochondrial membrane potential
9.	Mitochondrial electron transport chain complexes	Decreased activity of complex-I, II, III and IV of mitochondrial electron transport chain
10.	Mitochondrial ATP synthesis	Decreased ATP synthesis

2007). ROS initially functions to compensate the damage by the mitochondrial biogenesis (Chakrabarti et el, 2011). $O_2^{\bullet}$ and H_2O_2 exerted the oxidative damage to cellular macromolecules (Balaban et al, 2005) and $OH^{\bullet}$ damage macromolecules within mitochondria (Van Houten et al, 2006). Further the production of ROS increases with the increase in the age of the individual (Sohal et al, 1994; Sohal & Sohal, 1991) and the increased production of ROS is the main cause for age neuronal damage and degeneration (Harman, 1972). Exposure to the ROS inactivate complex-I, II, and III of ETC of mitochondria (Ghezzi & Zeviani, 2012). Further the reduced activity of complex I of ETC has been reported in patients of PD (Parker et al, 1989; Schapira et al, 1990; Swerdlow et al, 1996). ROS contribute to the development of vascular inflammation in aging (Ungvari et al, 2007) and accelerates senescence in endothelial cells in aging (Csiszar et al, 2004; Pearson et al, 2008). ROS promote the mitochondrial outer membrane permeabilization (MOMP) (Garcia-Perez et al, 2012) which further results in the release of cyt-c in to the cytoplasm further resulting in the activation of caspase responsible for cell death (Newmeyer & Ferguson-Miller, 2003). Further the high levels of the ROS activate p53-mediated apoptosis (Liu et al, 2008). Thus the raised levels and accumulation of ROS in the aged individuals (Rebrin & Sohal, 2008) results in the neuronal cell damage (Du et al, 2003).

MITOCHONDRIAL DYSFUNCTION IN NEURODEGENERATIVE DISORDERS

The neuronal degeneration arises due to the mitochondrial dysfunction is further linked with the genetic mutations (Table 2).

Table 2. Genes mutation responsible for the mitochondrial dysfunction responsible for neurodegeneration (Ebrahimi-Fakhari et al, 2012; Klein & Westenberger, 2012; Miklya et al, 2014; Sterky et al, 2011; West et al, 2007).

Sr. No.	Gene	Mutation and its Effect
1	*SNCA*	Mutations cause structural changes in mitochondria, oxidative stress, reduced complex-I activity, reduced generation of ATP, increase mitochondrial fragmentation and degeneration, altered mitochondrial membrane potential and MOMP leading to the leakage of pro-apoptotic molecules responsible for neuronal cell death.
2	*Parkin*	Mutation accounts for the reduced activity of complex- I and IV, reduced mitochondrial integrity, reduced mitochondrial enzyme activity and reduced mitophagy.
3	*PINK1*	*M*utation led to the reduced enzyme activity, reduced complex-1 activity, reduced ATP synthesis and reduced mitophagy.
4	*LRRK2*	Mutations induced mitochondrial fragmentation, increased the level of ROS and reduced ATP production.
5	*DJ-1*	Mutation results in the reduced activity of complex-1 and II, reduced ATP production, reduced oxygen consumption, reduced mitochondrial membrane potential and disruption of the mitochondrial integrity.
6	*APP*	Mutations induces the production and deposition of plaques of amyloid β (Aβ) peptide inhibit mitochondrial respiration; increased production of ROS, reduced production of ATP, increased entry of Ca^{2+} entry into neurons, opening of mtPTP, and trigger cell death in neurons.
7	*PSEN1*	Mutations increase the length of Aβ peptides responsible for the aggregation, increase ROS production and neurotoxicity.

Mitochondrial Dysfunction in Parkinson's Disease

Mitochondrial dysfunction plays a key role in the PD pathogenesis. PD is further characterized by the higher levels of the mit-DNA deletions in the SN region of the brain suggesting the involvement of the mitochondrial dysfunctioning in the brain of the PD patients (Hu & Wang, 2016). α-synuclein is synaptic protein (Bendor et al, 2013), important for synaptic vesicle recycling (Cheng et al, 2011; Murphy et al, 2000) aggregate to form protofibrils in response to oxidative stress (Bendor et al, 2013; Breydo et al, 2012; Fujiwara et al, 2002; Giasson et al, 2000). Mutations in α-synuclein gene or *SNCA* gene cause structural changes in mitochondria (Botella et al, 2008). α-synuclein aggregation mediated oxidative stress (Bendor et al, 2013; Breydo et al, 2012; Fujiwara et al, 2002; Giasson et al, 2000), structural changes in mitochondria (Botella et al, 2008) reduced complex-I activity of ETC and ROS formation (Devi et al, 2008; Parihar et al, 2008, 2009) reduce the generation of ATP (Rowland & Voeltz, 2012), increase mitochondrial fragmentation and degeneration (Martin et al, 2006; Plotegher et al, 2014), reduce mitochondrial Ca^{2+} retention (Calì et al, 2012) altered mitochondrial membrane potential (Luth et al, 2014) and MOMP leading to the leakage of pro-apoptotic molecules (Bandopadhyay & de Belleroche, 2010) responsible for the neuronal cell death. Previous reports suggested that *Parkin* plays a key role in the clearance of misfolded proteins. *Parkin* serves as an ubiquitin E3 ligase that degrades misfolded proteins (Yoshii et al, 2011; Zhang et al, 2000) and the *Parkin* mediated ubiquitination serve as signal for the degradation of ubiquitinated substance by UPS (Dawson & Dawson, 2010). *Parkin* maintain the proper functioning of mitochondria and mit-DNA (Kuroda et al, 2006), inhibits ROS formation (Kuroda et al, 2006; Temme et el, 2009), protects mit-DNA from damage (Rothfuss et al, 2009, Watson et al, 2004), regulates mitochondrial fission and fusion mechanism (Glauser et el, 2011; Narendra et el, 2008) and mutation in the gene encodes for *Parkin* accounts for the familial and sporadic cases of PD (Ebrahimi-Fakhari et al, 2012; Miklya et al, 2014; West et al, 2007) and its early onset (Klein & Westenberger, 2012). *PINK1* is responsible for the normal functioning of mitochondria and it is reported that the loss of mitochondrial membrane potential and increase accumulation of misfolded/altered protein led to the stabilization of *PINK1* on outer mitochondrial membrane, which is the sign of elimination of mitochondria (Pickrell & Youle, 2015). The ultimate target of *PINK1* is *Parkin* present in the cytoplasm. *PINK1* phosphorylate mitofusin2 (Mfn2) for the binding of *Parkin* to the mitochondria by the process of mitophagy (Pickrell & Youle, 2015). *PINK1* also phosphorylates *Parkin* at Ser65 position responsible for the activation of *Parkin* (Truban et al, 2016). *PINK1-Parkin* signaling plays a key role in the mitophagy (Narendra et al, 2010; Schapira, 2012) and the alteration in this signaling pathway is responsible for mitochondrial dysfunction (Sterky et al, 2011). Mitophagy is defined as the removal of the targeted or specific or damaged or excess of mitochondria by the process of autophagy (Lemasters, 2005). Mitophagy removes the mitochondria which becomes dysfunctional or produces excess ROS (Kim et al, 2007). High population of enlarged and swollen mitochondria has been reported in the sever models of PD (Martin et al, 2006; Poole et al, 2008; Yang et al, 2006) suggesting the role of the mitochondrial dysfunctioning in the pathogenesis of PD. *LRRK2* belongs to the Roco family proteins (Bosgraaf & Van Haastert, 2003; Marín et al, 2008). In the neurons *LRRK2* colocalizes with Dynamin like protein 1 (DLP1) and its expression induced mitochondrial fragmentation and increased the level of ROS (Niu et al, 2012; West et al, 2005). *LRRK2* is involved in the various cellular functions including vesicular trafficking, proteolysis, regulation of neuritic outgrowth and neuritic morphology (Li et al, 2014). *LRRK2* is known to regulate NF-κB activity (Gardet et al, 2010) which is further responsible for the induction of TNF mediated extrinsic pathway of the cell death and the inhibition of this pathway might reduce the

neuronal death in the PD (Dauer & Przedborski, 2003; Hayley et al, 2004; McCoy et al, 2006). *LRRK2* gene mutations results in the onset of autosomal dominant PD in the later ages most frequently (Klein & Westenberger, 2012). *DJ-1* is a predominantly cytosolic, homodimeric protein, ubiquitously expressed in both brain and provides the neuroprotection by protecting cells against reactive oxygen species (ROS) (Björkblom et al, 2013). *DJ-1* contains 3 cysteine residues of which only C106 is highly susceptible to oxidative damage and it is reported that the alterations in the normal functioning of this residue led to the loss of the DJ1 function completely. *DJ-1* quenches ROS (Ariga et al, 2013) inhibit p53 and stimulates SOD expression (Ariga et al, 2013). Further *DJ-1* mutations are responsible for the development of autosomal recessive form of PD but found in rare cases (Klein & Westenberger, 2012). The reports from the preclinical studies suggested that mitochondria are the potential target of the toxin used for the induction of neurodegeneration in the preclinical models (Greenamyre & Hastings, 2004). Toxin, for example MPTP induces PD in the preclinical animal models (Davis et al, 1979; Langston et al, 1983). MPTP rapidly crosses the BBB (Riachi et al, 1989) and is oxidized to 1-methyl-4-phenylpyridinium (MPP+) (Chiba et al, 1984) which is taken up by the dopaminergic neurons (Javitch et al, 1985), resulting in the inhibition of complex-I of ETC (Nicklas et al, 1987) leading to the production of ROS (Keeney et al, 2006; Perier et al 2005; Ramsay et al, 1987) and depletion of the ATP level (Chan et al, 1991; Davey & Clark 1996; Di Monte et al, 1986; Scotcher et al, 1990). The increased the production of ROS following the inhibition of the complex-1 is responsible for the death of the dopaminergic neurons (Jackson-Lewis et al, 1995; Tatton & Kish, 1997). ROS also damages lysosomal membranes leading impairment in the autophagic mechanism seen in the PD patients (Dehay et al, 2010). Another agent, 6-hydroxy dopamine (6-OHDA) a hydroxylated analogue of dopamine capable damaged the dopaminergic neurons in the SN region of brain (Ungerstedt, 1968). 6-OHDA following administration, uptake by the dopaminergic neurons, and inside the neurons it oxidizes to form ROS (Mazzio et al, 2004), reduced the antioxidants enzymes (Kunikowska & Jenner, 2001; Perumal et al, 1992), raised the levels of iron (Oestreicher et al, 1994), inhibits the activities of complexes I and IV of ETC (Glinka et al, 1997) and thus induced neurodegeneration. Paraquat is another agent uptake via the transporter in the brain (Shimizu et al, 2001) inside the neurons inhibits complex-I (Miller, 2007) and complex-III (Zhang et al, 2003) of ETC and thus induces neuronal degeneration by targeting mitochondria (Ascherio et al, 2006; Costello et al, 2009). Further rotenone, is a lipophilic toxin that crosses the BBB, enters into neurons inhibits the activity of the complex-I of ETC mitochondria, increased the production of ROS and reduced the levels of glutathione (Sherer et al, 2003a). Further rotenone in the brain activates the microglia cells (Sherer et al, 2003c) and inhibits proteasomal activity (Wang et al, 2006) and caused the oxidative damage in the striatum and cortex (Alam et al, 1997; Sherer et al, 2003a, b). Thus the blockade of mitochondrial ETC by inhibiting the oxidative phosphorylation and led to the degeneration of the dopaminergic neurons (Betarbet et al, 2000; Dauer & Przedborski 2003) while promoting the mitochondrial ETC protects the neurons against neurodegeneration (Tieu et al, 2003).

Mitochondrial Dysfunction in Alzheimer's Disease

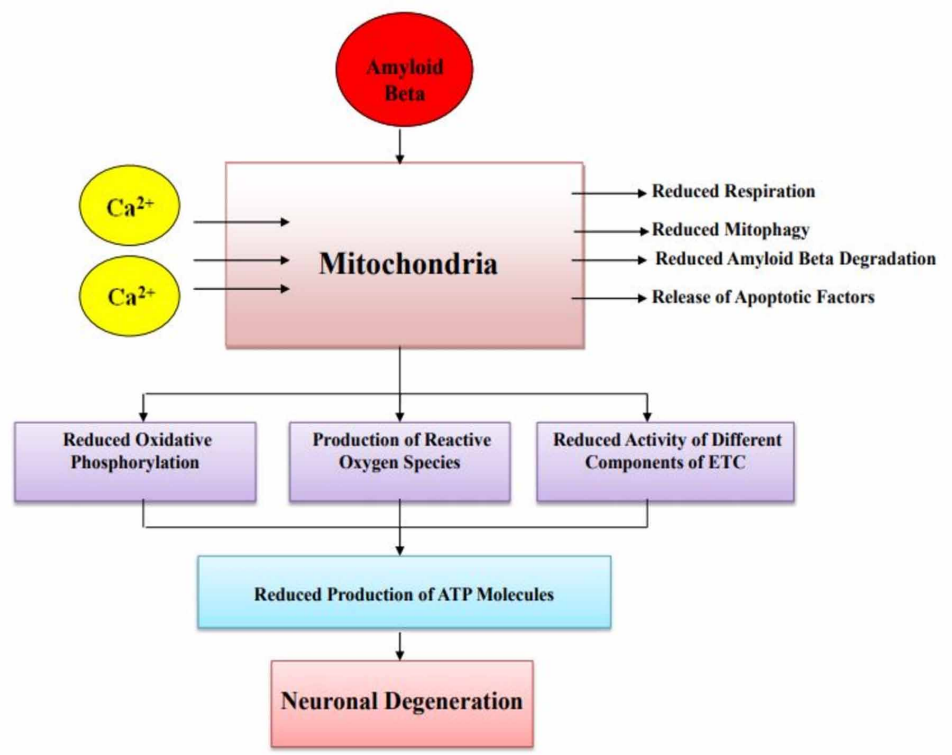
Alzheimer's disease (AD) is a NDs in which the patients suffers from the memory and behavioral deficits (Mattson, 2004; Reddy, 2008; Reddy & Beal, 2008). Several hypotheses have been formulated to explain the process of neurodegeneration in AD, out of which amyloid hypothesis is most acceptable (Hardy & Higgins, 1992). According to amyloid hypothesis accumulation or the reduced clearance of amyloid β (Aβ) peptide is responsible for neurodegeneration in AD (Hardy & Selkoe, 2002). Deposition of Aβ

peptide inhibit mitochondrial respiration (Casley et al, 2002); induces the increased entry of Ca^{2+} entry into neurons (Sanz-Blasco et al, 2008), opening of mtPTP (Reddy and Beal, 2008), trigger cell death in neurons (Giacomello et al, 2007). Previous reports suggested increased cyt-c oxidase, and reduced energy metabolism in the brain of AD patients prior to Aβ plaque formation (Hirai et al, 2001; Lin & Beal, 2006). Also the AD patients showed the down-regulation of complex-I and up-regulation of complex-III and IV genes (Manczak et al, 2004). Aβ results in the dysfunctioning of mitochondrial dysfunction and thus augmented ROS levels (Belkacemi & Ramassamy, 2012). Further the mitochondria-derived ROS increased the production of Aβ (Leuner et al, 2012). The cycle keeps on repeating and so is the neuronal degeneration in the AD patients suggesting mitochondrial dysfunction play a key role in the process of neurodegeneration in AD (Fukui & Moraes, 2008; Picone et al, 2014; Swerdlow et al, 2014) (shown in Figure 2). The dysfunctioning of mitochondria in AD is characterized by the reduced metabolism and utilization of glucose (Mosconi et al, 2011; Reiman et al, 1996), decreased activity of the cytochrome oxidase, pyruvate dehydrogenase and α-ketodehydrogenase (Reddy, 2008), increased levels and accumulation of the mit-DNA changes (Coskun et al, 2004; Lin et al, 2002), increased generation of ROS, oxidative damage and reduced ATP production (Butterfield et al, 2001; Devi et al, 2006; Maurer et al, 2000; Smith et al, 1996). Further the mitochondria isolated from the neurons of AD subjects showed significant reduction in mitochondrial length and increased width with a significant increased overall size consistent with unopposed fission suggesting alterations of mitochondrial dynamics (Wang et al, 2008). Further AD patients showed impaired mitochondrial biogenesis as compared to age matched control (Hirai et al, 2001; Qin et al, 2009; Sheng et al, 2012). The overproduction of Aβ overproduction further increased the number of fragmented mitochondria (Wang et al, 2008) mtDNA mutations (Hamblet et al, 2006) and decrease in oxidative phosphorylation and ATP synthesis (Chandrasekaran et al, 1996), suggesting Aβ affect the dynamics of mitochondria also (Calkins et al, 2011; Manczak et al, 2011; Wang et al, 2008). *Parkin* plays a key role in the clearance of the altered or misfolded proteins, and thus ubiquitinate Aβ for the proteosomal degradation and thus reduced the intracellular Aβ levels (Burns et al, 2009). *Parkin* reverses intracellular Aβ accumulation and its negative effects on proteasome function (Rosen et al, 2010). *Parkin*-induced autophagy facilitated clearance of vesicles containing debris and defective mitochondria counteracting oxidative stress and preventing mitochondrial dysfunction (Khandelwal et al, 2011). Further the reduced activity of *Parkin* has been observed in the cortex of AD brains (Rosen et al, 2010).

FUTURE RESEARCH DIRECTIONS

The future work should involve the determination of the exact mitochondrial population in the neurons of normal individuals and the aging individuals and the patients suffering from AD and PD. The research should focus on targeting the healthier mitochondria in the neurons. Since the neuronal cell death is preceded by the opening of the mitochondrial membrane transition pore, therefore inhibition of the opening of the pore might be beneficial. Molecules for e.g., olesoxime inhibits the opening of mitochondrial transition pore in response to oxidative stress (Bordet et al, 2007) and can protect the cells from cell death (Gouarne et al, 2015).

Figure 2. Mitochondrial dysfunction in the pathogenesis of Alzheimer's disease. Amyloid beta (Aβ) peptide deposition on neurons results in mitochondrial dysfunction characterized by the reduced respiration, reduced mitophagy, reduced degradation of Aβ and release of apoptotic factors responsible for the decreased production of ATP and neurodegeneration (Fukui & Moraes, 2008; Picone et al, 2014; Swerdlow et al, 2014).



CONCLUSION

Mitochondria are the dynamic organelle of the cell responsible for the various neuronal functions. Aging is an important factor that contributes to the mitochondrial dysfunction. Further aging increased the risk of various NDs. It is suggested that the aging induces the production of ROS which is responsible for the reduced functioning of the various components of the mitochondrial ETC suggesting the dysfunction of the ETC components as a cause of the neuronal degeneration. Therefore targeting mitochondria for the drug development in the treatment of the neurodegenerative disorder may provide a new direction for the treatment.

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Chapter 5
Alternation of Mitochondrial and Golgi Apparatus in Neurodegenerative Disorders

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ABSTRACT

Neurodegenerative disorders (NDs) are characterized by dysfunction and loss of neurons associated with altered proteins that accumulate in the human brain and peripheral organs. Mitochondrial and Golgi apparatus (GA) dysfunctions are supposed to be responsible for various NDs. Damaged mitochondria do not produce sufficient adenosine triphosphate (ATP) and produce reactive oxygen species (ROS) and pro-apoptotic factors. Mitochondrial dysfunctions may be caused by various factors such as environmental causes, mutations in both nuclear or mitochondrial deoxyribonucleic acid (DNA), that code many mitochondrial components. Three factors that are mainly responsible for the morphological changes in GA are certain pathological conditions, drugs, and over expression of Golgi associated proteins. In this chapter, common aspects of mitochondrial and GA dysfunction concerned about NDs are summarized and described for Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD).

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INTRODUCTION

NDs are characterized by bioenergetics defect, oxidative stress (OS) and progressive loss of physiologically or anatomically related neuronal system in the human brain (Schapira, 2008; Malkus et al, 2009; Oliveira, 2010). Neurons are the fundamental structure and functional unit of the nervous system of living beings which includes the spinal cord and brain. The neuronal diseases are incurable conditions result in progressive degeneration of nerve cells and cause ataxias or dementias (Beal, 2005; Manczak et al, 2005). The examples of NDs are AD, PD, ALS, prion disease, motor neuron diseases (MND), HD, spinocerebellar ataxia (SCA) and spinal muscular atrophy (SMA). The exact molecular, cellular and pathological mechanism responsible for the progression of these diseases and neuronal cell death are not fully understood. Every cell is a complex communications of various organelles such as endoplasmic reticulum (ER), GA, mitochondria, nucleus, etc. carrying out several functions. These organelles exchange materials and signals to make the cell functional properly without producing and defects. Nowadays, advanced techniques are allowing researchers to understand the connecting link between these organelles. Among the cell organelles, defective connections between mitochondria and GA have been concerned in several NDs. Generation of ROS in mitochondria and GA has been identified as an important factor for the cell death (Swerdlow & Khan, 2004; Lin & Beal, 2006; Reddy & Beal, 2008; Reddy, 2008). Mitochondria are exceptional amongst other organelles, as they dispose their own, mitochondrial DNA (mtDNA), which is mainly inherited from the mother. Their number is very high in neurons, mainly in synaptic terminals, as they are the major energy producers through tricarboxylic acid cycle (TCA) and oxidative phosphorylation. They undergo continual fusion and fission leading to their elongation or fragmentation respectively. GA is associated with protein trafficking in a cell and plays an important role in the pathogenesis of NDs. The objective of the chapter is to focus on the impact of dysfunctional mitochondria and GA on various NDs.

BACKGROUND

Various NDs have been recognized for centuries and research into their causes and effects has been taking place for decades. NDs are characterized by progressive loss of anatomically related neuronal systems. As life expectancy continues in developed countries, the occurrence of these disorders also increases. In the literature, much knowledge is being available concerning the mechanisms of disease, but the causing factors of these problems are still not well known. To date, many mechanisms have been recommended for explanation of protein aggregation metabolism, and misfolding, protein neuronal function, and cell signaling, but still it is difficult to understand the mechanism clearly at the cellular and molecular level (Tan et al, 2014). To understand these diseases, we need to understand how these cells function, their response to local environment and effect of dysfunctional organelles on these diseases. In this book chapter, authors focused on the role of mitochondria and GA on the dysfunction of neurons that result in various NDs. Mitochondrial play an important role in Ca^{2+} homeostasis, ATP generation, ROS formation, and even apoptosis etc. and any dysfunction in these processes results in the dysfunction of neurons in a large number of NDs (Baloyannis, 2006). Functional or structural alterations of the Golgi pathology also recognized as a constant pathological characteristic of various NDs including PD, AD, HD, ALS, and prion diseases (Canet-Avilés et al, 2004). The neuropathological changes observed in these diseases can vary with the type of mutation in mtDNA, and level of Golgi dysfunction. GA marked as

fragmentation into disconnected cisternae, stacks, vesicles and tubules, and as atrophy (Canet-Avilés et al, 2004). These morphological changes in GA alternate the retrograde and anterograde transport in the secretary pathway in all the NDs. Mutations in the PD-associated genes such as α-synuclein *(SNCA), Pink1, Parkin, LRRK2, DJ1* etc. have been shown to affect both functioning of mitochondria and Golgi structure (Lee et al, 2004).

However, this field of NDs faces further challenges. It will be crucial to evaluate that whether mitochondrial dysfunction and Golgi pathology is causative, contributory, or homeostatic in NDs. In particular, it is crucial to understand whether both organelles in theses disease is restricted to the types of neuron that are affected such as dopaminergic neurons in PD, motor neurons in ALS, striatal neurons in HD. Furthermore, we will need to determine whether alterations in mitochondria and GA provide a possible explanation for the non-cell autonomous disease spread observed in various neurodegenerative diseases. Finally there is a need to engage growing knowledge on the mechanisms of involvement of these organelles in NDs be translated into earlier diagnosis and emergence of new therapies for these neurodegenerative disorders.

ROLE OF MITOCHONDRIA IN NEURODEGENERATIVE DISORDERS

Mitochondria are cytoplasmic organelles termed "powerhouse of the cell" essential for the production of most of the cell energy in the form of ATP (Pagliarini & Rutter, 2013). They also perform several other cellular functions, including: maintain calcium fluctuations; the release of proteins that known to activate the caspase family of proteases; modification of the reduction-oxidation potential of cells; biosynthesis of amino acids and steroids; β-oxidation of fatty acids and; production and modulation of ROS (Reddy, 2007; Sas et al, 2007). Mitochondria are compartmentalized into the outer and the inner mitochondrial lipids membrane composed of phospholipid bilayers and proteins. The outer membrane is porous and allows the passage of low molecular-weight substances between the intermembrane space and the cytosol through porins (Silhavy et al, 2010). Unlike outer membrane, the inner membrane does not contain porin so highly impermeable to all molecules. Mostly mitochondria are transmitted maternally, however, rarely; a recombination of mtDNA and paternal inheritance have been reported (Reddy & Beal, 2005). Mitochondria are controlled by both nuclear and mitochondrial genomes where mtDNA consists of a 16,571 base-pair, circular double-stranded DNA molecule (Anderson et al, 1981). It contains 2–10 copies of mtDNA (Reddy, 2008). mtDNA encodes 13 polypeptide genes that encode essential components of the electron transport chain (ETC). mtDNA also contains the 22 tRNA genes and 12S and 16S rRNA genes required for mitochondrial protein synthesis (Reddy & Beal, 2005). Nuclear genes encode the remaining mitochondrial proteins and transport into mitochondria, DNA and RNA polymerases, metabolic enzymes, mtDNA regulatory factors and ribosomal proteins.

SITES OF FREE RADICAL PRODUCTION IN THE MITOCHONDRIA

Mitochondrial ATP is generated via oxidative phosphorylation within the inner mitochondrial membrane and various free radicals are produced as a byproduct of this. In the respiratory chain, complexes I and III leak electrons to oxygen, producing superoxide radicals (Jastroch et al, 2010). The manganese superoxide dismutase (Mn-SOD) converts superoxide to hydrogen peroxide (H_2O_2) and oxygen (Figure

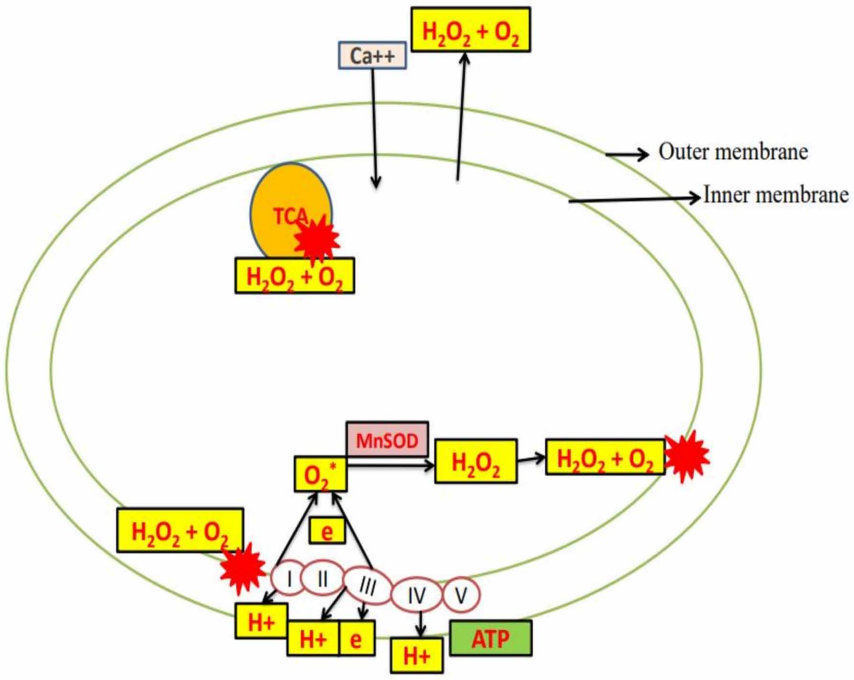
1). H_2O_2 and O_2 permeate by membranes and become a source of reactive hydroxyl radicals (Hroudova et al, 2014). Complex I generates electrons toward the mitochondrial matrix, whereas complex III generates toward both the matrix and the inter-membrane space (Brieger et al, 2012). The components of TCA i.e. α-ketoglutarate dehydrogenase, generate superoxide radicals in the matrix. These free radicals synthesized in mitochondria are carried to the cytoplasm via voltage-dependent anion channels, where they participate in lipid peroxidation, DNA and protein oxidation (Bolisetty & Jaimes, 2013).

Excitotoxicity and apoptosis are the two ways of neuronal cell death and the role of mitochondria is crucial in both the cases (Emerit et al, 2004; Davis & Williams, 2012). In apoptosis, the outer membrane of mitochondria is permeabilized, that leads to release of various apoptotic proteins like cyt *c*. There are many interrelated mitochondrial pathways that facilitate apoptosis or cell death:

- Opening of mitochondrial permeability transition pore (MPTP) lead to mitochondrial swelling and cell death through necrosis or apoptosis (Aronis et al, 2003);
- Increase in the permeability of the membrane causes leak of apoptotic factors i.e. second mitochondria-derived activator of caspases (SMAC) and cyt *c*, which trigger the caspase cascade and leading to apoptosis (Aronis et al, 2003); and
- Release of apoptosis-inducing factor (caspase-independent death effector) that triggers chromatin condensation, leading to DNA degradation (Aronis et al, 2003).

Mitochondria undergo breakdown or fragmentation during apoptosis before activation of caspases (Lu, 2009). Recently, attention is paid to the damage of ETC complex induced by ROS that is mediated by the oxidative and peroxidation damage of cardiolipin (Musatov & Robinson, 2012; Chaturvedi &

Figure 1. Different sites of free radical production in mitochondria

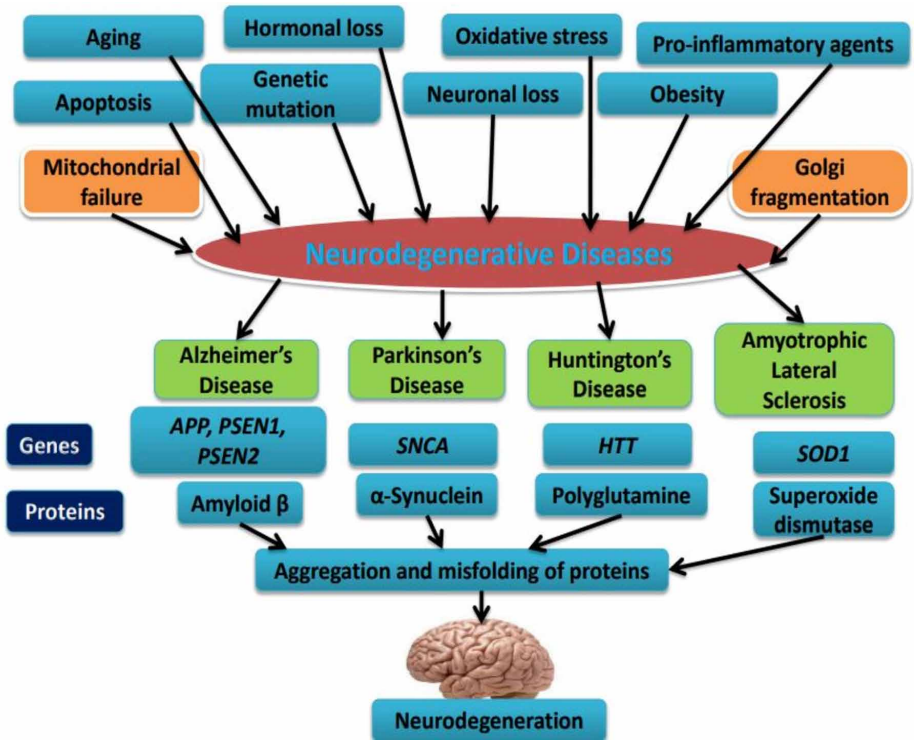


Beal, 2013). Cardiolipin, a membrane protein is required for both the stability of respiratory super complexes and as a diffusion microdomain for the ubiquinone (Paradies et al, 2014). It also plays an active role in mitochondrial mediated apoptosis, by oxidizing, and interacting with cyt *c* and Bcl-2 proteins (Yin & Zhu, 2012).

Mitochondria play an important role in the metabolism of all mammalian cells, including abnormality in mitochondrial structure and function and brain neuron that may lead to age-related NDs. The first evidence of participation of mitochondria in pathogenesis of neurodegenerative process was reported in platelet mitochondria of patients suffering from PD (Schapira et al, 1990). Later, scientists reported ETC deficiencies i.e. complex I and cytochrome *c* oxidase (complex IV, COX) in AD and complexes II and III in HD (Moran et al, 2012). Recently various cellular, molecular, biochemical, and animal model studies of NDs via mutant proteins associated (MPA) with mitochondria several (MS) revealed that mutant proteins such as amyloid beta in AD, mutant SOD1 in ALS, mutant H*TT* in HD, mutant DJ1, mutant P*arkin* and mutant S*NCA* in PD, and frataxin in Friedreich's ataxia (FRDA) are present on mitochondrial membranes (Figure 2), leading to a low production of cellular ATP due to the increased production of free radicals and that ultimately leads to cell death (Reddy, 2008).

Considering the nature of NDs and imperfect regenerative capacity of neurons, inappropriate functioning of mitochondria can have destructive effects on neuronal survival. There are various evidence of impair mitochondrial function as a cause rather than result of neurodegeneration.

Figure 2. Abnormal misfolding and aggregation of proteins due to gene mutations responsible for various neurodegenerative diseases



ABNORMAL MITOCHONDRIAL DYNAMICS IN NEURODEGENERATIVE DISORDERS

Alzheimer's Disease

AD is the most common neurodegenerative disorder of aging that lead to memory loss, disability in language, behavior and death (Lockrow et al, 2012). The disease is distinguished by a neuronal loss and deposition of 42-amino acid amyloid-β (Aβ) derivatives and presence of senile plaque and neurofibrillary tangles (Scheuner et al, 1996). Hardy & Higgins (1992) proposed "the amyloid cascade hypothesis" states that disturbed processing of amyloid precursor protein (APP) or change in Aβ results in imbalance between Aβ production and removal. Damage to the structure of mitochondria and increased OS are extensively reported in AD (Zhu et al, 2006). Dysfunctional mitochondria showed diminished respiratory capacity and deficiency in several key enzymes including α-ketoglutarate dehydrogenase complex (αKGDHC), pyruvate dehydrogenase complex (PHDC), two rats limiting enzymes of TCA and cytochrome oxidase (COX) (Maurer et al, 2000; Casley et al, 2002). In AD, cytoplasmic hybrids made from mitochondrial DNA and altered calcium homeostasis has also been reported in various studies (Khan et al, 2000). As compared to healthy organism, rearrangement of sporadic mtDNA or mutations is significantly increased in AD patients (Corral-Debrinski et al, 1994; Coskun et al, 2004). Lustbader and group (2004) demonstrated that blocking the association of Aβ and Aβ-binding alcohol dehydrogenase (Aβ-AD) can suppress the apoptosis and generation of free radicals in neurons (Crouch et al, 2005; Devi et al, 2006).

Studies on quantitative ultrastructural morphometric analysis revealed that as compared to age matched control group brains, AD brains contains lower percentage of normal mitochondria and higher percentage of mitochondria with broken cristae (Monte et al, 2000). This is further supported by the presence of longer mitochondria in fibroblasts, then those of age-matched normal human fibroblast (Wang et al, 2008).

Several studies reported that activity of complex I and gene expression of ND4 subunit of complex I get decreased in AD brains and in temporal cortex of AD patients (Chandrasekaran et al, 1996). Manczak and group (2005) observed differential expression of gene present in complex I, V and COX in AD brains. In the surviving neurons, gene expression of COX gets increased due to high oxidative damage and alteration of mitochondrial function (Manczak et al, 2004). Fusion and fission pathway also play an important role in relation to altered mtDNA as fusion of mitochondria enable exchange of mtDNA with other content. Mfn 2 knockout inhibit this process resulted in formation of mtDNA lacking mitochondria (Karbowski & Youle, 2003).

Disorder of Electron Transport Chain in Alzheimer's Disease

As the activity of COX was found to be very low in platelets, cortex and hippocampus of AD patients, indicates the anatomical specificity (Maurer et al, 2000). The mitochondrial deficiency was observed in the platelets of AD patients indicating reduction in COX and complex III activity (Valla et al, 2006). Reduction in acetylcholinesterase (AChE) indicates that it could increase the activity of Aβ (Fodero et al, 2004). Different mitochondrial malformation related with NDs result in oxidative stress, aberrant homeostasis of cytosolic calcium. Oxidative phosphorylation (OXPHOS) does not involve in thermodynamic equilibrium but increase a rate of uncoupling (Figure 3). Decrease in mitochondrial membrane potential ($\Delta\psi_m$) result in hydrolysis of ATP formed in cytoplasm, whereas increase in $\Delta\psi_m$ cause proton

leakage and result in increase in uncoupling. Overproduction of ROS, increase in mitochondrial permeability transition (MPT) and proton leakage result in apoptosis (Hroudova et al, 2014).

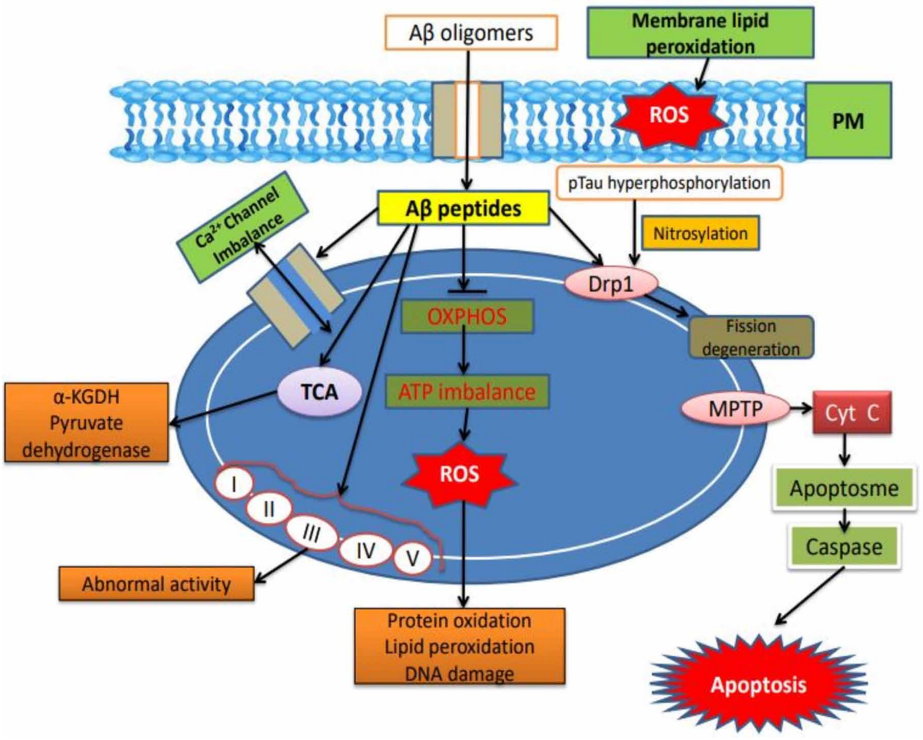
Parkinson's Disease

PD is the second common neurodegenerative disorder after AD. PD is a disorder of CNS that belongs to movement disorder and characterized by rigidity, loss of posture stability, resting tremor and bradykinesia (Ayano, 2016). The symptoms of PD arise due to loss of dopaminergic (DA) neurons in the substantia nigra. Surviving nigral neurons contains abnormal aggregates of proteins called Lewy bodies, an intracytoplasmic eosinophilic inclusion that is composed of fibrillar presynaptic α-synuclein protein (Spillantini et al, 1997). Various genetic studies in PD cases have identified mutation in five genes i.e. α-synuclein (*SNCA*), PTEN-induced putative kinse (*PINK-1*), *Parkin*, *DJ-1* and leucine rich repeat kinase 2 (*LRRK2*) (Abeliovich & Beal, 2006; Lesage & Brice, 2009).

α-Synuclein

Dysfunction of mitochondria plays a critical role in the pathogenesis of PD in transgenic mice, overexpressing nature of *SNCA* induces increase in OS, reduction in threshold for nigral breakdown and impaired

Figure 3. Mitochondrial damage in Alzheimer's disease
Where, Aβ: Amyloid β; PM: Plasma membrane; ROS: Reactive oxygen species; TCA: Tricarboxylic acid; OXPHOS: Oxidative phosphorylation; DRP1: Dynamin related protein 1; MPTP: Mitochondrial permeability transition pore (Adopted and modified from Kumar and Singh, 2015).

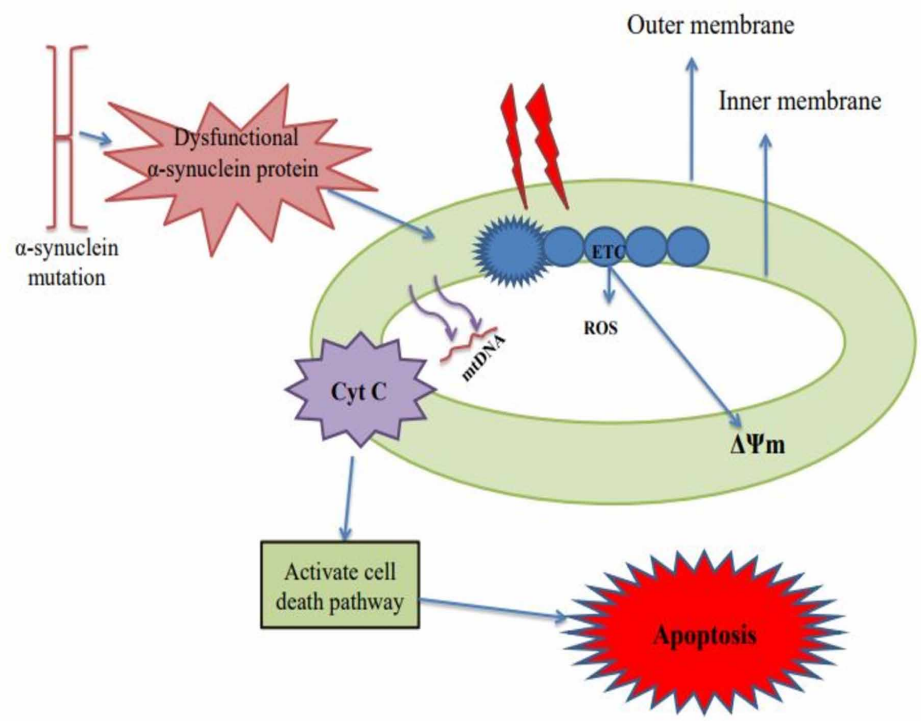


function of mitochondria (Figure 4). Martin et al (2006) undergoes α-synuclein immunostaining study in mice and evaluate that this protein affect mitochondria.

PINK1

The *PINK1* gene provides information for making a PTEN protein that induced putative kinase 1. *PINK1* gene encoding a 581 amino acid protein with N-terminal mitochondrial targeting sequence and a threonine/serine kinase domain (Mills et al, 2008). Mostly missense mutation impairs the kinase activity; that is essential for the neuroprotective nature of *PINK1*. Increased expression of *PINK1* provides protection from apoptotic death (Arena et al, 2013). Whereas loss of its function increase the vulnerability of cells to death induced by stress (Petit et al, 2005; Wood-Kaczmar et al, 2008). *PINK1* deficiency induced various effects on mitochondrial morphology and function such as decrease in $\Delta\psi_m$, activities of complex I and IV, mtDNA level, ATP production, increase in ROS and abnormal morphology (Deas et al, 2009). Gandhi et al (2009) observed that *PINK1* deficiency is responsible for the dysbalance of calcium homeostasis, where basal concentration of calcium in mitochondria is high and its overload disturb the Na^+/Ca^{2+} exchanges present in inner mitochondrial membrane.

Figure 4. Effects of mutated α-synuclein on mitochondria
Mutated SNCA gene cause dysfunction and aggregation of protein at inner mitochondrial membrane causing dysfunction of complex I, that reduces ATP formation, increase ROS production and initiate cell death (Adapted from Mounsey & Teismann, 2011).



Parkin

In 1998, mutated *Parkin* gene was identified as a cause of autosomal recessive PD in Japanese families (Kitada et al, 1998). The *Parkin* gene encodes total 465 amino acids protein attached with ubiquitin-like domain (UBL) at N-terminus and Ring-Between- Ring (RBR) domains at C-terminus. *Parkin* protect the cell against various stresses such as excitotoxicity, endoplasmic reticulum stress, overexpression of *α-synuclein*, Aβ peptide, tau, mitochondrial dysfunction, proteosome inhibition, and expanded polyglutamine fragments (Doss-Pepe et al, 2005; Winklhofer, 2007). Biochemical and genetic studies showed that mutation induce a loss of *Parkin* function leading to its accumulation cause neurotoxicity, results in death of dopaminergic neurons. Darios et al. (2003) observed that *Parkin* prevent swelling of mitochondria and release of cyt c in ceramide-treated cells. *Parkin* and PINK1 have a direct role in various cells mitochondrial control pathways, including reduced membrane potential and mitophagy. The "MitoPark" mice are an excellent example of "mitochondrial hypothesis''of PD (Johri & Beal, 2012). In MitoPark mice, on the elimination of mitochondrial transcription factor (*Tfam*) gene, mitochondrial function gets disturbed in DA neurons (Ekstrand et al, 2007). The *Tfam* gene is present in the nuclear genome and it is always imported into mitochondria, where it binds to DNA for maintenance of mtDNA and transcription in mammals. *Tfam* stabilise mtDNA by regulating copy number and also required for biogenesis of mitochondria (Larsson et al, 1998). Cellular changes observed in this problem is similar to those observed in PD such as degeneration of dopaminergic neurons (DA) pathways, intracellular inclusions in DA neurons and loss of dopamine.

DJ-1

DJ-1 belongs to Thij/Pfpl family and has common structure with stress-inducible *E. coli* chaperone (HSp31) (Lee et al, 2003). *DJ-1* gene encodes 189 amino acids proteins and mutation of this cause onset of autosomal recessive PD (Bonifati et al, 2003). Less expressions of *DJ-1* make neuron cells more susceptible to oxidative injury whereas its over-expression protects cells from damage induced by OS (Park et al, 2005; Paterna et al, 2007). *DJ-1* is converted into acidic pI variant against OS, on the formation of cysteine-sulfinic acid at cysteine 106 (Kinumi et al, 2004). Cysteine 106 is very important for the neuroprotective activity of *DJ-1* (Yokota et al, 2003; Waak et al, 2009). Various reports showed the presence of *DJ-1* in nucleus, cytosol and mitochondria, where OS disturb location of *DJ-1* in mitochondria (Li et al, 2005; Lev et al, 2008). In response to OS, endogenous *DJ-1* translocates to mitochondria and nucleus of human neuroblastoma cells (Junn et al, 2009).

In *DJ-1* knockout mice, isolated mitochondria show an increase in H_2O_2 accompanied by reduction in aconitase activity in mitochondria, indicating a problem in scavenging ROS (Andres-Mateos et al, 2007). From research on *Drosophila* model and human cell culturing it was observed that *DJ-1* does not function with *PINK1*/*Parkin* pathway (Exner et al, 2007).

LRRK2

LRRK2 gene mutation is most common cause of autosomal dominant PD associated with late-onset and sporadic PD (Paisan-Ruiz et al, 2005). *LRRK2* gene encodes various multidomain proteins of 2527 amino acids, such as a ROC domain, leucine rich repeats, WD40- repeat domain and COR domain (Biskup and West, 2009; Gandhi et al, 2009). *In vitro*, mutation increase the kinase activity of *LRRK2*, assessed

by phosphorylation or autophosphorylation of substrates that affects function mechanism (Greggio et al, 2006; Smith et al, 2006).

Amyotrophic Lateral Sclerosis

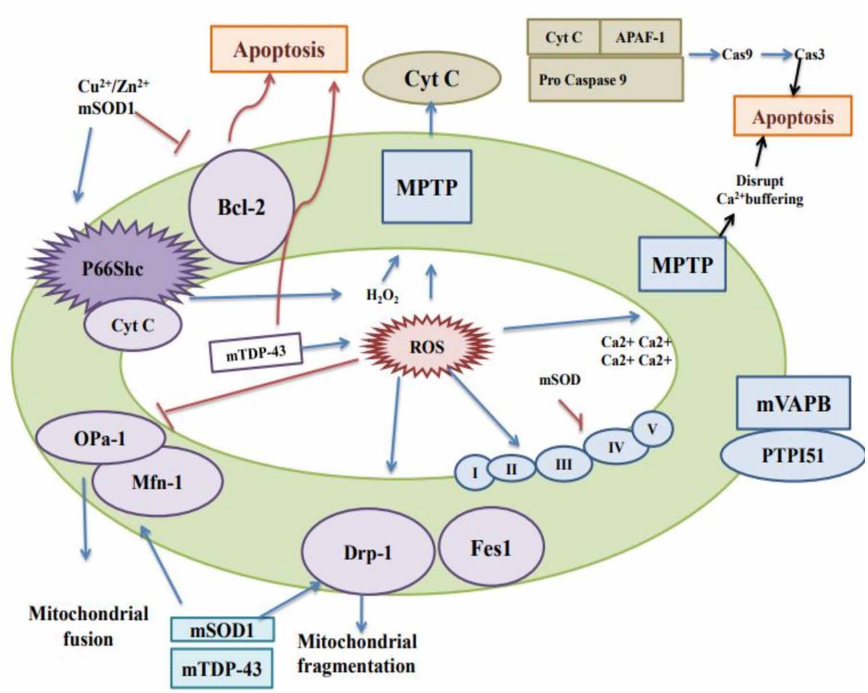
ALS is also known as Lau Gehrig's disease in humans, is a ND. ALS disease is characterized by a fatal degeneration of pyramidal neurons in the motor cortex with other nearby corticospinal tracts and motor neurons in the brain and spinal cord, resulting in atrophy, paralysis, muscle weakness, speech deficit and eventual death (Zarei et al, 2015). Sporadic in 90% of cases out of which 20% of the familial ALS cases are due to mutation in the copper-zinc superoxide dismutase (*SOD 1*) gene on chromosome 21 (Gros-louis et al, 2006). Mutation on *SOD 1* gene is considered to be a toxic gain of function rather than a loss of *SOD 1* activity (Rothstein, 2009; Su et al, 2010). Recently, mutation in two DNA/RNA binding proteins i.e. TAR DNA-binding protein-43 (TOP-43) and fused/translocated in liposarcoma (FUS/TLS) have also been found and responsible for 4% of ALS cases (Kwiatkowski et al, 2009; Vance et al, 2009; Da Cruz & Cleveland, 2011). The mutation in transitional ER also known as valosin-containing protein gene was reported to be the known cause of 1-2% of familial ALS cases. This mutation effects on the regulation of mitochondrial calcium homeostasis. Mitochondrial morphological changes such as deformed cristae, swelling, defected respiratory chain activity and reduced mtDNA copy number are the preliminary sign of disease onset in organism with *SOD 1* mutations (Nakano et al, 1987). Changes in mitochondrial ETC, in both neural and non-neural tissue have been noted by several groups from patient with ALS (Figure 5).

In patients with sporadic ALS, reduced activity of complex IV was observed whereas in patient with familial ALS, increased complex I activity was observed (Bowling et al, 1993). Deficiencies of complex I, II-III were observed in patients infected with familial ALS due to mutation in SOD 1 and also observed in SOD 1 transgenic mouse (Browne et al, 1998). In patients with sporadic ALS, both protein and lipid oxidation increased in glia and spinal cord motor neurons (Shibata, 2001). Mutant SOD1 aggregates at the outer membrane of mitochondria, inactivates Bcl-2 (antiapoptosis protein) resulting in release of cytochrome c. This results in intrinsic apoptosis.

Huntington's Disease

HD is a ND caused by the elongation of CAG repeats in first exon huntingtin (*HTT*) gene on chromosome 4 (Vonsattel & DiFiglia, 1998). This disease is characterized by intellectual decline, psychiatric illness, motor-impairment and personality change. There are many evidences for deficits and mitochondrial dysfunction in HD, like weight loss, increased lactate in basal ganglia and cerebral cortex, low activities of OXPHOS complexes II and III, membrane depolarisation of lymphoblasts and low aconitase activity in ganglia (Tabrizi et al, 1999). mtDNA deletion and damage were observed in animal models and HD patients (Acevedo-Torres et al, 2009). m*HTT* directly affect calcium in axon (Orr et al, 2008). It also inhibit mitochondrial fusion and reduced level of ATP, results in mitochondrial fragmentation (Wang et al, 2008) (Figure 6).

Figure 5. Amyotrophic lateral sclerosis linked mutant proteins mitochondrial malfunction
Mutant SOD1 accumulate at outer membrane of mitochondria and inhibit the activity of Bcl-2, an anti-apoptotic protein results in the release in cytochrome-c. Mutant SOD 1 causes various mitochondrial dysfunctions such as impaired protein import and activity of ETC, aberrant morphology and increased oxidative stress, etc.



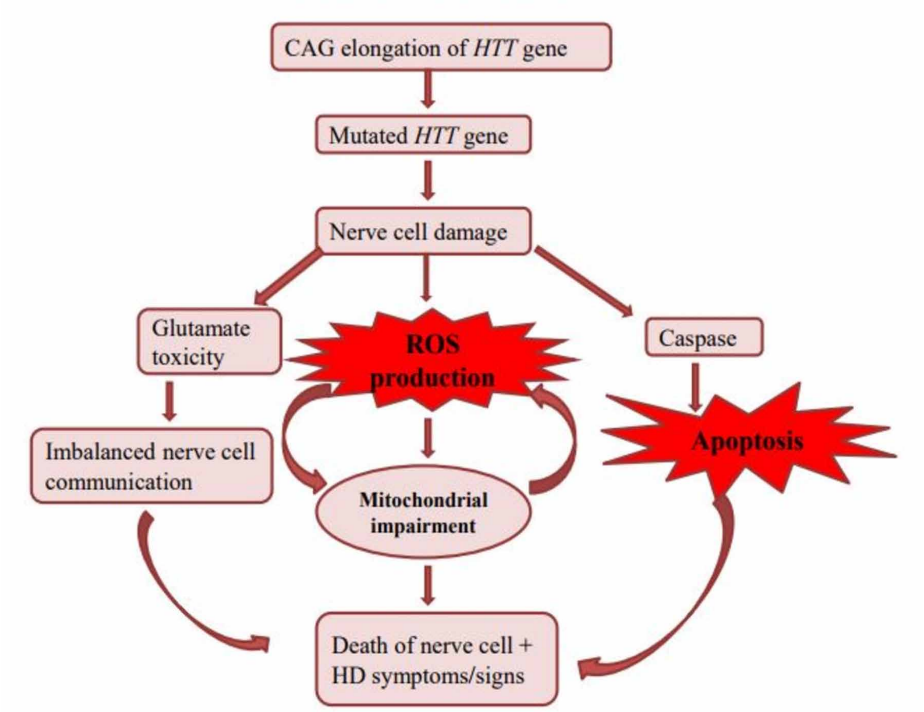
ABNORMAL GOLGI APPARATUS DYNAMICS IN NEURODEGENERATIVE DISORDERS

Morphology of Golgi Apparatus

GA is a secretory organelle with complex morphology and occupies an important position in this system. Structurally it is similar to smooth ER but relatively more compact (English and Voeltz, 2013). It consists of flattened, membrane-bound sacs called cisternae, which are involved in processing and sorting of luminal proteins together with a system of associated vesicles called Golgi vesicles. New cisternae are formed from buds derived from the smooth ER. Organization of GA is maintained by a proteinaceous matrix, inositol phospholipids, and cytoskeletal components. The post-translational modification of lipids and proteins mostly by glycosylation is carried out in GA therefore it has an important role to play in NDs (Ashaq et al, 2015).

The Golgi constitution is disrupted in a number of NDs, advocating a common mechanism and involvement of Golgi defects. Three factors that are mainly responsible for the morphological changes in GA are certain pathological conditions, drugs and over expression of Golgi associated proteins. Protein phosphatase inhibitor okadaic acid, fungal metabolite brefeldin A and nocodazole are some of the pharmacological agents that are responsible for collapsing of tubules and vesicles and shortening of cisternae or ministacks (Boe et al, 1991). GA fragmentation has been observed in an early, preclinical

Figure 6. Schematic representation of mitochondrial dysfunction in Huntington's disease



stage of NDs therefore it can be used as a dependable indicator of activity of neurodegeneration. Following Table 1 shows the pathological implications of GA in NDs.

Neurodegenerative Diseases and Accumulation of Misfolded Proteins

NDs share some common histopathologic abnormalities such as neuronal failure, gliosis and the occurrence of inclusion bodies in both neurons and glial cells, which correspond to intracellular accumulation of misfolded or aberrant proteins (Choonara et al, 2009). Since GA is a central organelle involved in handing of proteins, therefore its role in NDs is being explored seriously. Mutated forms of SOD1, α-synuclein and tau are the key proteins that have a direct correlation with GA degeneration and its loss of function (Fan et al, 2008).

Mutant SOD1

ROS are molecules which are derived from oxygen that have accepted extra electrons and can oxidize other molecules. ROS includes singlet oxygen ($^1O_2$), H_2O_2 and the highly reactive hydroxyl radical (■OH) (Waris & Ahsan, 2006). According to an estimate as much as 1% of the total mitochondrial O_2 consumption is used to produce superoxide (Jackson et al, 2016; Vyas et al, 2016). ROS have been implicated in many diseases. There are eight known sites that are capable of producing superoxide. ROS released

Table 1. The pathological alterations of Golgi apparatus in neurodegenerative disorders.

Disorder	Alterations in GA	Reference
Alzheimer's disease	• Mitochondrial alterations in the thalamus and the red nucleus showed fragmentation of the cisternae	Baloyannis et al, 2006
	• Phosphorylation of the GA stacking protein GRASP65 disrupted its function, resulting in GA fragmentation • Perturbing GA structure affects trafficking, processing, and sorting of proteins essential for synaptic and dendritic integrity	Joshi et al, 2015
	• GA stacks appeared disconnected and of reduced diameter, with the concomitant presence of vesicles in the vicinity of the stacks	Baloyannis, 2014
	• 20 genes are involved in lipid metabolism, inflammatory response and endocytosis constitute risk factors for late-onset AD	Giri et al, 2016
Multiple system atrophy	• Pathogenetic mechanisms causing inclusion body formation and abnormalities of the GA-trans-Golgi network. • Lesions of the inferior olivary nucleus may not always reflect changes of trans synaptic degeneration secondary to Purkinje cell loss	Sakurai et al, 2002
	• GA and trans-Golgi network of enlarged neurons lost the normal network, underwent fragmentation, reduction in number, and aggregation around nuclei	Takamine et al, 2000
Amyotrophic lateral sclerosis	• Golgi was reduced and fragmented appearing as disconnected punctate structures	Mourelatos et al, 1990; Gonatas et al, 1992
	• GA fragmentation is also present in spinal anterior horn cells in sporadic ALS patients with cytoplasmic mislocalization of WT TDP-43	Fujita et al, 1999, 2000, 2008
	• GA fragmentation was present in cells expressing ALS-linked mutant FUS, optineurin and vesicle-associated membrane protein B	Farg et al, 2012; Sundaramoorthy et al, 2015
Parkinson's disease	• GA fragmentation might trigger the aggregation of α-synuclein and the formation of inclusions, alterations in anterograde and retrograde transport between the ER and GA, and cytoskeleton damage • Fragmentation is directly related with alterations in the levels of Rab1, 2 and 8 and the SNARE protein syntaxin 5	Rendon et al, 2013
Corticobasal degeneration; Creutzfeldt-Jakob disease	• Ballooned neurons showed fragmentation of the GA • Reduction in the number of fragmented GA elements by a unique perinuclear distribution	Sakurai et al, 2000

from complex III are required for many biological processes including oxygen sensing, cell differentiation, and adaptive immunity.

The SOD family plays a vital physiological part in extenuating detrimental effects of ROS (Griess et al, 2017). SOD1 is an abundant intracellular enzyme with an indispensable role in antioxidant defense and its mutant form plays an important role in various NDs such as ALS (Cluskey & Ramsden, 2001).

The most frequently recognized mutations in SOD1 that affect protein activity are D90A, A4V and G93A. Mutated SOD1 leads to the accumulation of highly toxic hydroxyl radicals causing degradation of both nuclear and mitochondrial DNA and protein misfolding (Kaur et al, 2016). Misfolded protein aggregates, ubiquitin-proteasome system destruction and neuronal apoptosis carried out by receptor or mitochondrial-dependent pathways are implicated in mutant SOD1-induced toxicity (Fan et al, 2008). A third pathway of apoptosis has been proposed that is linked with ER stress. Neuronal fragmentation and degeneration may be due to aggregation of mutant SOD1 with the unfolded protein response components which are transported to ER (Turner & Atkin, 2006).

Key proteins involved in the anchorage of Golgi membranes with microtubules, could be early targets of mutated SOD1 (Karecla & Kreis, 1992). Motor neurons in the spinal cord and brain stem are mainly affected in ALS. This disease is familial (FALS) and inherited in an autosomal dominant manner. OS caused by human SOD1 mutations is supposed to play a significant role in the pathogenesis of familial ALS (FALS) and the FALS-like MND seen in the mutant SOD1 transgenic mice (Zhang et al, 1997). GA fragmentation has been observed in spinal cord motor neurons of transgenic mice expressing ALS-linked SOD1G93A and show neurodegeneration (Turner & Atkin, 2006). SOD insoluble protein complexes that disrupt both fast and slow components of axonal transport have been detected in cellular in motor neurons from ALS transgenic mice (Johnston et al, 2000). Mutant SOD1 toxicity may be due to its co-precipitation with Hsp25 because it deprives cells of the anti-apoptotic and other protective effects of Hsp25 (Strey et al, 2004). Overexpression of mutant SOD1 in ALS retards electron transport chain in mitochondria and decreases its calcium-loading capacity. SOD1 limits itself to the outer mitochondrial membrane, intermembrane space and matrix, targeting of mutant SOD1 to mitochondria causes cyte c release and apoptosis (Tan et al, 2014). Mutant SOD1 triggers anomalous mitochondrial ROS production and forms aggregates that may block the outer mitochondrial membrane protein importation machinery or bind and confiscate the antiapoptotic protein Bcl-2 (Guo et al, 2013).

α-Synuclein

α-Synuclein is a 14 kD cytosolic neuronal, acidic lipid binding presynaptic protein whose exact function remains unknown. It has been intimately linked with the etiology of PD. A mutation was identified in the *SNCA* gene, which codes for a presynaptic protein thought to be involved in neuronal plasticity (Polymeropoulos et al, 1997). These pathological inclusions have been implicated in neurodegenerative disorders, called 'tauopathies' and 'synucleinopathies'. Evidence indicates that tauopathies and synucleinopathies may be linked (Lee et al, 2004). Mutated or over-expressed, α-synuclein has considerable impact on many membrane trafficking and stress pathways, including exocytosis, ER-to-Golgi transport, ER stress, Golgi homeostasis, endocytosis, autophagy, oxidative stress, and others (Wang & Hay, 2015).

Stathmin

Stathmin, also referred to as Op18, is a 17 KDa cytosolic phosphoprotein (Redeker et al, 2000). It is involved in a relay integrating diverse intracellular signaling pathways involved in the control of cell proliferation, differentiation etc. (Redeker et al, 2000). It interacts with several putative downstream target and/or partner proteins. It is required for the regulation of cytoskeleton, motility, division and cell cycle. Microtubule remodeling according to the requirement of the cell is controlled by it. A reduced amount of this protein has been observed in the neocortex of patients with AD, whereas it was augmented in some neurons with neurofibrillary tangles (Jin et al, 1996). Curmi et al, (1999) have reported that its phosphorylation reduces its affinity for tubulin and hence its action on microtubule dynamics.

Structural integrity of GA is maintained by microtubules. Stathmin is also recognized to be a probable factor in mutant SOD1-mediated toxicity, however, these claims need further verification because spinal cord sections from paralyzed mice seldom show co-localization of stathmin with SOD1 (Strey et al, 2004).

Tau

Tau is involved in the formation of microtubules during the growing of axon. Tau is known to inhibit kinesin-dependent transport of peroxisomes, neurofilaments, and GA derived vesicles into neurites. Loss of peroxisomes makes cells susceptible to OS leading to degeneration (Stamer et al, 2002). Fragmentation of GA has been directly linked with phosphorylation of tau which is associated with a transient dissociation of tau from the cytoskeleton and a decrease of the acetylated tubulin. Mutant human tau P301L has been implicated in development of neurofibrillary tangles an important feature observed in degenerating neurons (Iqbal et al, 2010). It can safely be assumed that GA fragmentation is not due to the process of programmed cell death (PCD) because apoptotic hallmarks such as apoptotic nuclei and activation of caspases-3 were not detected. Calnexin, a marker of the rough ER, was found to be intact but elimination of the Golgi marker protein MG160 was observed (Gonatas et al. 1989).

CONCLUSION

Damaged neurons do not have the capacity to replace themselves; therefore neurodegenerative diseases are not curable. Considerable research has been carried out during the last many years to understand pathological mechanism responsible for the progression of these diseases. Thus far, studies on mitochondrial genome have not investigated the relation between mtDNA change and mitochondrial dysfunction, although loss of mitochondrial genomic integrity has been occupied in many neurodegenerative diseases. GA occupies an important position as a secretary organelle. Certain pathological conditions and over expression of GA associated protein are responsible for its degradation. Mutated forms of SOD1, α-synuclein and tau are the key proteins are implicated in neurodegenerative diseases. Therefore, there is a need to understand the exact molecular, cellular, and pathological mechanism responsible for these diseases so that therapies can be designed to slow down or prevent neuronal loss.

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Chapter 6
Neurodegenerative Disorders Progression: From Synaptic Dysfunction to Transmission Failure

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ABSTRACT

Neurodegenerative disorders (NDs) are a diverse group of disorders characterized by selective and progressive loss of neural systems that cause dysfunction of the central nervous system (CNS). The examples of NDs include Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), and Huntington's disease (HD). The aggregated proteins block or disrupt the normal proteosomal turnover, autophagy, and become abnormally modified with time, generating toxicity via pathways thereby resulting in neurodegeneration and neuron death. The chapter highlights the understanding in the areas of AD, PD, HD as illustrative of major research so as to define the key factors and events in the improvement of NDs. It defines the physiological functioning of neural transmission (presynaptic, postsynaptic activity) at neural signaling pathway, then the dynamics of neuronal dysfunctioning and its molecular mechanism. Further, it also discusses the progression from synaptic dysfunction to transmission failure followed by NDs.

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INTRODUCTION

Neurological disorders affect millions of people worldwide which can vary from the nerve disease that causes Tourette's into the serious CNS diseases, impacting either the brain or spinal cord, leading to the neurological or psychiatric deficits. It was observed that up to 1 billion people i.e., almost one in six of the world's population, suffers from either one or the other forms of neurological ailments such as AD, PD, stroke, brain injury, epilepsy, multiple sclerosis, neuroinfections and migraine (*Nearly 1 in 6 of world's population suffer from neurological disorders – UN report*, 2007). Also, it was being estimated in United Nations report issued, that around 6.8 million people worldwide dye of these maladies each year. Hence, understanding the neuronal dysfunctioning and resolving its pathological complexity becomes all the way a necessity now. The common aspects of the mentioned disease pathogenesis can be simply summarized with regards to the downstream implications of uncontrollable protein oligomerization and aggregations from post mitotic cells. It was being reported that the polyglutamine protein aggregates in the neurons causes the cells to undergo a stress reaction (Lim & Yue, 2015). Also, a study from the Gladstone Institutes showed for the very first time that mitochondrial damages (brain's cellular power plants) can diminish the energy levels and causes neural dysfunctions in a model of disease (Institutes, 2015). The normal autophagy, proteosomal turnover are disrupted by the aggregated proteins, which modifies with time abnormally thereby, causing toxicity through various mechanisms thereby, leading to neurodegeneration and cellular death (Sweeney et al., 2017). The postulation is coherent with the key genetic similarity between these diseases - e.g., the familial forms are generally caused by autosomal dominant mutation that favours aggregation (in case of PrP, tau, SOD1 and asyn) or formation of disease aggregation prone proteins (in case of CAG and APP repeat sequences) (G. F. Hall, 2011).

The synergistic interaction amongst proteins [synuclein and tau; amyloid precursor protein (APP)/ amyloid β (Aβ) and prion protein (PrP); tau and PrP; α-synuclein and PrP] occurs both at interneuronal and cellular level that lead to interneuronal lesion and eventually, pathogenesis of disease (Jellinger, 2012). Amongst all the NDs, AD is the most frequent and clinically known dementia in elderly population. It was recorded that almost 43% of elderly population that are above 85 years are suffering from AD and another CNS associated disorder PD; affects around 1-3% of population over 60 in USA (Qiu, Kivipelto, & von Strauss, 2009). Hence, owing to the above stated facts, the prevention, financial and societal effect of diseases, determination of causes, and exploration of effective treatment has been a foremost emphasis of clinical and basic research globally. Consequently, cellular mitochondria are known to play a key role in age related NDs as they are the important regulators of cell death, a critical characteristic of neurodegeneration (Jellinger, 2010). However, genetic mutations in mitochondrial DNA and oxidative stress cause ageing, attributing massively in initiating the progression of NDs (Lagouge & Larsson, 2013). This chapter focuses and highlights the basic understanding of neuronal irregularities that leads to NDs and its further progression, as illustrative of major research so as to define the key factors and events in the improvement of NDs.

BACKGROUND

NDs affect the CNS causing the dysfunction of nervous system. These incurable and debilitating conditions are indicated by loss in activity of neurons and are linked with degeneration of affected structures of nervous system (Ghavami et al., 2014). An integral subset of NDs includes dementia associated

with aging (Wood, Winslow, & Strasser, 2015). Neurodegeneration is continuous loss of structural and functional properties of neurons corresponds to some pathological conditions which including neurons death (Gorman, 2008). In manner, NDs signify a huge group of neurological disorders with varied clinical and pathological expressions disturbing particular neuronal subsets in detailed functional anatomic systems that progress in a persistent manner. Different NDs like AD, PD, HD, and AML are common in therapeutic research studies. The NDs are mostly characterized through the factors like genetic risk factors, certain age ranges, courses of progression, clinical symptoms, dysfunction and death of specific subsets of neurons, particular biochemical abnormalities, and presence of intracellular and extracellular protein (Kovacs, 2016). In the advance study, the beginning of NDs is instigated by the aggregation of proteins called proteinopathies

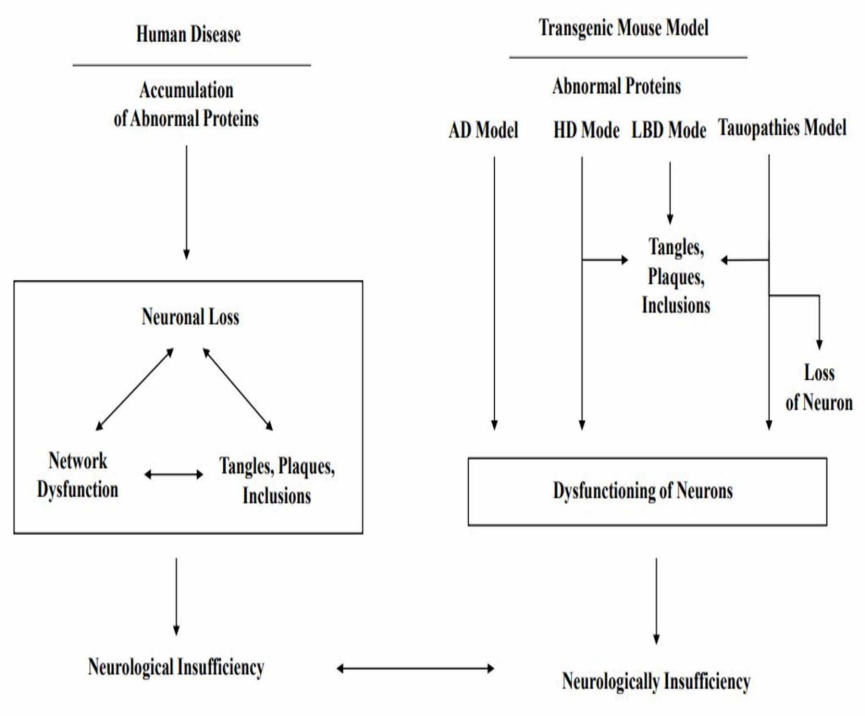
DYNAMICS OF NEURONAL DYSFUNCTIONING

With the increase in counts of NDs cases universally, the research and findings has improved over the years but clinical trials have generated unsatisfactory results. While, gradual loss in neuron is the characteristic of NDs, some neurodegeneration may indicate neurological dysfunction instead of neuronal loss (Nixon & Yang, 2012). The abnormal proteins activate atypical activation of neurons, cause modifications in receptors of neurotransmitters and signalling cascades thereby, leading to neural network disintegration, synaptic insufficiencies and finally, breakdown of neurological functions. It was revealed in various *in vivo* models; that many pathogenic pathways can be reversed or prevented by taking off the abnormal proteins or pharmacologically regulate activities of neurons (Palop, Chin, & Mucke, 2006). Also, the increased plasticity of neurons benefits the remaining neuronal circuits to counteract for broken or lost circuits and improve the neuronal function and performance of networks (Greenwood & Parasuraman, 2010).

As the gradual neurological decline in NDs is directly related to the loss of neurons but, this association is also debatable. Further, it is doubtful that the variations in neuronal number credits for reversible and rapid fluctuations in neurological functions (Andres, Ducray, Schlattner, Wallimann, & Widmer, 2008). These variations possibly indicate the multifaceted fluctuations in molecules, modifications in synapse, neuronal circuits, neuronal networks and interactions between different networks (Figure 1). Many research studies have shown that the transgenic mouse models express abnormal proteins related with PD, AD, HD, ALS acquired disease linked neurological impairments. Further, the removal of abnormal proteins in them can inverse the neurological deficits without causing the changes in neuronal number. Hence, indicating towards the fact that the neurological destruction is also linked with neuronal dysfunction instead of loss in neurons. The surviving neurons left at various phases of impairment, comprise of functional neuronal state in the affected area and compensate to the alternative neural network for the lost ones, so if a probable target for therapeutic intrusion can be directed towards exploring the strategies to overcome vascular insufficiencies, co morbidities and genetic aspects may prove to be a more targeted approach.

However, even in the absence of disease, the neural system is depicted by enormous “degeneracy”- the capacity of structurally dissimilar elements to carry out the same function or produce the same result (Price & Friston, 2002). The nervous-system degeneracy can be helpful to elucidate reason for neuron in substantia nigra dies and NDs progresses quickly. The intricacy of compensatory mechanisms is exemplified by many alterations that happen in cortical-basal-ganglia-thalamocortical network at various

Figure 1. Schematic diagram presenting the neurodegenerative models (Alzheimer's, Huntington's, Lewy body and transporters model)



levels of PD and linked animal models. The gradual breakdown of the compensatory mechanisms may lead to the pronounced daily alterations in efficacy of drug L-DOPA (L-3,4 dihydroxyphenylalanine) which is frequently noticed in advanced PD (Rinne, Sonninen, & Siirtola, 1970). The processes that can disrupt or promote plasticity of neurons can be an effective therapeutic target.

NEURODEGENERATIVE DISORDERS MODELS

In NDs, the aggregation of proteins, neurological shortfalls and network dysfunction are linked with pathological characteristics (tangles, inclusion bodies and plaques) and loss of neurons (Takalo, Salminen, Soininen, Hiltunen, & Haapasalo, 2013). Transgenic mouse models are used to check specific hypothesis concerning the association between the features (Figure 1). The study underlined below supports model HD and Lewy body disease (LBD) model which includes dementia with Lewy bodies (DLB) and PD displaying that neurological insufficiency and neuronal dysfunction produced by congregation of abnormal proteins can be independent of tangles, plaques, loss of neurons and inclusions. It also elucidates that decreasing the production, increasing the removal or neutralizing the activity of the abnormal protein assembly efficiently reverses the neurological insufficiency (Palop et al., 2006).

Oxidative injury precedes deposition of Aβ in transgenic APP mice (Praticò, Uryu, Leight, Trojanoswki, & Lee, 2001), with increase of enzymes pertaining to apoptosis and mitochondrial metabolism process occurring sooner and colocalizing with the neurons undertaking cognitive impairment (Reddy et al.,

2004). In addition, dysfunction of mitochondria and oxidative injury probably promote the pathogenesis of AD. In the neurons of fetal guinea pig, the treatment with hydrogen peroxide upregulated intracellular levels of Aβ (Ohyagi et al., 2000). Also, the treatment of astrocytes with mitochondrial carbonyl cyanide m-chlorophenylhydrazone (CCCP) promote cells to mimic the processing of amyloidogenic APP and accumulation of intracellular Aβ which is seen in the astrocytes suffering from Down syndrome (Busciglio et al., 2002). In a transgenic mouse which was APP mutant, deficiency of the anti-oxidant mitochondrial enzyme MnSOD significantly enhanced Aβ plaque (F. Li et al., 2004). In another study, a transgenic APP deficient mouse, inhibitors of energy metabolic procedure (kainic acid, insulin, 3-nitropropionic acid and 2-deoxyglucose) increased the activity of β-secretase levels and Aβ amounts. The knockout mice also displays hyperphosphorylation of tau, behavioural and motor deficiency, and neural degeneration (Liou, Sun, Ryo, & Zhou, 2003).

FACTORS CAUSING NEURONAL DYSFUNCTION

Oxidative Stress and Mitochondrial Dysfunction in Neurodegenerative Disorders

The evidences propose that mitochondria play a key role in age-related NDs and regulate the cell death, a characteristic aspect of neurodegeneration (Martin, 2010). Now, a mutation in the DNA of mitochondria and oxidative stress contributes towards the process of ageing, an utmost risk for NDs. There has been evidences that dysfunctioning of mitochondria occurs early and proceeds casually in the pathogenesis of NDs along with disease-specific proteins which interacts with the mitochondria (Table 1).

Mitochondria and Alzheimer's Disease

AD is symbolized by gradual cognitive degeneration and clinically by the existence of extracellular senile plaque (mostly composed of Aβ) and intracellular neurofibrillary tangles (NFTs, composed of hyperphosphorylated tau) (Murphy & LeVine, 2010). Approximately, 5-10% of the Alzheimer's cases are hereditary, happening at premature onset and autosomal-dominant way however, there are 3 proteins associated with AD specifically: amyloid precursor protein (APP that is consecutively broken by β - and γ-secretases to form Aβ), presenilins 1, and presenilins 2 (PS 1 and PS 2) (components of γ-secretase complex (O'Brien & Wong, 2011). There are considerable literature supporting a function for mitochondrial dysfunction and cognitive injury in the development of AD (Mancuso et al., 2009). Many pathways linking AD pathology and oxidative stress have recently been discovered (Bennett, Grant, & Aldred, 2009). Pathways that alter tau processing or amyloid precursor protein (APP) might be activated by stress. In a study, PIN1 (prolyl isomerase) was discovered to be very susceptible to cognitive impairment (Sultana et al., 2006). PIN1 helps in catalysing the conformational changes in the protein that affects both tau and processing of APP. Pin1 knockout intensifies amyloidogenic processing of APP and intracellular Aβ levels in mice (S. L. Ma, Pastorino, Zhou, & Lu, 2012). There are evidences which show that mtDNA (mitochondrial DNA) might be associated with dysfunctioning of mitochondria observed in AD (Mancuso, Orsucci, Siciliano, & Murri, 2008). When mtDNA of patient is moved to cell lines which are mtDNA deficient, the cybrid produces the respiratory enzyme deficiency observed from the mind along with some other cells in AD, indicating that the defect is conceded at least in part by abnormalities of

Table 1. Specific proteins that involve with mitochondria in major neurodegenerative disorders.

Type of Disease	Genetic Causes	Function	References
Alzheimer's disease	*APP*	Forms Aβ, main component of senile plaques.	(Murphy & LeVine, 2010)
	PS1, PS2	Component of γ-secretase, that cleaves APP to form Aβ	(Ya-Ping Tang & Elliot S. Gershon, 2003)
Parkinson's disease	*SNCA*	The principal constituent of Lewy body	(Stefanis, 2012)
	Parkin	Ubiquitin E3 ligase	(Dawson & Dawson, 2010)
	DJ-1	Protection of cell from oxidant-induced cell death.	(Lev, Roncevic, Ickowicz, Melamed, & Offen, 2006)
	PINK1	Protein kinase localized in mitochondria and protects the cell against death. Mutation in *PINK1* leads to building up of improper folded proteins in mitochondria of human cells ad fly.	(De Castro et al., 2012; Pickrell & Youle, 2015)
	LRRK2	A protein kinase. Mutation in *LRRK2* can cause cell death and PD by impairing the pathways responsible for protein degradation. *LRRK2* is essential for regulation of autophagy-lysosomal pathway.	(J.-Q. Li, Tan, & Yu, 2014; Tong et al., 2012)
	HTRA2	Serine protein kinase in the intermembrane space of mitochondria. HTRA2 helps in degradation of proteins within mitochondria. Helps in degrading the inhibitor of apoptosis proteins and stimulate cell death if released to cytosol.	(Strauss et al., 2005)
Amyotrophic lateral sclerosis	*SOD1*	Forms hydrogen peroxide from superoxide. Mutations in the enzyme lead to toxic functional gain.	(Bunton-Stasyshyn, Saccon, Fratta, & Fisher, 2015)
Huntington's disease	*HTT*	The protein interacts with the proteins of the brain. Thus, mutant protein is disruptive for the nerve cells and leads to expanded polyglutamine repeats.	(Zheng & Diamond, 2012)

mtDNA (Swerdlow et al., 1997). Nonetheless, recognizing AD particular mutations of mtDNA was a struggle. mtDNA sequencing from 128 controls and 145 AD patients did not uncover any considerable link with mutations of mtDNA and haplogroup of mitochondria (Elson et al., 2006). There was no link observed in the obtained mutations of mtDNA while examination of coding region for cytochrome c oxidase subunit I (CO1) (Lin, Simon, Ahn, Kim, & Beal, 2002). Nevertheless, in the similar manner, the promoters seemed more susceptible to injury than the coding region of genes 15, control region of mtDNA which displayed an enhanced mutation in AD (Coskun, Beal, & Wallace, 2004). The cortical areas suffering from AD had approximately 63% rise in heteroplasmic mtDNA control-region mutations, and in individuals there was a 130% increment in mutations (Coskun et al., 2004).

Mitochondria and Parkinson's Disease

PD is marked clinically by bradykinesia, tremor and progressive rigidity and biochemically by occurrence of Lewy body-loss of pigmented neurons in the substantia nigra and the presence of Lewy bodies-characteristic inclusions in cytoplasm which immunostain for ubiquitin and α-synuclein (Lin & Beal, 2006). Mitochondria was first associated in PD as MPTP (1-methyl 4-phenyl-1,2,3,6-tetrahydropyridine), whose metabolite MPP^+ obstructs the complex I of the mitochondrial ETC (electron-transport chain), lead to parkinsonism in drug-designer abusers. The model is refined in lab animals, wherein rotenone's

(Betarbet et al., 2000) (MPTP or inhibitor of Complex-I) chronic infusion-outcomes clinically at a parkinsonian phenotype and pathologically in degeneration of nigral with inclusions in cytoplasm for ubiquitin and α synuclein (Fornai et al., 2005).

The toxicity mechanism in the inhibition of complex-I models possibly includes stress (Sherer et al., 2003). Oxidative stress and complex-I inhibition have been presented to be pertinent to PD when glutathione deficiency and complex-I depletion were present in substantia nigra of patients suffering from pre-symptomatic PD and idiopathic PD (Schapira et al., 1990). To date, polymorphisms or mutations in mtDNA and 9 nuclear genes have been recognized as causing the risk of PD. These genes are: parkin, phosphatase and tensin homologue *(PTEN)*-induced kinase 1 *(PINK1)*, α-synuclein, leucine-rich-repeat kinase 2 *(LRRK2)*, *DJ-1*, ubiquitin carboxy-terminal hydrolase L1, the nuclear receptor *HTRA2*, *NURR1* and tau. Of the nuclear genes: parkin, α-synuclein, *DJ-1*, *HTRA2*, *PINK1* and *LRRK2* directly or indirectly implicate mitochondria (Deas, Wood, & Plun-Favreau, 2011). In a number of cases, inherited mutations in mtDNA resulted in parkinsonism, generally as one characteristic of a larger syndrome. It was discovered that the Leber's atrophy G11778A mutation was associated with L-DOPA-responsive parkinsonism, variably co-occurring with ophthalmoplegia, ataxia, dementia and dystonia, and (D. Simon et al., 1999). Notably, this mutation is at a subunit of complex I. Mutations in the nuclear-encoded mtDNA polymerase-γ (POLG) receptor impair mtDNA replication and result in multiple mtDNA deletions, typically causing chronic progressive external ophthalmoplegia and myopathy. POLG mutations also co-segregate with parkinsonism, myopathy and ophthalmoplegia (Luoma et al., 2004). There's less evidence for mtDNA participation in non-syndromic PD. Nigral neurons from PD patients contain increased levels of clonally expanded mtDNA deletions compared with those from controls, although elevated levels can also be seen in ageing (Bender et al., 2006; Kraytsberg et al., 2006) and discovered no distinction between PD and control subjects in inherited or acquired complex-I or tRNA point mutations (D. K. Simon et al., 2004; Vives-Bauza et al., 2002). Interestingly, however, several groups have discovered that particular continent-specific clusters of polymorphisms, termed mtDNA haplogroups, might decrease the probability of developing PD. Among Europeans, the haplogroup cluster UJKT is associated with a decreased risk for PD compared with haplogroup H (Pyle et al., 2005). The haplogroups underrepresented in PD patients are overrepresented in healthy centenarians (Tanaka, 2002). Protective mtDNA lineages seem to have arisen from areas requiring cold-adaptation, including uncoupling of mitochondria to increase heat generation at the expense of ATP production. It's been suggested that this partial uncoupling increases longevity and decreases risk of neurodegeneration by decreasing free-radical generation (Wallace, 2005). Mutations in α-synuclein are associated with autosomal dominant familial PD. α-Synuclein is a significant component of Lewy bodies, along with the primary effect of α-synuclein mutations is likely to be an increased formation of fibrillar or oligomeric aggregates (Recchia et al., 2004). Nevertheless, there seem to be close interrelationships between protein accumulation or degradation, oxidative stress and mitochondrial dysfunction. In transgenic mice, overexpression of-synuclein impairs mitochondrial function, increases oxidative stress and enhances nigral pathology induced by MPTP (Song, Shults, Sisk, Rockenstein, & Masliah, 2004). Furthermore, at a latest research study of mice overexpressing alpha A53T mutant α-synuclein mitochondria were immune stained for α-synuclein, raising the possibility that mutant α-synuclein may damage mitochondria directly (Martin et al., 2006). Whereas overexpression of α-synuclein increases sensitivity to MPTP, α-synuclein-devoid-mice are more immune to MPTP41 along with other mitochondrial toxins like malonate and 3-nitropropionic acid (Klivenyi et al., 2006). Therefore, α-synuclein seems to mediate the toxicity effects of MPTP. Mutations in parkin are associ-

ated with autosomal recessive juvenile PD. Parkin encodes ubiquitin E3 ligase, and also the primary abnormality, therefore, is in the ubiquitin proteasome system (UPS).

Mitochondria and Amyotrophic Lateral Sclerosis

ALS is marked clinically by spasticity, progressive weakness and atrophy of muscular tissue, indicating the degeneration of both lower and upper motor neurons in the brainstem, spinal cord and cortex. About 90% of cases are sporadic ALS (SALS) and 10% are familial ALS (FALS). Approximately, 20% of FALS cases are triggered by Cu/Zn-superoxide dismutase (SOD1) mutations (Rezania et al., 2003). In both SALC and FALC, biopsy and post mortem samples from the nerves, muscles and spinal cord present anomalies in structure of mitochondria, localization and number. Nonetheless, it's hard to analyse from glimpses of already symptomatic individuals if mitochondria contribute to progression of disease or are harmless bystanders. So, a study on the involvement of mitochondria in ALS has focussed on expression of mutant SOD1 in animal and cellular models of ALS. Overexpression of G93A SOD1 mutation induces impaired mitochondrial energy metabolic process in the spinal cord and brain at the onset of disease (Mattiazzi et al., 2002). Nonetheless, before the onset of disease, the calcium loading capacity is decreased in the mitochondria from spinal cord and brain, but, not in the liver of mice overexpressing G85R or G93A mutant SOD1 (Damiano et al., 2006). Back in G93A mice, there's an explosive upsurge in degeneration of vacuolar mitochondria thereby, leading to death of motor neuron, which suggests that abnormalities in mitochondrial trigger onset of the disease (Kong & Xu, 1998). Interestingly, SOD1 is concentrated within vacuolated mitochondria (Jaarsma et al., 2001). SOD1 has conventionally been believed to be a cytoplasmic protein, although localization of a portion of mobile SOD1 to the mitochondrial intermembrane space, matrix and outer membrane has now been confirmed (Higgins, Jung, & Xu, 2003; Vijayvergiya, Beal, Buck, & Manfredi, 2005) and only the affected cells localize SOD1 (Liu et al., 2004). Interaction between mitochondria and SOD1 suggests different mechanisms by which cell survival and mitochondrial function might be negatively influenced. The targeting of mutant SOD1 to mitochondria triggered apoptosis and release of cytochrome c, while targeting to nucleus or endoplasmic reticulum (ER) did not trigger cell death (Takeuchi, Kobayashi, Ishigaki, Doyu, & Sobue, 2002). It was suggested that mutant SOD1 collects and accumulates from the outer membrane of mitochondria and interrupts the importation of protein, thus, leading to dysfunctioning of mitochondria (Liu et al., 2004). Mutant SOD1 is suggested to encourage production of ROS, and cause oxidative damage to proteins and lipids of mitochondria, together with impaired synthesis of ATP and respiration in mice expressing mutant human SOD1 (Mattiazzi et al., 2002).

Mitochondria and Huntington's Disease

HD is characterized by psychiatric disturbances, dementia and chorea and biochemically by damage of long projection neurons, and anticipated to cause the development of cytosine, adenine and guanine (CAG) trinucleotide recurrence in the huntingtin (*HTT*) gene, that leads to polyglutamine stretch expansion from the consequent protein (Finkbeiner, 2011). The standard number of repeats of CAG repeats is less than 36 and greater than 40, which leads to occurrence of disease. Many evidences establish the association of dysfunctioning of mitochondrial in HD. NMR (Nuclear magnetic resonance spectroscopy) shows enhanced lactate from basal ganglia and cortex (Jenkins, Koroshetz, Beal, & Rosen, 1993). Biochemical researches reveal reduced performances of complexes II and III of the ETC (electron- transfer chain)

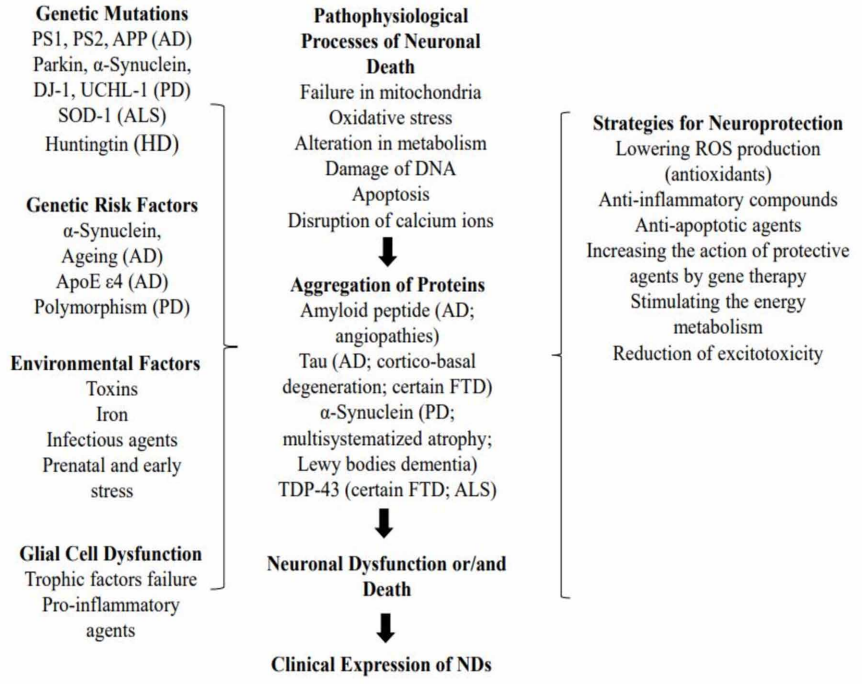
in the human HD brain (Gu et al., 1996). In striatal cells of mutant HTT-knock-in mouse embryos, the production of ATP and respiration in mitochondria were considerably damaged (Milakovic & Johnson, 2005). The dysfunctioning of mitochondria noticed previously is important pathogenically, as malonate-mitochondrial toxins and 3-nitropropionic acid selectively restrains succinate dehydrogenase and complex II- stimulates a clinical and behavioural phenotype that looks like HD closely (Brouillet et al., 1995). Also, by adding 82 glutamines to 171 amino acids of *HTT*, restoration of complex-II activity, obstruction of cell death and dysfunctioning of mitochondria was observed in striatal neurons (Benchoua et al., 2006). Many mechanisms are known by which the mutation can lead to dysfunctioning of mitochondria. Firstly, there can be a direct interaction between *HTT* and mitochondria. In a research (Panov et al., 2002), mitochondria from lymphoblast of HD patients and mitochondria from brain of YAC transgenic mice expressing *HTT* with 72 repeats was discovered to have a membrane potential and had an ability to depolarize in lower calcium loads in comparison to mitochondria of control.

Other Causes for Neuronal Dysfunction

The factors causing the NDs still remain unidentified till now. For AD and possibly PD, the significant risk factor is ageing due to the increased prevalence of the disease with age. In case of AD the situation is apparent, however in the other case such an assessment is open to question since for a sizable proportion of patients the starting place of PD is quite premature, and disguised with a long prodromal stage of the disease. Certain recognizable kinds of the diseases find a genetic component but monogenic forms are extremely infrequent and even exceptional (Corti, Fournier, & Brice, 2009). It is the case in early-onset of AD where the amyloid hypothesis is supported by mutations of genes causing the disease, such as mutations of gene encoding amyloid protein precursor (chromosome 21) or presenilins (PS1 and PS2 found on chromosomes 1 and 14 (respectively) in rare autosomal dominant kinds (<5%) (Ya-Ping Tang & Elliot S Gershon, 2003). A comparable situation can be found, for instance, at autosomal dominant forms of PD, with the gene encoding LRRK2 (mutation PARK8) and α- synuclein (mutation PARK1 and PARK4) among 15 varied known mutations (Figure 2). In some families, where ALS and FTD co-segregate, mutations on a single gene associated to chromosome 19 can cause both clinical phenotypes, that affirms the hypothesis of a common mechanism, as discovered by new data on accumulation of proteins (Sleegers, Cruts, & Van Broeckhoven, 2010). While, it is contemplated that environmental factors are also involved in the development of a certain NDs (Cicchetti, Drouin-Ouellet, & Gross, 2009). For example, compounds like heavy metals, pesticides, fungicides, chemicals derived from viruses and addictive drugs may perhaps play a part in causing PD (Moisan et al., 2011). Nevertheless, epidemiologic research has to be further developed since present conclusions are usually not adequately apparent, therefore suggesting that only exposures to these environmental factors even when prolonged and intensive aren't usually sufficient to cause the diseases (Dick, 2006). Interestingly, in relation to environmental factors that could influence the occurrence of diseases, a brand new direction has recently been taken focusing on anxiety. Intensive chronic stress in humans was for instance associated with decreased hippocampal and right orbito-frontal volumes, (Gianaros et al., 2007) which might affect cognitive and emotional functions.

Abbreviations: PS1, Presenilin1; PS2, Presenilin2; APP, Amyloid precursor protein; UCHL-1, Ubiquitin carboxyl-terminal hydrolase isozyme L1; SOD-1, Superoxide dismutase 1; Apo E ε4, Apolipoprotein E ε4; FTD, Frontotemporal dementia; ROS, reactive oxygen species; TDP-43, TAR DNA-binding protein 43; NDs, Neurodegenerative disorders.

Figure 2. Summary of the processes that can be associated in neurodegenerative disorders, comprising of genetic factors and mutations that interfere with environmental factors to cause disease



PROTEIN AGGREGATION AND INTERNEURONAL LESION

NDs like AD, PD, HD, ALS and prion diseases are increasingly being realized to have common cellular and molecular mechanisms including protein aggregation and inclusion body formation (Lansbury & Lashuel, 2006). The aggregates usually consist of fibres containing misfolded protein with a β-sheet conformation, termed amyloid. The more than likely explanation is that inclusions along with other protein aggregates represent an end phase of a cascade of steps, and that earlier phases in the cascade can be more directly connected to pathogenesis than the inclusions themselves. For diseases, genetic variants help in describing the pathogenesis of the more common sporadic forms and developing mouse along with other models. There's now increased understanding of the pathways involved with protein aggregation, and a few latest hints have emerged as to the molecular mechanisms of toxicity. These are leading to strategies toward rational therapeutics.

Genetic and Neuropathological Features in the Pathogenesis of Neurodegenerative Disorders

The main focus of preliminary research into the pathogenesis of NDs is on the processes and its mechanisms accountable for protein aggregation as well as the description of cytotoxic changes that accompany and result from the aggregation (G. Hall, 2011). As a result, events which are associated to aggregation and downstream implications of aggregation like loss of protein turnover mechanism in neurons are among

the best-characterized features of NDs. This work has created a broad consensus that aggregation leads to the breakdown of normal protein turnover mechanisms and the subsequent growth of abnormal toxicity routes of protein disposal are main pathogenic events of the NDs that affect the human CNS. Common toxicity elements which are downstream of protein aggregation in NDs consist of:

- Association of aggregation which harms the protein turnover mechanisms (De Baets et al., 2011),
- Dysfunctioning of mitochondria or/and maldistribution resulting in changes associated with apoptosis because of oxidative stress generation, low ATP and abnormal Ca^{2+} fluxes and (Cui, Kong, & Zhang, 2012)
- Sequestration of normal proteins because of aggregation thereby, leading to damage in normal functioning of sequestered proteins (Yang & Hu, 2016).

Alzheimer's Disease and Tauopathies

AD is a late-onset dementing illness, with progressive memory loss, task performance, speech, and recognition of people and objects. There's degeneration of neurons (particularly in the basal forebrain and hippocampus), however at least as necessary for pathogenesis could be synaptic pathology and modified neuronal connections (Hardy & Selkoe, 2002; Selkoe, 2002). AD involves two types of protein aggregates. Extracellular aggregates known as neuritic plaques have as their major constituent the Aβ peptide that can be derived from proteolytic processing of the APP. The Aβ-containing aggregates have β-sheet structure along with Congo red (an azo dye) and reactivity characteristic of amyloid (Serpell & Smith, 2000). There are also intracellular aggregates of the microtubule-associated protein tau, called neurofibrillary tangles. The pathogenesis of AD has been greatly clarified by the identification of genetic mutations accountable for rare forms of the disease. These mutations have been in APP itself and also in the presenilins, that are involved with the cleavage of APP (Citron, 2002; Esler & Wolfe, 2001). Additionally, tauopathies like frontotemporal dementia with parkinsonism may be brought on by mutations in the tau protein (Goedert, 2004; Ingram & Spillantini, 2002). The characteristic example of a neuropathogenesis pattern which suggests the lesion spread in NDs (outside of prion diseases) is stipulated by AD. It is evident after the studies of Heiko and Eva Braak (Braak & Braak, 1991) that neurofibrillary degenerative changes of AD progress in a distinctive order which comprehends the development of symptoms (Armstrong, Cairns, & Lantos, 2001; Su, Deng, & Cotman, 1997). The initial alterations happen in particular limbic regions which are associated with, spatial localization, olfaction and formation and consolidation of episodic memory (entorhinal, pyriform and transentorhinal cortices), functions which are usually compromised in the earliest preclinical and clinical phases of AD.

It is followed by increasing involvement of paralimbic and limbic centers which includes the insula, anterior cingulate cortex, hippocampus and adjacent allocortical regions of the medial temporal lobe (e.g. subiculum). These neuropathological changes match the progression of AD symptoms with alterations in short term memory and emotional processing becoming obvious by the time AD can be recognized as such in the clinic, along with the beginning of cognitive changes. The most significantly affected limbic centers are intensely interrelated with one another functionally and synaptically as will be essential for propagation of lesion by transsynaptic toxicity transfer (Su et al., 1997).

The developing association of synaptically interconnected brain regions as observed in AD is reflected in non-AD pathophysiological conditions like Pick's disease (PiD), frontotemporal dementia (FTD), corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) implicates some areas of brain (insula, frontal/prefrontal cortex temporal cortex). Likewise, PD and LBD share a joint set of susceptible loci (olfactory bulb, dopaminergic neuron, neocortical loci) nevertheless, differ immensely in extent of involvement of other parts of brain and initial nidus of vulnerability (Aguzzi, Sigurdson, & Heikenwaelder, 2008; Clinton, 2007; Cookson, 2009). Additional characteristic of NDs as a group is the appearance of each disorder in both familial and sporadic forms, with intronic or exonic mutations in a particular aggregation-susceptible protein synthesises a dominant allele which is able to replicate all the attributes of the sporadic disease with high penetrance (Spillantini, Bird, & Ghetti, 1998). The interesting characteristics of this pattern are a) the extent of similarity between familial and sporadic disease forms, b) higher tendency of sporadic as compared to familial, disease forms to present the asymmetric development, particularly in non-AD conditions (Dickson, 2010; Lee, Goedert, & Trojanowski, 2001).

Linking Aggregation to Lesion Spreading-Prion Protein

The prion protein (PrP) is an example of protein which is prone to aggregation that spreads its misfolded state of protein at protein, cellular and organismal level. NDs brought on by prions may be sporadic or could be obtained either by genetic mutations or environmental transmission (Pruisner, 2001). Mutations in the prion gene cause the disease thereby, leading to changes in the prion protein. The pathology of the disease includes the formation of amyloid plaques that appears comparable to AD which can be labelled by prion antibody. Prion disease is caused by changes in protein conformation and the research has shown that it is brought out by construction of abnormal protein. The prion disease mechanism is lit from the finding of prion like protein conformation changes in yeast (Lindquist, Krobitsch, Li, & Sondheimer, 2001; Scheibel, Bloom, & Lindquist, 2004). In all cases, disease occurs by the presence of abnormally folded prion proteins. The aggregation of prion protein might take place extracellularly and intracellularly (J. Ma & Lindquist, 2002; J. Ma, Wollmann, & Lindquist, 2002). The misfolding of PrP facilitates a range of neurological degenerative diseases like transmissible spongiform encephalopathy in humans. The "Prion hypothesis" states that the individual subunit of PrP is misprocessed and misfolded in a way that makes it form a neurotoxic conformation (PrP^{Sc}), and promotes the transmission of this conformation to other prion proteins with normal conformation (PrP^{C}). The controversial and peculiar history of prion biology offers us the example of how the misprocessed protein aggregation-prone protein can lead to interneuronal propagation with neurotoxic characteristics and thereby influence the spreading of neurofibrillary lesions to postsynaptic, adjacent and presynaptic neurons. The relevance of misprocessing mechanism of PrP to development of tauopathies, NDs and synucleinopathies is highlighted by various findings that massive differences in the misprocessing of PrP and PrP^{Sc} structure appear to cause neuropathological and clinical manifestations of different prion diseases (Caughey & Baron, 2006; Collinge & Clarke, 2007; Parchi et al., 1996). Additionally, various studies of the physiological functions of PrP^{C} propose its involvement in function of cell adhesion, actin-rich subcortical cytoskeleton and its interaction with microtubules, signal transduction pathways (Cushman, Johnson, King, Gitler, & Shorter, 2010). PrP^{C} plays an integral role in synaptic plasticity. The similarities in the localization, misprocessing and cellular functions of asyn, tau, APP/Abeta and PrP recognize likely points of interactions between these proteins and synergy in the process of misprocessing.

PROGRESSION FROM SYNAPTIC DYSFUNCTION TO TRANSMISSION FAILURE

Neural plasticity is extremely adaptive during the disease and health. It allows the animals to interact efficiently with the environment and to manage better with neurological damages. A chief constituent of neural plasticity is located in synapse, which are actively weakened and strengthened by complicated methods to form the dynamic network and circuit which stores memory and generates thought process. Particularly, the abnormal proteins that are supposed to cause NDs hamper the function or integrity of postsynaptic specializations and presynaptic terminals (Mahley, Weisgraber, & Huang, 2006; Muchowski & Wacker, 2005b; Walsh & Selkoe, 2004). Many mechanisms can be included, such as excitotoxicity (Hynd, Scott, & Dodd, 2004; Mark, Ashford, Goodman, & Mattson, 1995), inflammation (Wyss-Coray & Mucke, 2002), cognitive stress (Beal, 2005) along with other processes (Handley, Naji, Dunnett, & Rosser, 2006; Mattson, 2004; Muchowski & Wacker, 2005b). In AD, synaptic loss surpasses the neuronal loss, and reduction of synaptic proteins and synapses relates better with cognitive degeneration than the massive quantity of tangles or plaques (Honer, 2003; Levine, Cepeda, Hickey, Fleming, & Chesselet, 2004; Van Dellen, Grote, & Hannan, 2005). Chronic variations in neurotransmission and synaptic plasticity can impact expression of gene and activity-dependent signalling, thereby, causing the degeneration of neural network and, in the end, the collapse of functioning of neurons. Conversely, in mouse models, environmental stimulation, upsurges the synaptic plasticity and can both decrease and delay pathological alterations (Lazarov et al., 2005; Van Dellen et al., 2005). The lipid provider (APOE) regulates sensitivity to typical bronchial ailments and neural plasticity. Different injuries produce an efficient neural plasticity reactions with the protective APOE3 and APOE2 isoforms (not the APOE4) which intensifies the menace and accelerates the onset of PD AD, and different neurological conditions (Mahley et al., 2006).

FUTURE RESEARCH DIRECTIONS

There is a constant research to discover mechanism by which disease-associated proteins aggregate, misfold and produce toxicity (Moreno-Gonzalez & Soto, 2011). Presently, various efforts are focussed on eliminating the abnormal protein assembly themselves (Muchowski & Wacker, 2005a; Selkoe & Schenk, 2003). By increasing the removal, nullifying the actions of the assembly and decreasing the synthesis helps in improving the survival of neurons. If the functional decline in NDs is produced by the neuronal loss, it might take many years for the detection of benefits of disease-modifying intrusions-a discouraging possibility that depresses developing better drugs for AD (Tasakis & Tsolaki, 2015). The continued progress in our ability to examine amyloid-forming protein and the association with some proteins provide assurance that novel treatments will be recognized for different disease states (Kaiser et al., 2012). The therapeutic options are explored which includes the targeting of the interaction between a chaperone-protein at various points from the route, thereby, encouraging the clearance of proteins and network rebalancing (Saibil, 2013). Nevertheless, the recognition and *in vivo* validation of new therapeutics is obstructed by the deficiency of the drivers of diseases and biomarkers for examining the therapeutic responses in model organisms. Nonetheless, the acceleration in research and collaboration amongst the community of drug discovery (regulatory agencies, pharmaceutical businesses, academia, advocacy groups, foundations, patients, contract research organizations, clinicians) is a constructive change which may help hasten the identification of novel therapeutic modalities.

CONCLUSION

In the research of neuroscience, the arena of NDs is one of the most studied with respect to both medical and concerned social issues. The current studies have significantly increased our knowledge of the role of mitochondria in the pathogenesis of NDs. The interaction of mitochondria with a particular protein which is related to the disease unties the prospects for discovery of therapeutic targets. Whereas, in PD, ALS and AD, genetic aspects of disease relate to only small fraction of cases and the significance of interaction of mitochondria with these proteins should be established for sporadic cases. The advances in this area have led to the essential information of the diseases, assessment of pathological processes and estimation of therapeutic approaches to deal with them. These strategies include therapies which are based on better understanding of the physiopathological mechanisms and efficient neuroprotection. These approaches to NDs are perhaps extremely global to be effective in short term. Nonetheless, advances in the understanding of etiopathological factors of the disease at genetic and molecular levels will cause new developments. The information of NDs has advanced rapidly in the previous years, and the area holds an immense promise for expanding our knowledge and understanding and subsequent treatment of the destructive taupathies.

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Chapter 7
Stroke:
A Potential Risk Factor of Neurodegenerative Disorders

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ABSTRACT

The brain relies on a specialized endothelial system, the blood brain barrier (BBB), which is capable of regulating the transfer of substances from the blood to the neurons. Stroke is the most frequent cause of disability in adulthood. Lesions of vascular origin also include asymptomatic small infarcts, microbleeds, dilated perivascular spaces, and atrophy. Vascular cognitive impairment (VCI) is the second most prevalent cause of dementia. Several mechanisms are implied, including strategic infarct dementia, post-stroke dementia, cerebral amyloid angiopathy, and subcortical vascular dementia. As there is no disease modifying therapies currently available, treatment of comorbidities and adequate control of the vascular risk factors remain the standard strategies to reduce the vascular contributions to neurodegeneration. This chapter represents the basic concepts of pathophysiology of cerebrovascular diseases, and describes the subtypes of VCI, as well as treatment and primary prevention strategies.

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INTRODUCTION

There is no single mechanism that satisfactorily explains the complex relation between stroke and neurodegenerative disorders, predominantly those related to cognition impairment. Rather, this relation may be explained by multiple pathophysiological mechanisms, such as microstructural defects, leading to blood brain barrier and neurovascular unit dysfunction; by vascular mechanisms, when traditional vascular risk factors lead to failure on the capacity of cerebral blood flow regulation; and by genetic predisposition, exemplified by CADASIL, apolipoprotein ε polymorphisms and variations of homocysteine´s metabolism. Furthermore, these are not necessarily exclusive, and a combination of these factors may occur in individual patients (Iadecola, 2013; Schneider *et al*, 2003).

In patients with cerebrovascular disease, cognitive decline, affecting mainly executive domains and language functions, may occur. A variety of cerebrovascular conditions will result in distinct profiles of cognitive impairment, by either lowering the threshold for neurodegenerative diseases or unmasking an already present, often mild or subclinical, dementia.

Vascular cognitive impairment (VCI) is a condition in which vascular lesions can lead or contribute to impaired cognitive function, and ranges from mild cognitive disorder to dementia (Bowler and Hachinsky, 1996; Gorelick *et al*., 2011). It is the second most prevalent cause of cognitive impairment, and remains vastly underdiagnosed (Godefroy *et al*., 2013).

There are several clinical subtypes of VCI, such as poststroke dementia, with a short-term incidence after stroke as high as 40% (Pendlebury and Rothwell, 2009); strategic infarct dementia, caused by interruptions of strategic networks, leading to impaired executive functions; subcortical vascular dementia, by far the most common subtype of VCI; microinfarcts dementia, caused by small lesions detected only by high resolution brain imaging or biopsy; microbleeds related VCI, which could be caused either by hypertensive vasculopathy or cerebral amyloid angiopathy; hypoperfusion dementia, as a consequence of hemodynamic failure in border zone (watershed) regions; and mixed disease, when vascular pathology and Alzheimer Disease (AD) overlap.

In this context, VCI appears as a continuum of different clinical entities, which makes it the perfect prototype to understand the fascinating connection between cerebrovascular disease and neuronal degeneration (Iadecola, 2013; Schneider *et al*, 2003).

This chapter review the concepts of blood brain barrier, neurovascular unit and brain autoregulation; define stroke and its subtypes (ischemic, hemorrhagic and cerebral venous thrombosis), with their main risk factors, clinical features and morbidity; explain the impact of cerebrovascular diseases on cognition and neurodegeneration; and describe the subtypes of VCI, as well as treatment and primary prevention strategies.

BACKGROUND

The attempt to divide normal ageing from pathological senility began in the late 19th century, which was a critical period for developing the concept of dementia as we know it today. At that time, the definition of dementia was similar to the one used nowadays, although much more inclusive: a general compromise of intelligence, with prominent memory loss and alterations of personality. Studies by French and German psychiatrists were crucial to separate psychotic syndromes, such as schizophrenia, from other forms of cognitive impairment. This interest in understanding pathological aging has encouraged a great number

of histological studies, which helped divide organic and psychiatric diseases into different nosological entities (Caixeta *et al.*, 2014).

In 1907, Dr. Alois Alzheimer first described the case of August Deter, a 51 year-old female patient showing language comprehension and memory disturbances. The pathological study of her brain revealed neurofibrillary tangles and amyloid senile plaques, establishing the typical histopathological findings of Alzheimer's disease. After that, the amyloid hypothesis became the most accepted explanation for senile dementia (Ramirez-Bermudez, 2012).

The vascular contributions to dementia were first described simultaneously to Alzheimer's work. Another neuropathologist, Dr. Gaetano Perusini, also studied the brain of August Deter, and described that "*the large cerebral vessels, the arterial circle of Willis and the Sylvian arteries showed no significant signs of arteriosclerosis*" (Ramirez-Bermudez, 2012). Despite that, until the 1990's, there was a general belief that cerebrovascular disease only caused dementia in the presence of many cortical infarcts – the "multi-infarct" approach. In 1974, Dr. Vladimir Hachinski stated that most cases of senile dementia were attributable to Alzheimer-like degeneration and not to atherosclerosis - for the Canadian doctor, cerebral infarcts accounted for only a minority of cases of mental deterioration in the elderly, often associated with hypertension or extracerebral vascular disease (Hachinski V.D. *et al*., 1974).

In the past three decades epidemiological studies showed that dementia dramatically increases with cerebrovascular diseases and vascular risk factors and the vascular hypothesis for neurodegenerative process began to be better understood (O'Brien *et al*., 2015).

Until the 21st century, VCI and neurodegenerative dementia (Alzheimer's disease) where thought to be two distinct nosological entities. However, in the past two decades, the vascular contributions to the pathology of every types of dementia have been increasingly recognized (O'Brien *et al*., 2015). Nowadays we know that mixed dementia, with the co-existence of amyloid and vascular pathological processes, is the rule, and not the exception (Schneider, J.A. *et al.*, 2007).

THE BLOOD BRAIN BARRIER AND THE NEUROVASCULAR UNIT

Composed mainly by vascular endothelial cells, the blood brain barrier (BBB) also interacts with different vascular, immune and neural cells (Daneman and Prat, 2015). Different from the vasculature from other tissues, BBB allows the brain to stringently regulate the transfer of ions, molecules and cells between the blood and brain tissue itself, through tight junctions, enzymes and other transport systems (Ramirez-Bermudez, 2012). In order to maintain brain homeostasis, the endothelial cells deliver oxygen and nutrients, thus guaranteeing proper neuronal function, and filter substances from the brain back to the bloodstream, protecting the neural tissue from toxins and pathogens (Daneman and Prat, 2015).

BBB is involved in the pathology and progression of different neurological diseases. There is a great number of proinflammatory cytokines and other proteins related to specific diseases, which might mediate BBB disruption. Such dysfunction can be seen in traumatic brain injuries, viral encephalitis, Alzheimer's disease (AD), brain expanding lesions, stroke, epilepsy, multiple sclerosis and idiopathic Parkinson's disease (Persidsky *et al*., 2006).

Together, endothelial cells, pericytes, basement membrane, neurons and glial cells form the neurovascular unit (Sá-Pereira *et al*., 2012). Similar to the BBB, the neurovascular unit has many regulating and protective mechanisms, a process also called "neurovascular coupling", which refers to the capacity of the brain vasculature to regulate tissue perfusion, responding to changes in neuronal activity, systemic

perfusion pressure and local changes to the chemical environment (Sá-Pereira *et al*., 2012). Through vasodilation and vasoconstriction, the neurovascular unit maintains oxygen and nutrients in appropriate levels (Muoio *et al*., 2014).

Autoregulation of cerebral blood flow is the main component of brain vasculature reactivity responsible for keeping cerebral blood flow constant. Regulation of cerebral blood flow predominantly occurs in parenchymal and leptomeningeal arterioles, where the precapillary sphincters dynamically change their resistance to blood flow through either contraction or dilatation (Muoio *et al*., 2014).

Chemical, neurogenic and myogenic mechanisms are implied in cerebral autoregulation. Byproducts of metabolism, such as H^+, K^+, O_2 and adenosine, are vasoactive substances that cause arterial dilatation. Metabolic parenchymal substances, monoamine neurotransmitters, secreted by dorsal raphe nucleus, locus coeruleus and oral pontine reticular nucleus, also play a role regulating vessel tone (Hilz *et al*., 2000). In addition, sympathetic noradrenergic fibers, which modulate mainly proximal large vessels tone, exert significant vasoconstrictor effects on these arteries. Parasympathetic and vasodilating impulses are of lesser influence (Hilz *et al*., 2000). Finally, the smooth muscles of cerebral vessels constrict in response to elevated pressure and dilate in response to decreased pressure. If these mechanisms are compromised, significant brain injury occurs (Cipolla, 2009).

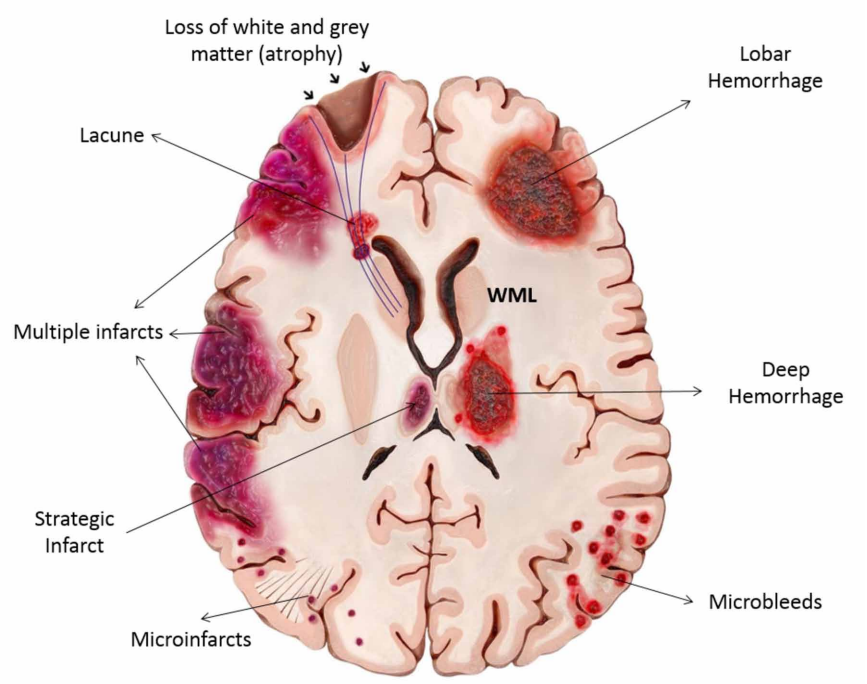
Cerebrovascular injury to the brain happens when the vasculature becomes diseased, contributing to cognitive impairment and neurodegeneration. This type of cerebrovascular injury may be easily detected by magnetic resonance imaging (MRI) (Smith *et al*., 2017). Most cerebral infarcts are actually clinically unrecognized. As silent cerebral infarcts occur over time, cognitive impairment worsens and the risk for dementia increases. White matter lesions of vascular origin, microbleeds, dilated perivascular spaces and atrophy represents the broad neuroimaging spectrum of cerebrovascular disease found on brain MRI (Figure 1) (Smith *et al*., 2017).

Cerebral microinfarcts are thought to represent the pathological link between cerebrovascular disease and dementia and are clinically associated with stroke and cognitive decline. There are probably multiple causes for small, deep cerebral infarcts, such as cerebral small vessel disease, amyloid angiopathy, microemboli and hypoperfusion mechanisms (Van Veluw *et al*., 2017).

Apart from small vessel disease, large vessel intracranial and extracranial atherosclerosis also co-occurs with cerebral microinfarcts (Van Veluw *et al*., 2017). In a sub analysis of the SAMMPRIS trial, 49.5% of subjects with stroke due to intracranial stenosis also showed patterns of small vessel disease in brain imaging (Kwon *et al*., 2016). These patients scored significantly less in the Montreal Cognitive Assessment (MoCA) examination, confirming the association between intracranial stenosis, microinfarcts and cognitive decline (Kwon *et al*., 2016). As for extracranial atherosclerosis, in 2017 a prospective study demonstrated an incidence of 13.8% of cerebral microinfarcts after carotid endarterectomy. Previous abnormal neurological exam and the necessity of shunting during surgery were the main risk factors for small cerebral infarctions (Gwon *et al*., 2017).

In patients with small vessel disease and microinfarcts, cognitive decline occurs independently from Alzheimer's pathology. Executive domains and language functions are most commonly affected (Van Veluw *et al*., 2017) and these dysfunctions are thought to be secondary to disruption of structural brain connections. It is estimated that a $0.2mm^3$ lesion may cause pathological alterations at least 12-fold greater than the volume of the lesion core (Summers *et al.,* 2017). Perilesional alterations include astrogliosis, reduced expression of aquaporin-4 and demyelination. Small-vessel disease also leads to dysfunction of the glymphatic system, responsible for the clearance of beta-amyloid peptide aggregates (Van Veluw *et al*., 2017).

Figure 1. Figure 1. Lesions of vascular origin on brain pathology, WML = White matter lesions.



STROKE

Stroke is the second most common cause of death and the most frequent cause of disability in adulthood worldwide (Obviagele *et al*., 2013). According to the World Stroke Organization, 1 out of 6 people will suffer a stroke in their lifetime. Stroke diagnosis is essentially clinical, based on the sudden onset of a focal neurologic deficit, leading to motor and/or sensory disabilities. It is primarily classified as ischemic stroke (IS), which represents 87% of all cases, and intracranial hemorrhage (ICH), completing the remaining 13% (Roger *et al*., 2011).

Ischemic Stroke

Further categorization of subtypes of ischemic stroke (IS) is important to estimate the odds of permanent disability, as well as mortality and recurrence rates, as determining the cause of stroke directly influences on the choices for management and secondary prevention. According to the TOAST classification, IS can be divided into large-vessel atherosclerosis, cardioembolism, small-vessel occlusion, other etiologies and stroke of undetermined etiology (Adams *et al*., 1993).

The prevalence of risk factors in patients with IS varies according to subtype and the population studied. Hypertension, smoking habit, history of diabetes mellitus, waist-to-hip ratio, alcohol intake, cardiac causes and psychosocial issues are risk factors for stroke consistent in all studied populations (O'Donnell, M.J. et al., 2016).

For the acute phase treatment, intravenous administration of recombinant tissue-type plasminogen activator (rtPA) is associated with significantly less disability for patients treated within a treatment window of 4.5 hours since the last time they were known to be well (asymptomatic) (Hacke *et al*., 2008). Among patients with occlusions of intracranial large vessels, endovascular mechanical thrombectomy results in higher rates of reperfusion than intravenous t-PA alone (Church, E.W. *et al.*, 2017). Unfortunately, reported intravenous rT-PA treatment rates are still low, ranging from 3.4 to 9.1% for patients with IS (Scholten *et al*., 2013).

In the Framingham Heart Study (Romero and Wolf, 2013), among survivors of IS, follow-up at six months after stroke showed that 26% were dependent for activities of daily living (ADL), 50% had reduced mobility or hemiparesis, 19% had aphasia and 35% exhibited signs of depression (Ma V.Y. *et al*., 2014).

Hemorrhagic Stroke

Spontaneous ICH, the second most common subtype of stroke, is defined as non-traumatic bleeding into the brain tissue, which may extend into the ventricles and subarachnoid space (de Oliveira Manoel *et al*., 2016). It affects more than 5 million people worldwide annually (Krishnamurthi *et al*., 2013) and its most important modifiable risk factor is chronic arterial hypertension (Ariesen *et al*., 2003). ICH survivors are more frequently left with severe disability, when compared to IS patients. In some series, less than 40% of patients regained functional independence (Qureshi *et al.*, 2009) and death rates at 1 month after ICH may be as high as 40% (van Asch *et al*., 2010).

Cerebral Venous Thrombosis

Cerebral venous thrombosis (CVT) is not as common as ischemic stroke or intracerebral hemorrhage, representing about 0.5% to 1% of all strokes (Stam, 2005). It affects mainly adults in their third and fourth decades, with an estimated incidence of 4 cases per million of the population (Algahtani and Aldarmahi, 2014).

Clinically, CVT may present as isolated headache, symptoms of elevated intracranial pressure, seizures, focal lobar syndrome or decreased level of consciousness. The main risk factor is an underlying hypercoagulable state, either genetic (hereditary thrombophilias) or acquired (oral contraceptives, pregnancy and puerperium, smoking habits, infection - especially mastoiditis -, underlying malignancy, and head injury - skull fractures extending to a dural venous sinus) (Algahtani and Aldarmahi, 2014).

Treatment is based on temporary anticoagulation and long-term prognosis is usually favorable. Nevertheless, about 15% of patients remain dependent or die, particularly if there is a diagnostic delay (Ferro *et al*., 2009).

GENETIC SUSCEPTIBILITY TO CEREBROVASCULAR DISEASE

Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an autosomal dominant, inherited, small artery disease which causes a combination of cognitive

impairment, migraine with aura, lacunar ischemic infarction and mood alterations. The pathology results from *NOTCH3* gene mutations, an exon located on chromosome 19p13.2 – p13.1 (Bersano *et al*., 2017).

CADASIL has an estimated prevalence of 10.7 per 100.000 individuals and is now considered the most common cause of inherited stroke and vascular dementia in adults. Ischemic strokes usually occurs between 30 and 66 years of age (medium age of 49 to 57 years) (Majersik, 2017; Moreton *et al*., 2014).

The *NOTCH3* gene encodes for a 2321-amino-acid-long single pass transmembrane receptor protein (Joutel *et al*., 1996) and is mostly expressed in the vascular smooth muscle cells of small arteries and pericytes of the brain (Joutel *et al*., 2010). This receptor is composed by a large extracellular domain containing 34 tandem epidermal growth factor like repeats, as well as transmembrane and intracellular domains. THE EGF-like domains are formed by 6 cysteine residues, which form 3 disulfide bridges that stabilize the EGF-like domain structure (Smith *et al*., 2008). There are more than 150 documented *NOTCH3* gene dominant mutations that can cause CADASIL and most of them are missense mutations. These mutations result is alteration of the number of cysteine residues in one of the 34 EGF-like domains, which causes tottering disulfide bridge formation in the mutant extracellular domain, with increased multimerization properties. These alterations may impair arterial differentiation, maturation of muscle cells and also blood pressure regulation. Nonetheless, the way this correlates with neurodegeneration and dementia remains uncertain (Smith *et al*., 2008).

As for clinical features, migraine is found in 70% of patients, typically with aura (Eikermann-Haerter *et al*., 2011). Stroke or transitory ischemic attack (TIA) happens in 61%, commonly in the absence of typical cerebrovascular risk factors (Singhal *et al*., 2004). Cognitive impairment is observed in 48%, with prominent reduction in executive function and processing speed (Chabriat et al., 2016), and psychiatric disorders are seen in 47% (Eikermann-Haerter *et al*., 2011).

Diagnosis of CADASIL is based on clinical history and complementary diagnostic tests, such as MRI, skin biopsy (with accumulation of granular osmophilic material – GOM) and genetic tests of *NOTCH3* gene exons, the latter being considered as the gold-standard diagnostic tool (Peters *et al*., 2005; Joutel *et al*., 1997).

No specific treatment has been established yet, so treatment is focused on symptoms' control and management of vascular risk factors (Di Donato et al., 2017).

Homocysteine

Serum elevation of homocysteine is an independent risk factor for either cerebrovascular, coronary and peripheral arterial occlusive disease or peripheral venous thrombosis (Fridman, 1999).

Homocysteine is an amino acid formed by the demethylation of methionine. In healthy individuals, it is catalyzed to cystathionine by cystathionine beta-synthase, one of the pyridoxal phosphate-dependent enzymes. Following that, homocysteine is remethylated to methionine by methionine synthase, a cyanocobalamin-dependent enzyme. Therefore, nutritional conditions such as vitamin B12, vitamin B6 or folate deficiencies may contribute to the increasing of plasma homocysteine levels (Ganguly and Alam, 2015).

Elevation of plasmatic homocysteine causes atherosclerosis by several mechanisms: not only it promotes direct damage to the endothelium, but also stimulates proliferation of smooth muscle cells, enhances peroxidation of low-density lipoprotein and increases platelet aggregation, affecting the coagulation system (Ganguly and Alam, 2015).

As a result of the disruption of the BBB, after a stroke for example, the brain is exposed to constituents of plasma, including homocysteine (Sharma *et al*., 2015). This molecule is also a direct neurotoxic

agent, acting through the overstimulation of N-methyl-D-aspartate (NMDA) receptors. The excessive stimulation of NMDA receptors allows high levels of calcium to enter the nerve cells, a pathological process known as excitotoxicity. This contributes to neuronal damage and neurodegeneration (Ganguly and Alam, 2015; Sharma *et al*., 2015).

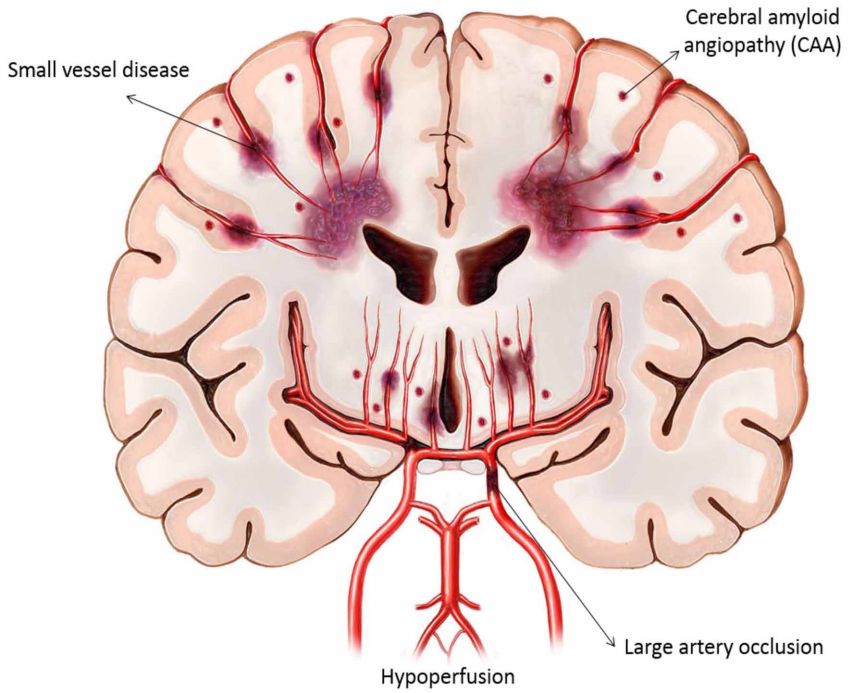
VASCULAR COGNITIVE IMPAIRMENT

The ways that vascular brain injury contributes to cognitive impairment depend on the patient and the nature of the vascular insult itself (Figure 2). Location of lesions within networks with an important role in cognition, and also size and number of lesions are important determinants of the type and severity of cognitive impairment (Alexander *et al*., 1986).

The co-occurrence of vascular and neurodegenerative pathologies, such as AD (amyloidopathy and tauopathy) and Lewy body disease (synucleinopathy) occurs rather frequently, especially with increasing age (Schneider *et al*., 2007; Arvanitakis *et al*., 2011; Soontornniyomkij *et al*., 2010). Sufficient evidence suggests that neurodegenerative lesions and ischemic infarcts combine to increase the risk of cognitive decline and dementia (Schineider *et al*., 2004; White, 2009; Troncoso *et al*., 2008; Toledo *et al*., 2013).

Cognitive decline and behavioral changes may reveal vascular cognitive impairment even in the absence of acute symptoms like stroke; in fact, this is possibly by far the most frequent situation (Godefroy, 2013). These "silent infarcts" constitute a major cognitive risk factor. Thus, diagnosis of VCI may be very difficult and needs to be evaluated in two different settings: the post-stroke outpatient and non-stroke patients evaluated for cognitive complaints (Godefroy *et al*., 2013; Moorhouse and Rockwood, 2013).

Figure 2. Mechanisms underlying vascular cognitive impairment.



Epidemiology

Previous meta-analysis and systematic reviews have shown that the prevalence of major post-stroke cognitive impairment ranges from 7% to 67.3%, depending on the study setting (hospital or population-based studies), type of stroke (ischemic or hemorrhagic), frequency of pre-stroke dementia, frequency of recurrent stroke and the post-stroke interval (Middleton *et al.*, 2014). Compared with normal controls, previous stroke doubles the risk of subsequent dementia over 10 years (Ivan *et al*., 2004). History of diabetes and high systolic blood pressure are associated with a greater risk of dementia in late life, especially among those with the apolipoprotein Ɛ4 (APOE Ɛ4) allele. The relationship between APOE Ɛ4 and diabetes as an increased risk factor for dementia seems to rely on an increased risk of cerebral amyloid angiopathy formation (Peila *et al*., 2002; Elias *et al*., 2005).

Clinical Subtypes of Vascular Cognitive Impairment

Poststroke Dementia

Cognitive dysfunction is among the most common and severe consequences of stroke, considered by patients and caregivers one of the top 10 priorities in post-stroke long-term care (Pantoni, 2017; Pollock *et al*., 2014).

Short-term incidence of post-stroke dementia may be as high as 40% (Pendlebury and Rothwell, 2009), while mild cognitive impairment (MCI) might be observed in as much as 80% of patients (Popovic *et al*., 2007). Long-term incidence of dementia starting from 3 months after stroke has been estimated to be 3% to 6% per year, with slightly lower rates reported for patients with TIA and minor stroke (Pendlebury and Rothwell, 2009).

Risk factors for cognitive impairment at the time of stroke include older age, lower education levels, diabetes mellitus, atrial fibrillation, smoking, female sex and pre-stroke cognitive decline (Mandzia *et al.,* 2016; Allan *et al*., 2011; Pendlebury, 2009; Yang *et al*., 2015). As for those related to stroke itself, the most important predictors are left hemisphere stroke, stroke severity, early seizures, hypoxic ischemic episodes and hypotension. Brain imaging predictors of post-stroke dementia include silent brain injury, white matter hyperintensities and medial temporal lobe atrophy (Yang *et al*., 2015; Mandzia *et al.,* 2016).

Liu and colleagues, in a recent study with 72 persons with cognitive impairment after stroke/TIA, found that those with positive amyloid-β deposition after the index event, as detected by positron emission tomography (PET) imaging with C-labeled Pittsburgh Compound-B (C-PIB), experienced a more severe and rapid cognitive decline on cognition evaluation by the Mini Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) during a 3-year follow-up as compared with those with negative amyloid PET scans (Mandzia *et al.,* 2016).

Data on the cognitive profile of post-stroke dementia and post-stroke MCI is somewhat limited. The most pronounced and early abnormalities are deficits in executive function and attention, but other cognitive domains (orientation, memory and language) are also affected, particularly in those with more severe cognitive impairment (Stephens *et al*., 2004). Therefore, recent secondary stroke prevention trials are including cognitive endpoints to their study protocols, such as the Cambrigde Assessment Mental Disorder in the Elderly, section B (CAMCOG-R), a standardized test (maximum score of 107), encompassing memory, orientation, language, comprehension, praxis, executive function and calculation (Diener *et al*., 2008; Pearce *et al*., 2014).

Strategic Infarct Dementia

Dementia can also occur after a single strategic infarct. The left angular gyrus, the inferomesial temporal gyrus and the medial frontal lobe are considered strategic regions perfused by large arteries. When it comes to executive functions, the frontal-subcortical loops are considered strategic networks located in the prefrontal cortex, the dorsomedial and the anterior thalamic nuclei, the head of the caudate, the anterior limb of the internal capsule and the capsular genu (Cummings *et al.*, 1993; Duering M *et al.*, 2011).

Subcortical Vascular Dementia

By far, the most common cause of vascular cognitive impairment is subcortical vascular dementia (SVD), which typically manifests itself with white matter lesions, termed white matter hyperintensities (WMH) on MRI and lacunes, mainly confined to subcortical white and grey matter (Vermeer *et al.*, 2002).

In the general population, prevalence rates for WMH rise from 50% around 45 years of age to 95% for people in their eighties (Wen *et al.*, 2009; de Leeuw *et al.*, 2001). Small brain infarcts are also common, and like WMH, they have been shown to be associated with cognitive deficits and dementia (Vermeer *et al.*, 2007; Debette *et al.*, 2010).

In addition to post-stroke dementia and the strategic location infarct dementia caused by small vessel disease, subcortical arteriosclerotic encephalopathy and lacunar state are included in the subcortical vascular dementia (Dozono *et al.*, 1991).

Lacunar state is a striking phenotype of SVD, characterized by multiple lacunar infarcts in thalamus, the basal ganglia, and white matter. Clinical features comprise abrupt onset hemiparesis, lack of volition, dysarthria, akinetic mutism, pseudo-bulbar palsy and affect, urinary incontinence and small-stepped gait (Dozono *et al.*, 1991).

The consequences of SVD may extend into the cortex, manifesting both as microscopic vascular lesions and cortical atrophy and now cortical changes are considered a clinically relevant component of SVD (Duering *et al.*, 2015; Peres *et al.*, 2016; Gouw *et al.*, 2011; Smith *et al*., 2012).

Subcortical arteriosclerotic encephalopathy, the so-called Binswanger's syndrome, is characterized by demyelination of deep white matter, attributed to stenosis of deep penetrating arteries (Roman, 1987; Bennett *et al.*, 1990). The typical clinical triad is comprised of a slowly progressive dementia, urinary incontinence and gait apraxia. Binswanger's disease may easily be misdiagnosed as normal pressure hydrocephalus because of similar clinical findings (Erkinjuntti *et al.*, 2000).

Clinical criteria for SVD include executive dysfunction, cognitive slowing, extrapyramidal signs, depression and gait disturbances (Erkinjuntti *et al.*, 2000).

Multi-Infarct Dementia

The presence of multiple infarcts has been recognized as a cause of dementia (Hachinski *et al.*, 1974), and both the number and the volume of the lesions are related with impaired cognitive performance and higher risk of dementia (White *et al.*, 2005; Sonnen *et al.*, 2007; Vemuri *et al*., 2015). There are no clear criteria for what should be considered a threshold of overall volume of brain lesions required for the occurrence of the VCI or vascular dementia. Other than that, countless factors need to be taken into account to this definition. First and foremost, some brain regions (pre-frontal cortex, for example) are more eloquent to cognitive functions than others; second, many patients have associated comorbidities

such as AD; and finally, there are individual variations in the ability to compensate for both vascular and neurodegenerative pathologies (Zieren *et al.*, 2013; Cordonnier *et al.*, 2010).

Silent Vascular Brain Injury

The prevalence of silent brain injuries is up to 5 times greater than that of symptomatic stroke and, as shown in the Rotterdam study, they are common in elderly people (Vermeer et al, 2002). It increases progressively with age and is even higher in subjects with risk factors for vascular disease (Vermeer *et al.*, 2007); most silent infarcts are related to SVD. The Rotterdam scan study concluded that the presence of silent brain injury doubled the risk of dementia, and also led to worse results in the performance of cognitive testing and a steeper decline in the cognition (Vermeer *et al.*, 2003). Non-thalamic infarcts were related to decreased psychomotor speed, whereas thalamic infarcts were related with worsening of memory performance. Recent studies have shown similar results (Debette *et al.*, 2010).

Microinfarcts: Imperceptible Lesions

Cerebral microinfarcts are ischemic injuries almost exclusively detected through brain biopsy, typically smaller than 1 mm (Sonnen *et al.,* 2007; Vemuri *et al.,* 2015). Usually attributable to SVD, they could also be related to vasoconstriction, microemboli and cerebral hypoperfusion. The presence of 1 or 2 microinfarcts in a cerebral biopsy specimen corresponds with the presence of hundreds of microinfarcts throughout the brain (Cordonnier *et al.,* 2010). However, this type of injury is also common in patients with AD, as wells as otherwise healthy people. Additionally, some cohorts have shown that the presence of microinfarcts increases the risk of dementia (Arvanitakis *et al, 2011)*. The cognitive profile of patients with microinfarcts is not well established, but it may be associated with disturbances in semantic and episodic memory, and perceptual speed (Arvanitakis *et al.,* 2011).

Microbleeds and Cortical Superficial Siderosis

Cerebral microbleeds (MBs) are round hypointensities, smaller than 10 mm in diameter, apparent on gradient echo T2*-weighted scan MRI (Cordonnier *et al.,* 2010). MBs are usually considered in the presence of SVD caused by either cerebral amyloid angiopathy (CAA) or hypertensive vasculopathy (Yates *et al.,* 2014). Strong evidence suggests that MBs discontinue structural connectivity and, consequently, network function (Reijmer *et al.,* 2015). Similar to strategic infarcts, the location of MBs is of the utmost importance, as lobar and deep MBs are associated with hypertensive vasculopathy and only lobar MBs are related with CAA (Yates *et al.,* 2014).

Cortical superficial siderosis (cSS) is linear deposits of blood products within the leptomeninges, subarachnoid space and superficial cortical layers. This condition is closely connected to CAA (Linn *et al.,* 2010).The prevalence of cSS in patients evaluated in memory clinics ranges from 2% to 6%, whereas in non-demented elderly people it is estimated to be around 0.5%. (Zonneveld *et al.,* 2014; Wotlenweber *et al.,* 2014; Na *et al.,* 2015). There is some association between cSS and the apolipoprotein Ɛ4 allele, confirming the relation between cSS and CAA (Keage *et al.,* 2009). Despite that, the process by which cSS affects cognition still needs to be better understood.

Cerebral Amyloid Angiopathy

Cerebral amyloid angiopathy (CAA) is a consequence of the accumulation of β-amyloid in the media and adventitia layers of small and mid-sized arteries of the brain. It is an important cause of lobar hemorrhage and dementia in the elderly (Charidimou *et al.,* 2012).

The incidence of CAA is highly age-dependent; very rarely presenting before 50 years of age, whereas in a study with 784 autopsies, 12% of people over 85 years old exhibited pathological features of CAA (Greenberg *et al.,* 1997). There is a significant association with AD, and in these patients the frequency of CAA may reach 98% (Keage *et al.,* 2009).

Although asymptomatic in most cases, CAA might result in dementia, ICH and transient neurologic spells. ICH is the most recognized result of CAA, and this diagnosis should always be suspected in patients above 55 years with consecutive cortical bleedings (Passero *et al.,* 1995). It is known that CAA contributes to cognitive impairment and dementia - moderate to severe CAA was related to lower performances in some specific cognitive domains, mainly perceptual speed and episodic memory (Boyle *et al.,* 2015).

Although definitive diagnosis can only be made with full postmortem examination, according to the Boston Criteria (Knudsen *et al.,* 2001), CAA has typical neuroradiological findings that lead to *in vivo* diagnosis. Gradient echo T2*-weighted brain MRI allows the detection of cerebral MB, typically found in the cortical-subcortical transition over the posterior regions of the brain (Pendlebury *et al.,* 2009). White matter changes, convexity subarachnoid hemorrhage, cSS and silent acute ischemic lesions also represent the spectrum of hemorrhagic and ischemic manifestations of CAA seen on brain MRI (Pendlebury *et al.,* 2009).

Currently, there are no specific disease-modifying agents available for treating CAA. In subjects with previous ICH, the adequate management of hypertension is a wise strategy to avoid a new episode of bleeding, as patients with ICH have an annual recurrence risk of up to 10%, and anticoagulant therapy appears to increase this risk by 7 to 10 fold (Izumihara *et al.,* 1999).

Hypoperfusion Dementia

Reduction of cerebral perfusion can lead to transient or permanent ischemia, and consequently to cognitive decline. The RECON trial (Randomized Evaluation of Carotid Occlusion and Neurocognition) showed that hemodynamic failure was associated with cognitive impairment (Marshall *et al.*, 2012). Histopathologically, global hypoperfusion induces border zone infarcts, hippocampal sclerosis and cortical laminar necrosis contributing to cognitive impairment (Jellinger KA *et al.,* 2013).

Mixed Dementia

Many patients with dementia have a high prevalence of mixed disease with vascular and AD pathology contributions (Schneider *et al.,* 2007). A longitudinal cohort study (Rush Memory and Aging Project) found that the most cases of dementia in community-dwelling older persons were of the mixed type, due to a combination of vascular and AD-type pathology (Schneider Ja *et al.,* 2004). Subjects with multiple pathologies had a 3-times higher chance of developing dementia in their life. In most cases, it is difficult to say how these multiples pathologies contribute individually to cognitive decline, but it is assumed that vascular brain injuries lower the threshold of AD-pathology required to induce dementia. On the other

hand, AD-like pathology increases the chance of dementia after stroke (Toledo *et al.,* 2013; Mathews FE *et al.,* 2009). The relationship between AD-like and vascular pathology remains quite complex considering its additive and/or multiplying effect (Launer *et al.,* 2011; Chui *et al.,* 2015).

Atrophy of the hippocampus and amnesia are consistent with early AD, while the cognitive profile of vascular cognitive impairment is widely variable and depends on size and region of vascular lesions. Mostly, the cognitive profile of mixed dementia is dominated by that found in isolated AD.[149] Emerging amyloid PET scans findings could help to differentiate between pure dementia from mixed dementia (Heiss *et al.,* 2016).

TREATMENT

The general principles for management of VCI, MCI and dementia are basically the same and encompass the treatment of comorbidities, adequate control of the risk factors, treatment of psychological and the behavioral symptoms, providing support to the patients themselves and their caregivers, with the goal of maximizing independence for ADLs. Trials with acetylcholinesterase inhibitors showed at best only modest effects on global functioning, and discreet improvements in cognition. Despite the small effects on cognition, it is reasonable to consider using donepezil in patients with vascular dementia (Pase *et al.,* 2017; O'Brien and Thomas, 2015).

PREVENTION

Prevention includes control of the lifestyle risk factors (such as lower educational level, Western diet, sedentary lifestyle, smoking habit and obesity) and can be separated in primary prevention with early identification and reduction of risk factors for atherosclerosis, such as arterial hypertension, type 2 diabetes mellitus and dyslipidemia; and secondary stroke prevention (Pase *et al.,* 2017).

FUTURE RESEARCH DIRECTIONS

Currently, the most effective strategy to eliminate the vascular contributions to neurodegeneration is the aggressive control of vascular risk factors. Primary prevention politics, early diagnosis and adequate long-term care of stroke victims are important ways to prevent and/or reduce the morbidity associated with neurodegenerative disorders (Pase *et al.,* 2017).

In 2016, the Framingham Heart Study demonstrated a progressive decrease in the incidence of dementia (Pase *et al.,* 2017). This could be explained by increasing scholarity, better cardiovascular health and better management of stroke risk factors. Therefore, there is great hope that the vascular contributions to cognitive impairment can be prevented and treated. For therapeutic development, the most success has been achieved with symptomatic treatments. The scientific community is still hoping for a disease modifying therapy, which should probably aim to improve neurovascular unit function or enhance cerebral resilience to injury (Smith *et al.,* 2017).

CONCLUSION

There is a close interaction between stroke and neurodegenerative disorders, predominantly AD. From the disruption of the vascular unit to neurological progressive deterioration, there is a broad spectrum of pathologies, including white matter brain abnormalities, transient ischemic attacks, symptomatic stroke and vascular cognitive impairment, that contribute to varying degrees. However, further studies are still needed to uncover the link between cerebrovascular disease and neurodegeneration in all its aspects.

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Chapter 8
Zinc and Neurodegenerative Disorders

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ABSTRACT

Zinc (Zn) is an essential trace element that is abundantly present in humans. Despite its importance in normal brain functions, alterations in zinc homeostasis cause various neurological pathologies such as dementia, Parkinson's disease, Prion's disease, etc. A growing body of evidence has shown that zinc might play a dual role: in which both zinc depletion and excess zinc cause severe damage and hence neurotoxicity develops. Homeostatic controls are put in place to avoid the accumulation of excess zinc or its deficiency. This cellular zinc homeostasis results from the actions of a coordinated regulation effected by different proteins involved in the uptake, excretion, and intracellular storage or trafficking of zinc. Further investigation has also shown the role of endogenous carnosine (beta-alanyl-L-histidine) in binding excess zinc. Hence, it has the ability to prevent neurotoxicity. Also, the role of a zinc-rich diet cannot be overemphasized. The authors of the chapter, however, provide an insight into the link between zinc homeostasis and neurodegenerative disorders (NDs).

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INTRODUCTION

One of the most important mineral identified in the human system is zinc, a crucial trace element in the metabolic activities, cell division, immune system and as a co-factor of over 300 well-known enzymes (Hambidge, 2000) in the control of different cellular activities and signaling pathways expedient for both neuro and systemic operation (Takeda, 2000). This divalent metal constitutes a cofactor of a number of enzymes like carbonic anhydrase, alcohol dehydrogenase, alkaline phosphatase, phospholipase, carboxypeptidase, zinc/copper superoxide dismutase (SOD) and other allosteric proteins (McCall *et al*., 2000). This is the reason why zinc is referred to as antioxidative element in human beings because these enzymes which have zinc as cofactor are involved in combating oxidative stress (Feng *et al*., 2013). Zinc is used to make the hormone thyrotropin-releasing hormone (TRH) that signals the thyroid to make thyroid hormones. It converts the protein we eat into amino acids, including tyrosine which powers the thyroid hormone production. Finally, it is involved in the making of triiodothyronine (T3) the active form that is used in the muscles (Soh *et al*., 2012). Furthermore, in the formation of bone, zinc is used by enzymes in the production of collagen and alkaline phosphatase (ALP), which are important for bone formation (Hyun-Ju *et al*., 2010). It is also used to make calcitonin, a hormone that inhibits the breakdown of bone. Zinc is also a critical component of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) polymerases and has a fundamental role for nucleic acid metabolism and gene activation and repression. 30% of the zinc found in a cell is found in the nucleus (Ali *et al*., 2012). This makes sense as it is very involved with DNA and the replication of cells and proteins needed by the body. At the transcription level during protein expression, zinc fingers structure enables transcription factors to anchor to DNA helix. Cyclins and cyclin-dependent kinases are directly influenced by this divalent metal and in essence regulate cell cycle. (Chesters and Petrie, 1999). The activities of many growth factors are zinc dependent, hence cell proliferation is regulated by the concentration of zinc ions (Hamza *et al.,* 2012). Zinc functions as a neurotransmitter (Tóth, 2011); in addition, it modulates the function of glutamate and other neurotransmitter receptors. Recent studies have indicated zinc to play important signaling roles in different human biological activities (Hirano *et al*., 2008). Zinc deficiency in neonates is known to cause dwarfism, the retardation of mental and physical development, immune dysfunction, furthermore, learning incapacities and in grown-up certain neurodegenerative issue, for example, sadness, schizophrenia, Alzheimer's diseases (AD), Parkinson's diseases (PD), maturing, or amyotrophic horizontal sclerosis (AHS) (Prasad, 2009).

The mechanism of action of zinc is that, it modulates certain receptors at the post synaptic cleft. During the neuronal activity, when zinc with glutamate is released from synaptic vesicles into synaptic cleft, zinc interactions with postsynaptic receptors may occur (Morris and Levenson, 2012). The well-known process of zinc inhibition of *N*-Methyl-D-aspartic acid receptors (NMDAr) in synapses is one of such interaction. Excessive influx of zinc into neurons has been found to result in neurotoxicity and damage to post synaptic neurons. Zinc is additionally proposed as a hazard factor for melancholy, AD, maturing and other neurodegenerative issue (Izumi, 2006).

Then again, a developing assemblage of proof proposes that a lack as opposed to an overabundance of zinc prompts an expanded hazard for the improvement of neurological issue (Szewczyk, 2013). Without a doubt, zinc insufficiency has been appeared to influence neurogenesis and increment neuronal apoptosis, which can prompt learning and memory deficiencies. There is need for homeostatic controls to be put in place to avoid the accumulation of excess zinc or its deficiency. Disturbances of zinc homeostasis are considered as important factors in neurodegenerative brain disorders (Konoha *et al*., 2006). The involve-

ment of zinc in the pathology of neurodegenerative has been reported hundreds of times. It is, however, still a matter of debate whether the disease progression can be influenced by modifying zinc in the diet or regulating amount of zinc in the body (Foster *et al*., 2012). Zinc activities could be as a supporter of the sickness in one section, and as a defender in another. Therefore, zinc may assume a part like that of Janus, who is the antiquated Roman divine force of entryways and who has 2 unique countenances, in the cerebrum: both zinc exhaustion and abundance zinc make serious harm neurons (Dai and Masahiro, 2013). This chapter aims at discussing the current findings relating to neuronal zinc metabolism and the way in which zinc can modulate normal brain activity. To be discussed also is the contribution of zinc to the formation, aggregation, and mechanism of zinc induced toxicity, the contribution of zinc to the pathogenesis of NDs. Possible treatment will also be looked into for zinc induced neurotoxicity.

BACKGROUND

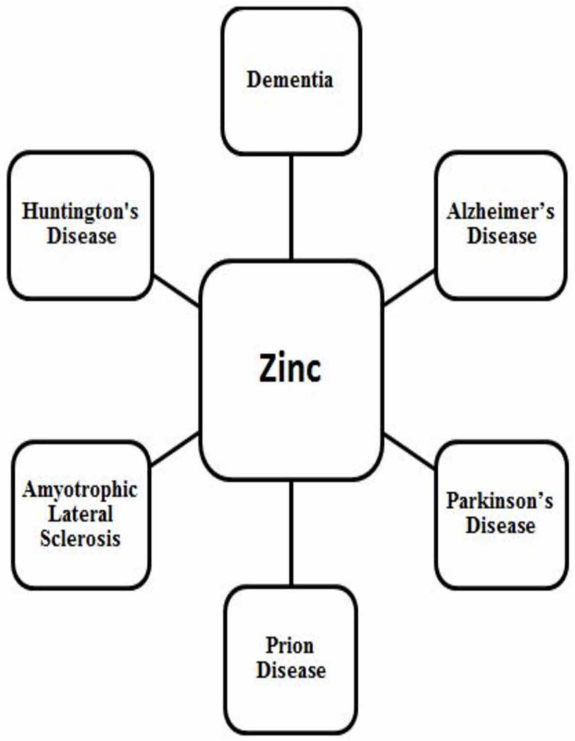
NDs such as AD, PD, Huntington's disease (HD), AHS and Prion disease (PrD) etc. are the major neurological diseases being reported lately (Vijay *et al*., 2016 a). Unfortunately, the pathogenesis of these chronic NDs is not fully understood, and current treatments do not stop or slow down progression of these pathological conditions. Increased accumulation of heavy metals, such as iron (Fe), zinc and manganese (Mg) in the brain patients emphasizes their possible role in NDs (Dexter et al., 1991). Knowledge about zinc has rapidly evolved over the years with the last two decades have brought, interesting new insights about the role of zinc in molecular and cellular processes as well as health and disease (Bernadeta, 2013) stated in Figure 1.

Actual fields of research in neurobiology are not only aimed at understanding the different aspects of central nervous system but also at developing strategies useful to preserve brain compensatory capacity and to prevent the onset of NDs. Consistent with this trend much attention has been addressed to zinc metabolism (Mocchegiani *et al*., 2005).

ZINC AND THE CENTRAL NERVOUS SYSTEM

In the central nervous system (CNS), zinc occurs in two forms: the first being tightly bound to proteins and, secondly, the free, cytoplasmic, or extracellular form found in presynaptic vesicles (Bernadeta, 2013). In the brain, zinc is present in its free ionic form (Zn^{2+}) within synaptic vesicles, mostly at the glutamatergic terminals (Frederickson *et al.,* 2000; Paoletti *et al*., 2009; Sensi *et al.,* 2011). In this role, zinc is highly concentrated in the synaptic vesicles of a specific contingent of neurons called "zinc containing" neurons, which co-release zinc with the neurotransmitter glutamate upon excitation. The majorities of these "gluzincergic" neurons (Frederickson and Bush, 2001) have their cell bodies located in either the cerebral cortex or the limbic structures of the forebrain (Slomianka *et al*., 1990), and so an extensive network uniting limbic and cerebrocortical functions is created (Koh, 2005). These neurons are discovered solely in the fore mind, where in well evolved creatures they have advanced into an intricate and expand associational system that interconnects a large portion of the cerebral cortices. There is increasing evidence that zinc not only act as neurotransmitter to mediate intercellular communication, but also act as intracellular signaling molecule much like calcium (Hirano *et al*., 2008).

Figure 1. The relationship between zinc and neurodegenerative disorders



Recent studies have suggested that secreted Zn^{2+} plays crucial roles in information processing, synaptic plasticity, learning, and memory (Vijay *et al*., 2016 b). Indeed, Zn^{2+} has been shown to be essential in the hippocampus for the induction of long-term potentiation, a form of synaptic information storage that has become a well-known paradigm for the mechanisms underlying memory formation (Tamano and Takeda, 2011).

Highest concentrations of zinc in the brain are found in the hippocampus, amygdala, cerebral cortex, thalamus, and olfactory cortex (Frederickson *et al*., 2000). Because the hippocampus is the region of the brain which plays a critical role in memory, learning and neurogenesis, the impact of zinc deficiency or zinc supplementation on these processes will be critical (Muhammad and Sandrine, 2012). Indeed, it was found that a zinc deficient diet, decreases the number of progenitor cells and immature neurons in the dentate gyrus (DG) in rodents and that reversal to a normal diet containing zinc restored a number of these cells (Gao *et al*., 2009; Suh *et al*., 2009). In human, the dietary zinc is mostly absorbed in duodenum, ileum and jejunum by active transport. Zinc is transported from blood trough blood brain barrier system, mostly in the form of complexes with amino acids, especially L-histidine and cysteine (Costello *et al*., 2011; Pavlica and Gebhardt, 2010).

ZINC HOMEOSTASIS AND NEUROTOXICITY

Intracellular zinc is tightly controlled because zinc is essential but potentially toxic. Adequate zinc level is critical for CNS development and the differentiation of nervous stem cells in mammals (Levenson and Morris, 2011; Xu *et al*., 2011). The exact controls of zinc homeostasis are basic for focal sensory system and for the entire creature. As perturbations of zinc either above or below physiological concentrations are detrimental to cell survival, neurons must maintain tight homeostatic control on their zinc content.

Disturbances of zinc homeostasis are considered as important factors in neurodegenerative brain disorders. Adequate zinc intake is crucial for proper cognitive functions, especially in children and elderly human (Brewer, 2010; Lovell *et al*., 2006; Levenson and Morris, 2011; Pavlica and Gebhardt, 2010; Toren *et al*., 1996; Yasuda *et al*., 2011). Zinc lopsidedness can come about from inadequate dietary admission, as well as from disabled movement of zinc transport proteins and zinc subordinate direction of metabolic pathways. Under normal CNS physiology, homeostatic controls are put in place to avoid the accumulation of excess zinc or its deficiency (Szewczyk, 2013). This cellular zinc homeostasis results from the actions of a coordinated regulation effected by different proteins involved in the uptake, excretion and intracellular storage/trafficking of zinc. Several different groups of proteins are involved in managing cellular levels of zinc. The first group consists of are membranous zinc transporters (ZnTs) mediating the zinc efflux from cells or influx into cellular compartments or organelles (Huang and Tepaamorndech, 2013). The second group is members of the zip family (zinc-regulated and iron regulated transporter proteins) that promote zinc transport from the extracellular space or from intracellular vesicles to the cytoplasm (Cousins *et al*., 2006). The changes in zinc levels can be caused by the altered expression of zinc transporters, especially ZnT1, 3, 4, 6 (Zinc transporters) and metallothionein proteins. The extracellular concentration of zinc in hippocampus and cerebral cortex depends on the activity of zinc transporter-ZnT3 (Math and Gordon, 1997). The abnormally increased activity of ZnT3 may additionally elevate the extracellular zinc and in that way it induces the formation of β-amyloid plaques. β-amyloid plaques are the protein fragment which is also a biomarker to identify people at risk for AD (Christian, 2011). This process is thought to be the first step in zinc homeostasis disruption in course of that pathological state. The evidently, unbalanced homeostasis of this biometal affects cell function. Free or chelatable zinc which is not associated with proteins or amino acids ligands appears to participate in the neurotoxic accumulation of zinc in neurons. Damage to the CNS induced by seizure, trauma, or ischemia can all result in the accumulation of zinc from vesicular and non-vesicular zinc pools (Deborah and Cathy, 2012). Under these conditions, excessive free zinc is released into the synaptic cleft and in return, zinc modulates a number of postsynaptic neuronal receptors, with excess zinc leading to death of neurons (Inoue *et al*., 2015). There is evidence that the influx and accumulation of excess zinc causes excitotoxicity, generates oxidative stress, and impairs neuronal energy production (Morris and Levenson, 2012). *N*-methyl-D-aspartate receptors (NMDA), for example, have a high-affinity zinc-binding site that can bind synaptically released zinc at nanomolar concentrations. Zinc is thus responsible for fine-tuning the activity of these important glutamate receptors. Additionally, there is now evidence of mutations in NMDA receptors with altered zinc affinities that may have implications for neurodevelopment leading to a variety of developmental disorders including childhood epilepsy and cognitive deficits (Serraz *et al*., 2016).

Other toxic effects that zinc can potentially induce include the disruption of normal tubulin assembly (Kress *et al*., 1981), and the over activation of calcium-mediated enzymes (Csermely *et al*., 1988). Furthermore, zinc reacts with the thiol and imidazole moieties of many proteins (Chvapil *et al*., 1972) thus, can disrupt structure and function by binding proteins.

ZINC TOXICITY AND NEURODEGENERATIVE DISORDERS

Neurodegenerative disorder (ND) is an umbrella term for a range of conditions which primarily affect the neurons in the human brain. Neurons are the building block of the nervous system which includes the brain and spinal cord. NDs are incurable and debilitating conditions that result in progressive degeneration and / or death of nerve cells. This causes problems with movement called ataxia, or mental functioning called dementias (Choi *et al*., 1988; Perry *et al*., 1997).

In physiological concentrations, zinc exhibits neuroprotective activity, but at high concentrations, zinc can be neurotoxic (Cote *et a*l., 2005; Plum *et al*., 2010). Also, effects of malnutrition may be particularly relevant for NDs as the brain is the organ with the highest zinc levels (in mean: approx. 150 μmol/l) separated in delicately balanced pools (Weiss et al., 2000). Zinc dyshomeostasis have also been reported in such diseases as depression and attention deficit hyperactivity disorder (ADHD), Senile dementia which can be classified into AD and vascular dementia (VD), PD as well as in brain ischemia and traumatic brain injury (Bernadeta, 2013).

Zinc and Senile Dementia

Senile dementia is characterized by a decrease in cognitive abilities. This may include the person's ability to concentrate, to recall information, and to properly judge a situation. Senility is a deterioration of body and mind associated with advanced aging. Senile dementia is mostly divided into AD and vascular-sort dementia (VSD) (Mizuno and Kawahara, 2013). VD is a degenerative cerebrovascular disease, and its peril factors join age, the male sex, diabetes, and hypertension. The most generally perceived sort of VSD is caused by a movement of little strokes or ischemia (Lee *et al*., 2000).

In ischemic conditions, a considerable amount of zinc (up to 300 μM) is associated with glutamate in synaptic clefts due to membrane depolarization. Zinc causes the apoptotic downfall of basic refined cortical neurons. Also, chelatable zinc evidently moves from presynaptic terminals into postsynaptic neuronal cell bodies. A development in intracellular Zn^{2+} levels, zinc translocation, occurs in vulnerable neurons in the districts of the hippocampus going before the start of conceded neuronal going after transient overall ischemia (Koh et al., 1996). This zinc translocation has been represented to enhance the nearness of infarcts. Thus, Zn translocation has been recognized as the primary event in the pathway of Zn-induced neuronal death. (Sensi *et al*., 2003) a process that might be involved in the pathogenesis of VSD (Plum *et al*., 2010; Weiss *et al*., 1993). Understanding the molecular mechanisms of Zn-induced neuronal death is of great importance for the treatment of VSD.

Zinc and Alzheimer's Disease

Another chronic ND is AD and it is the most common cause of dementia. It is estimated that AD represents 60– 80% of all dementia cases (Daviglus *et al.,* 2010). AD is a progressive ND that symptomatically leads to intellectual decline including memory loss, language breakdown, difficulties in learning and orientation, and changes in behavior with neurofibrillary tangles (NFTs), the aggregates of hyperphosphorylated tau protein which are most commonly known as the primary marker (Goedert *et al*., 2006). It is described as amyloid accumulation in the cerebral neuropil and vasculature. These amyloid deposits contain primarily fragments and full-length (40 or 42 residue) forms of the amyloid β-protein (Aβ) structured into fibrillar assemblies (Louise, 2000).

The neurotic highlights of AD are the collection of β-amyloid (Aβ) and the total of Aβ is recommended as the reason for neurodegeneration saw in AD (Small and Cappai, 2006). Aβ is the result of proteolytic cleavage from the amyloid antecedent protein (AAP) by the catalyst known as β-secretase or β-site AAP severing chemical 1(BACE-1) (Masters *et al.,* 1985). Although the key part of Aβ in the pathogenesis of AD is unequivocally settled now, the instrument by which Aβ prompts lethality or the causes and factors related with the hazard or movement of AD is still inadequately caught on (Paul and Harry, 2010).

One of the several hypotheses proposed for the pathophysiology of AD is the trace elements hypothesis, with zinc taking the center stage. Zinc was first described as a possible factor leading to dementia by Burnet (1981) and, since then, the knowledge base regarding the role of zinc in the pathogenesis and therapy of AD has evolved rapidly. Several path ways for the involvement of zinc in AAP processing or Aβ aggregation has been suggested. As stated earlier, AD is characterized by the presence of extracellular amyloid plaques and intracellular neurofibrillary tangles within the afflicted brain, which cause neuronal loss in the neocortex, hippocampus, and basal forebrain, leading to progressive cognitive and behavioral decline (Selkoe, 2001). It was found that AAP synthesis is regulated by zinc-containing transcription factors nuclear factor-kappa B (NF-κB) and specificity protein 1 (sp1) (Grilli *et al.,* 1996). Zinc is also involved in processing of AAP protein (Lee *et al.,* 2009).

Zinc and Prion Disease

PrD represents a group of conditions that affect the nervous system in humans and animals. In people, these conditions impair brain function, causing changes in memory, personality, and behavior; a decline in intellectual function (dementia); and abnormal movements, particularly difficulty with coordinating movements (ataxia) (Hernández *et al*.,1999). The signs and symptoms of PrD typically begin in adulthood and worsen with time, leading to death within a few months to several years. The prion protein (*PRNP*) gene provides instructions for making a protein called cellular prion protein (PrP^C), conformational change of PrP^C into pathological prion protein PrP (scrapie) leads to onset of PrD (Laura *et al*., 2007). Although the precise function of this protein is unknown, researchers have proposed roles in several important processes. These include the transport of copper into cells, protection of brain cells (neurons) from injury (neuroprotection), and communication between neurons and recently it was discovered that

it facilitates zinc uptake (Frederickson *et al*., 2006). A valuable evidence of PrP^C–zinc interaction is that not only does PrP^C facilitate zinc uptake, zinc also potently stimulates the endocytosis of PrP^C. PrP^C via α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptors directly influences the zinc content of neuronal cells (Spevacek *et al*., 2013). Hence changes in zinc levels will definitely affect the protein. PrP^C has been identified as a neuronal zinc sensor, modulating zinc binding, and promoting zinc uptake via α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, with a subsequent downstream effect on the activity of intracellular protein tyrosine phosphatases (Hajo and Lothar, 2009). Research has shown that zinc concentration decreases in PrD (Wong *et al*., 2001). Mutation in PrP^C prevents the inter-domain interactions, and disrupts the interaction between PrP^C and the AMPA receptor, providing a possible explanation for the reduction in zinc in PrD -affected brains.

Zinc and Parkinson's Disease

PD is a severe, progressive motor disorder caused by changes in the central nervous system, tightly linked to degeneration of dopaminergic neurons of basal ganglia known as substantia nigra (Pietro *et al*., 2012). PD is characterized by extensive loss of dopaminergic neurons in the substantia nigra. Recently, it has been found that zinc ions directly bind to the peptide fragments from the PD gene Park9 (Remelli *et al*., 2013). Expulsion of Zn from parkinson protein 2 (Park2) causes almost total unfurling of the protein and loss of its movement. In any case, vague and opposing outcomes exist in the writing with respect to circling Zn levels in PD patients. For instance, a few examinations detailed a lessening of circling Zn in patients with PD contrasted and wellbeing controls, and different investigations found no critical distinction or even expanded Zn levels in PD patients (Remelli *et al*., 2013).

Actually, altered metal homeostasis has been reported in PD. While zinc is required for normal functioning of the brain, its excessive exposure may lead to PD. Clinical studies with PD patients suggested significantly decreased zinc status in patient blood serum compared with healthy elders control group. Another meaningful observation concerned protein deposits connected with metal ions disturbances in patient brain compartments, which showed some similarities to those observed in AD (Brewer *et al*., 2010). Additionally, lowered zinc concentration may have influence on pathophysiology of PD by increased inflammation processes, generation of reactive oxygen species and affected neurotropic factors levels, resulted in the proceeding neuronal degeneration.

ZINC AND AGING

Aging is an inevitable process associated with progressive pathological features such as: oxidative stress, altered cell metabolism, damaged nucleic acid, or deposition of abnormal forms of proteins (Bernadeta, 2013). In the brain, aging is characterized by neuronal loss, cognitive impairment, and susceptibility to neurological disorders (Mocchegiani *et al.,* 2005). Recent progress in studies involving age related processes provide evidence that changes occurring in the brain during aging are related to zinc homeostasis and that zinc deficiency is a common cause of morbidity among the elderly (Mocchegiani *et al*., 2005). Because aging changes dietary habits as a result of physiological, psychological, and social reasons, (McClain *et al.*, 2002) the elderly may be at particular risk of a zinc deficiency and influencing malnutrition. The UK national diet and nutrition survey reported that the mean average daily intake was 8.8 mg for men and 6.9 mg for women aged 65 years or older (Smithers *et al*.,1998) while the intake for men

and women in the age range 19–64 was 10.2 and 7.4 mg/day respectively (Henderson *et al*., 2003). Data from the second and third national health and nutrition examination survey (NHANES II, NHANES III) study reported that serum Zn levels peak between the age of 18–25 years, slowly decrease in adulthood and drop off after the age of 65–70 years (Hotz *et al*., 2003). Serum Zn levels of the oldest-old (age range 90–107) were consistently found to be lower than the levels of adult (20–65 years) and elderly control groups (65–89 years) (Maret and Sandstead, 2006; Ravaglia *et al*., 2000). When adequacy of zinc intake was defined as a total intake of more than 77% of the 1989 recommended daily allowance (RDA) (12 mg for non-pregnant and non-lactating women and 15 mg for males > 11 years) only 55.6% of the total sample had an adequate intake with the elderly at particular risk of malnutrition.

In aging, zinc deficiency is usually the result of an inadequate zinc dietary intake. It has been reported that only 40% of elderly people have a sufficient intake of zinc (Andriollo-Sanchez *et al.*, 2005; Mocchegiani *et al*., 2008). Studies comparing old and young mice fed with low dietary zinc indicated that zinc is an important nutritional factor for a proper inflammatory/immune response (Kelly *et al*., 1996). Accordingly, zinc has anti-inflammatory properties and a low zinc status is associated with increased susceptibility to infection plus intracellular zinc has been found to play a key role in signaling in immune cells (Haase and Rink, 2009; Hasan *et al*., 2012). On the other hand, aging is characterized by the progressive dysregulation of immune responses. Therefore, zinc has been suggested as a good factor in providing the remodeling of some age- associated changes and also as leading to healthy ageing through the reduction of inflammation (Kahmann *et al*., 2008). The other mechanism linking age, zinc and inflammation is associated with Metallothionein (MT). It was found that ageing is associated with a higher MT expression and consequently, low availability of intra-cellular zinc for normal immune responses. On the other hand, the supplementation of zinc in aging improves immune function and leads to decreased mortality from infections (Mocchegiani *et al*., 2010). In another study, Mocchegiani *et al*. (2011) showed evidence that zinc deficiency and an altered immune response is more evident in people with a polymorphism in interleukin 6 (IL-6) and metal-response element binding transcription factor-1 (Metallothionein 1A, MT1A) and that these individuals will benefit more from zinc supplementation.

REMEDY FOR ZINC-INDUCED NEUROTOXICITY

Since zinc deficiency is prevalent in patients with NDs, the appropriate preventive measures should be considered. Sufficient endogenous buffering must normally be present to prevent release of zinc in concentrations which can cause neurotoxicity (Michelle *et al*., 2000). Hence, zinc homeostasis is necessary in the prevention and treatment of zinc neurotoxicity. The body has its own way of preventing neurotoxicity of zinc one of such is production of carnosine. Carnosine, a dipeptide has been discovered as one of the endogenous protection against zinc neurotoxicity particularly in cases of dementia (Mizuno and Kawahara, 2013). It is abundantly present in muscles of fishes, birds and mammals (Severin and Boldyrev, 1991). Carnosine play important role in body pH Balances (Abe, 2000), serve as endogenous suppressor of oxidative damages, plays protective role in zinc induced neurodegeneration in after ischemia. Carnosine has been discovered to decrease in aged animals, therefore dietary supplementation is required. The molecular mechanism of carnosine for the prevention of zinc induced neuronal death involves binding of zinc and inhibitory effect is generated (Baran, 2000). Physiologically relevant concentrations of carnosine provide a protective effect against toxicity induced by zinc. The chelating ability of the histidine residue of this dipeptide (Brown and Antholine, 1979) may contribute to its attenuation of zinc

mediated toxicity. Another means of preventing zinc neurotoxicity is modification of zinc diet in order to lower the risk of related diseases. Due to the lack of mechanisms which allow storing this biometal for a long time in the body, it is essential that zinc homeostasis be ensured by the body. It is evident that zinc supplementation may be useful in aging to prevent age-related NDs (Andriollo-Sanchez *et al*., 2005; Mocchegiani *et al*., 2008). If zinc supplementation is performed with caution, it may be beneficial for cognitive functions in several age related NDs. Another remedy for treatment of zinc neurotoxicity is treatment of cells *in vitro* and in animals with a zinc chelator, named N,N,N',N'-tetrakis (2-pyridylmethyl) ethylenediamine (TPEN), it attenuated neurological deficit, reduced the rate of neuronal apoptosis and the cerebral infarct area, increased superoxide dismutase activity and reduced plasma concentrations of malondialdehyde and IL-6 (Dilina *et al*., 2017). An alternative approach to minimizing the consequences of zinc dyshomeostasis could be to promote mechanisms which enhance reuptake.

FUTURE RESEARCH DIRECTIONS

The maintenance of discrete subcellular pools of zinc is critical for the functional and structural

Integrity of neuronal and other body cells that is dependent on zinc (Cuajungco and Lees, 1997). Zinc metabolism in the brain: relevance to human NDs. One of the least understood but very important areas in zinc-related NDs is the relationship of these disorders to physiological and pathological changes in altered zinc homeostasis (Bernadeta, 2013). Why, for instance, does zinc deficiency primarily increase diseases like PrD, depression etc.? While the presence of free zinc in neurons and the role of excess zinc in neuronal damage and death have been known for almost three decades, the mechanisms responsible for zinc-mediated neurotoxicity are still being explored and debated.

Another area that is very much underdeveloped is the relationship between zinc and ND, in particular, the fluxes of zinc that either participate in or result from biological and pathological processes (Frederickson, 1989). There is relatively little knowledge of the differences in content and distribution of pools of zinc in different cells, tissues and organs at different stages of development, in different metabolic states and in local or systemic disease, nor do we understand how these fluxes of zinc interact with the pathways causing cell death. Much has yet to be learned about how cells handle and use zinc, concentrate it in organelles and insert it in zinc MT (Truong-Tran *et al.,* 2000). Zinc in relation to several tissues should be appraised. After exocytosis, where and how is the secretory zinc reacquired? It is only when the cellular biology of zinc is better understood will the full implications of zinc-related toxicity become apparent. Recently, the zinc-homeostasis regulating proteins such as transporters and MT have been gaining more prominence in related literature indicating they may be very important players in the pathophysiology of NDs. Therefore, more studies are needed to fully understand the influence of peripheral zinc deficiency or an overdose on these proteins (Szewczyk, 2013).

CONCLUSION

The disruption of zinc homeostasis, namely zinc depletion and excess zinc, cause severe damage to neurons and linked with various NDs. Whereas, zinc plays an essential role in the number of processes crucial for proper cells and organism function. During human growth, zinc can influence development and proper function of nervous system and neuronal plasticity. The adequate zinc levels in specific brain

compartments seem to be critical for the proper brain functioning because even slight disturbances in zinc homeostasis may lead to or participate in the development of several disorders. However, the beams of search light of researchers are needed to explain the exact mechanisms linking zinc and its various underlying processes involved in diseases. First, zinc deficiency is prevalent in patients with psychiatric and NDs. Conversely, even if the beneficial effects of zinc supplementation were reported either in treatment or in the prevention of ND, zinc supplement users should be overly cautious and avoid overdosing. Understanding the role of endogenous compounds with putative neuroprotective actions, such as carnosine, may be helpful in the development of clinical approaches for the treatment of neuropathy that involves metals.

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Section 2

Imperious Neurodegenerative Disorders

Chapter 9
Neurodegenerative Disorders: An Introduction

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ABSTRACT

Neurodegenerative diseases (NDs) are characterized by specific dysfunction and damage of neurons related to pathologically changed proteins that deposit in the patient brain but also in peripheral organs. These proteins can be used for therapy or used as biomarkers. Except for a plethora of alterations revealed for dissimilar neurodegeneration-related proteins, amyloid-β, prion protein, TAR DNA-binding protein 43 (TDP-43, transactive response DNA binding protein 43 kDa), tau and α-synuclein, or fused in sarcoma protein (FUS), molecular classification of NDs depend on the full morphological assessment of protein deposits, their spreading in the brain, and their correspondence to clinical signs with specific genetic modifications. The current chapter represents the etiology of neurodegeneration, classification of NDs, concentrating on the maximum applicable biochemical and anatomical characteristics and most imperative NDs.

INTRODUCTION

NDs are usually characterized as disorders with particular loss of neurons and distinctive association of utilitarian frameworks characterizing clinical symptoms (Kovacs et al., 2010). Full biochemical, and molecular pathological inspections have extended this definition. Many investigations have proven that proteins with changed physicochemical properties were aggregated in the human brain in NDs. Deposition of proteins has controlled to the meaning of the conformational ailments (Carrell and Lomas, 1997). Thus, the physical compliance of a physiological protein adjustment, which outcomes in a changed capacity or harmful intra or additional cell deposition. Changes in the encoding genes are identified with innate types of infection. Every one of these investigations have prompted recategorization of many issues, and opened new ways for remedial methodologies. The focal part of proteins has been converted into biomarker explore and furthermore into the advancement of novel restorative procedures. To be sure, immunization against α-synuclein, amyloid-β (Aβ), or tau has been investigated, specifically

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that these proteins appear to proliferate cell-to-cell and might be available to antibodies (Kovacs et al., 2010; Kovacs and Budka, 2010). Infection changing remedial methodologies may require decreasing the production, keeping the conglomeration or potentially upgrading the leeway of the neurotic types of proteins. These perspectives likewise stress the significance of protein-based grouping of NDs and its interpretation into in vivo biomarkers equipped for distinguishing illnesses as right on time as could be allowed. Protein-based biomarkers would be required for the stratification of patients for against protein treatments, specifically since a significant number of the NDs demonstrate covering clinical highlights and furthermore consolidated affidavit of proteins (Kovacs and Budka, 2010). Many scatters are related to the degeneration of neurons, including immunological clutters; besides, a few quality changes prompt the brokenness of the encoded proteins (Kovacs et al., 2010). Be that as it may, not these procedures connect with minutely perceivable protein testimonies, in any event not with the right now connected systems. For instance, in inherited spastic paraplegia, the neuropathological examination, without learning of the clinical manifestations, can propose the condition yet there are no particular protein incorporations that enable the onlooker to connect the pathology to a particular gene transformation (Kovacs et al., 2010; Kovacs and Budka, 2010). Using specific antibodies against ND-related proteins leads to a specific of description of novel neuropathological phenotypes and the development of trusted diagnostic standards (Rahimi and Kovacs, 2014). There are a reasonable number of possible mixtures of proteinopathies, also related to in the link of varied pathologies (Rahimi and Kovacs, 2014; Kovacs, 2016). The objectives of the chapter are to focus on causes of NDs, factors which are implemented in the pathophysiology of different NDs, classification of NDs and the outline of the some important NDs.

BACKGROUND

Neurodegeneration is a big term for a range of conditions which mainly affect cells (neurons) in the brain. These cells degenerate, which result in the development of dementia and/or movement disorders. Alzheimer's disease (AD) and Parkinson's disease (PD) are the two most public neurodegenerative disorders (Tutar and Tutar, 2010). At present much knowledge is being accumulated concerning the disease mechanisms, but the causative factors of these conditions are still largely unknown. Development of NDs has not been illustrated for a long time. To date, an assortment of components have been proposed for clarifying protein misfolding and protein accumulation, in any case we can't comprehend the system plainly at the molecular and cell premise. Useful proteins must pass a quality control process as far as collapsing to perform catalysis, cell transport, signal transmission and direction. In any case, an assortment of basic and ecological variables impact this procedure adversely (Tutar and Tutar, 2010). The rate of sickness movement (i.e., the length of a given neuropathological arrange) and clinical introduction additionally fluctuate starting with one patient then onto the next. Youthful beginning PD patients, for instance, regularly have a more incessant family history of PD and a more factor survival rate in respect to those without the familial history (Tutar and Tutar, 2010). A few investigations of the Aβ protein totals, which cause AD, likewise demonstrate that the presence of particular shapes in Aβ totals, 40 deposit Aβ (Aβ40) and 42 buildup Aβ fibril structures, and distinguish the unmistakable strain-particular qualities (characterized as "strainness") of the types of AD by the diverse adaptation of the totals (Tutar and Tutar, 2010).

There is however restricted learning about the components that decide singular variety. People that convey a similar transformation in a similar illness causing quality may show a scope of various clinical

indications. For instance, evaluating 6-year change in verbal memory, preparing pace, and official capacity in AD distinguished impacts of MS4A4E, CLU, and NME8 in whites and of ZCWPW1 and CDS33 variations in African Americans (Przedborski et al., 2003). For MS4A4E and CLU, this affiliation was just noteworthy in people bearing no less than one APOE ϵ4 allele (AD hazard quality) (Przedborski et al., 2003). Aside from way of life and condition, these individual contrasts are caused by the one of a kind hereditary foundation of every individual. The hereditary foundation, subsequently, could be characterized as the hereditary cosmetics of all alleles that associate with the malady identified with the "sickness causing" transformation.

CAUSES OF NEURODEGENERATION

The causes of NDs are principally unidentified, and when they have been recognized, the factors by which they start the disease remain unclear (Przedborski et al., 2003). One of the most important reasons related to the etiology of NDs depends on the basis of hereditary and environmental inducers at the beginning of these diseases. Some NDs have a strong familial incidence, signifying a genetic origin (Przedborski et al., 2003). Furthermore, these genetic NDs, others are basically infrequent but display a small depending on patients in whom the disease is congenital. Exactly as PD, AD, and even amyotrophic lateral sclerosis (ALS), of which about 10% of all cases are clearly familial (Przedborski et al., 2003).

When the disease is actually infrequent, it seems that any genetic involvement to the neurodegenerative course is insignificant (Tanner et al., 1999). As an alternative, poisonous ecological elements may be the primary reason for introducing neurodegenerative mechanisms. Accordingly, the case for the PD-ALS difficult, which is, due to a poisonous component in *Cycas circinalis*, a plant usually consumed as a food or treatment by the Chamorros of Guam (Kurland, 1988). poisoning cases with 1-methyl-4-phenyl- 1,2,3,6-tetrahydropyridine, a by-product of the production process of a meperidine compound, is known to make a hard and permanent parkinsonian condition, which is nearly matching to PD (Przedborski et al., 2001). Additionally, numerous great scale epidemiological literatures were unsuccessful to demonstrate any relative relationship between ecological influences and incidence of diseases such as PD (Tanner, 1989). All these outcomes say that infrequent cases are neither obviously genetic nor noticeably environmental, but maybe, they arise from both hereditary and ecological triggers. The opportunity that such both triggers characterize a respected idea causal of infrequent neurodegeneration needs serious attention.

Risk factors for ND can be gender, endocrine disorders, oxidative stress, viral or bacterial infection, inflammations, dietary habits, vascular diseases, depression, and cancer (Marder et al., 1998). Ethnicity and culture can also have consequences and be responsible for intuitions into the prognosis of neurodegeneration (Marder et al., 1998). Especially, smoking, caffeine, and alcohol intake have been assumed to have a relation with neurodegenerative syndromes. There is less proof for a relationship among smoking and parkinsonian conditions, but single study revealed a defensive influence for multiple system atrophy (MSA) but not for progressive supranuclear palsy (PSP) (Vanacore et al., 2000). Likewise, caffeine intake has been shown to be defensive against the progress of PD (Ross and Petrovitch, 2001), although there is less reliable evidence for a relationship with AD (Tyas et al., 2001; Lindsay et al., 2002; Brown et al., 2005).

Neurodegeneration and Oxidative Stress

Mitochondrial dysfunctions, excitotoxicity, lastly apoptosis have been demonstrated as neurotic reason for neurodegenerative sicknesses, for example, PD, AD, MS, and ALS (Janus et al., 2000). Free radical generation catalyzed by redox particles have been shown to assume a basic part in overseeing redox responses bringing about receptive nitrogen species (RNS) and receptive oxygen species (ROS), principle reasons in neurodegeneration (Janus et al., 2000). ROS incorporates hydrogen peroxide (H2O2), nitric oxide (NO), receptive hydroxyl (OH•), and monoxide radicals (NO•). Impeded mitochondria and animated microglia play as pool of ROS. ROS age was believed to be because of lopsidedness amongst generation and leeway of ROS and RNS yet numerous sciences have been uncovered controlling ROS those assume a real part in managing key cell capacities (Apel and Hirt, 2004). Free radicals have been expressed for their significant impact to neuronal harm in cerebral ischemia, seizure issue, schizophrenia, PD and AD (Cadet, 1988). Neuronal biochemical piece is for the most part powerless to ROS since it includes pool of unsaturated lipids those are labile to peroxidation and oxidative adjustment. Twofold obligations of unsaturated fats are problem areas for assault by free radicals those start course or fasten response to harm neighboring unsaturated fats (Zaleska and Floyd, 1985). A few analysts viewed cerebrum as anomalous delicate to oxidative harm and many examinations decisive of the simplicity of peroxidation of brain membranes bolstered this idea. Brain contains abnormal state of unsaturated fats which are more affordable to peroxidation, that expends an over the top part (20%) of aggregate oxygen utilization for its moderately little weight (2%). Moreover, it isn't especially advanced in cell reinforcement barriers. Brain is brought down in cell reinforcement action in examination with different tissues, for instance, around 10% of liver. In addition, human cerebrum has more elevated amount of iron in specific districts and as a rule has large amounts of ascorbate. As apparent from above information, neural cells are thought to be more powerless to oxidative harm when contrasted with other body tissues (Zaleska and Floyd, 1985).

Protein Misfolding and Aggregation in Neurodegenerative Disorders

Protein misfolding prompts protein total and collection of these totals is embroiled as the principle reason of NDs. In brain, some local proteins (prion, tau, β-amyloid, α-syn, and Huntington) experience conformational changes through hereditary and natural variables (Soto and Estrada, 2008). In this way, optional structures of protein change over from α-helix/irregular coil to β-sheet. Thusly, neurotoxic misfolded protein totals are accumulated in CNS and cerebrum harm that prompt NDs (Soto and Estrada, 2008).

Factors Affecting Protein Aggregation in Neurodegenerative Disorders

Protein Structures

The principal basic factor is protein structure. Particularly, essential and optional structures of a protein are two of the most imperative variables for physical and synthetic highlights. Encoded data in amino acid grouping of a protein decides the three dimensional structure. Position and number of various specific amino acids buildups in essential structure may prompt an expansion or a diminishing in total synthesis. Number of hydrophobic amino acids in proteins is relative to propensity of accumulation (Wang, 2005). Auxiliary structures of proteins include in protein misfolding and in addition steadiness.

Proteins frequently crease locally into stable structures that incorporate α-helix and β-sheet. For the most part, some β-sheet-rich proteins, (for example, scrapie tainted prion protein) connect with neurotic states. Amid protein collection, the auxiliary structure is changed over from α-helix to β-sheet. In this manner, protein gets strictness and wide surface region (Philo and Arakawa, 2009).

Protein Concentration

Protein concentration is a critical parameter in protein collection. High protein concentration can improve the probability of accumulation. Protein-protein collaborations and intermolecular associations (particularly cooperations among hydrophobic amino acids) may produce irregular protein structures. Some misfolded protein accumulations can be constituted neurodegenerative sicknesses over a specific concentration. In addition, proteins are refolded at low concentrations unexpectedly. For instance, lysozyme and immunoglobulin G refold itself at low protein concentration be that as it may, refolding yield diminishes with expanding protein concentration. In this manner, the ideal unconstrained protein concentration extend is acknowledged as 10-50 μg/ml. (Treuheit et al., 2002).

Post-Translational Modifications

After a protein is manufactured, the posttranslational adjustments (PTM) of amino acids may expand the decent variety of proteins by extra useful accumulations (acetic acid derivation, phosphate, different proteins and so on.) and auxiliary changes (Karve and Cheema, 2011). Specifically, phosphorylation assumes a huge part in NDs. It is likewise realized that, event of AD is related with tauopathy because of conglomeration of the tau protein. In the brain, tau protein is found in neurons and it can be phosphorylated with kinase catalysts. Therefore, deviant tau totals are framed and they can be amassed in neurons, in this manner their harmful impacts are caused neuronal misfortune and synaptic adjustment (Karve and Cheema, 2011). Glycosylation is an essential PTM for protein solidness and conglomeration potential. Human prion protein has two potential N-glycosylation destinations (Asn181 and Asn197). Notwithstanding, in prion pathology, transformation of PrPc to PrPSc happens effortlessly if the PrPc is glycosylated. In AD patients, hyperglycosylated tau protein is found in brains. Hyperphosphorylation and hyperglycosylation are appeared to be required for protein collection and misfolding in neurodegenerative sicknesses. Also, alternate PTMs, for example, glycation, nitration, truncation, polyamination and so forth include in protein misfolding infections (Martin et al., 2011).

Oxidative Stress

Oxidative tension prompts protein oxidation which is a biomarker for some neurodegenerative disorders. Specifically, free radicals and ROS (receptive oxygen species) leads to protein oxidation. An assortment of oxidants can be happened in ordinary oxygen consuming digestion (Rudd et al., 2001). Additionally, absence of cell reinforcements, abundance of oxygen and lipid and metal particles can create free radicals. The oxidation of proteins greatly relies upon their amino acid synthesis. For the most part; lysine, histidine, arginine, methionine, cysteine, phenylalanine, tryptophan, threonine, glutamic acid, and proline buildups slant oxidation. A few proteins have metal restricting districts alone structure. Metal particles, for example, copper, zinc, and iron, are equipped for redox responses and electrons are exchanged from particles to oxidizing mixes. In this way, lethal free radicals are shaped and proteins can be changed

over into conglomeration structures or proteins can be amassed by conformational changes (Moulton and Yang, 2012).

Mutations

Transformations assume determinative part in protein collection and they may drastically change solvency, strength, and accumulation propensity of proteins (Lee and Yu, 2005). Thermally steady proteins may change its solidness even with a point transformation in its structure. For instance, a human lysozyme I56T and D67H mutants significantly diminish the lysozyme efficacy and subsequently the lysozyme accumulates effortlessly after warming. Promote conglomeration cause amyloid fibrils and these fibrils are kept in tissues and are related to neurodegenerative sicknesses (Lee and Yu, 2005). As of late, researchers have been proposed another protein for comprehension of ALS, AD, cystic fibrosis (CF) and frontotemporal lobar degeneration (FTLD) systems. The TDP-43 is found by every single mammalian tissue, conformational changes in this protein cause collection and loss of capacity. TDP-43 has been appeared to chelate to DNA (deoxyribonucleic acid) and mRNA (dispatcher ribonucleic acid) and partake in control of transcription and translation. TDP-43 has a glycine rich C-terminal tail and change happens from this area. Thus, TDP-43 is changed over to amassed frame which is gathered in tissues (Wilson et al., 2011).

pH

Ecological pH is to be basic for protein collection because of changes in net charge on protein. Protonation condition of ionizable destinations of protein and positive net charge are expanded in acidic conditions. Particularly, association of salt scaffolds is changed in parallel with formed new optional structures. In prion sickness, acidic pH encourages production of PrPSc. At low pH, PrPc picks up β-sheet structures and shows accumulation inclination. As per the Finl (2006), α-syn brooded at various temperature and pH esteems, and the best development conditions were resolved as pH 7.4 and 37˚C (Fink, 2006). α-syn can be lost its local structures and PD is quickened in these conditions.

CLASSIFICATION OF NEURODEGENERATIVE DISORDERS

Organization of NDs is built on scientific demonstration, structural areas and cell kinds damaged, conformational changed proteins complicated in the pathogenesis (Kovacs, 2016). In many cases, there is a similarity of the medical signs in the progression of the disease. Thus, medical categorization is important when early clinical signs are assessed (Kovacs, 2016).

Clinical and Anatomical Classification

Behavioral Disorders and Changes in Brain Functions

The main anatomical sections affected are the hippocampus, limbic system, and neocortical sections. In focal cortical signs, deterioration of the frontal, temporal, or the occipital lobe can be affected. Fronto-

temporal dementia (FTD), which is famed with deterioration of the frontal and temporal sections (Kovacs, 2016).

Movement Changes and Motor Dysfunction

The main anatomical sections affected are the basal ganglia, thalamus, brainstem nuclei, cerebellar cortex and nuclei and lower motor neurons (Kovacs, 2016).

Mixed

Behavioral and movement disorders both of these signs may be detected in certain disease early during the clinical course and during the progression (Kovacs, 2016).

Altered Proteins Associated Classification

The following proteins are mostly associated with NDs:

- The microtubule-associated protein tau (MAPT) is essential for the assembly of microtubules (Kovacs et al., 2010).
- Amyloid-β (Aβ), which originates from the amyloid precursor protein (APP). Additional genes with relation to the pathogenesis of AD include presenilin-1 (*PSEN1*) and *PSEN2*.
- α-syn is a 140-amino acid protein that related to a group of brain proteins (α, β, and γ-synuclein).
- Prion protein (PrP) is a 253-amino acid protein significant in the pathogenesis of prion diseases or spongiform encephalopathies.
- TDP-43 is a 414- amino acid nuclear protein. This protein is encoded by the *TARDBP* gene. Among others, also the most related genes for TDP-43 proteinopathy include progranulin and C9orf72 (Ou et al., 1995).
- FET proteins, which contain the fused in sarcoma (FUS), Ewing's sarcoma RNA-binding protein 1 (EWSR1) (Neumann et al., 2011).

Neuropathological Classification

It depends mainly on the assessment of the structural spreading of neuronal damage, and other histological properties, and the type of intracellular and extracellular protein aggregations, which are identified by immunohistochemistry and biochemistry (Kovacs, 2016). It is important to differentiate between the subcellular site of the intracellular aggregations and if they are nuclear, cytoplasmic, or neurotic, or in cellular processes. In certain cases, only morphological principles are used for classifying, but in certain other cases biochemical alterations or gene polymorphism are also included (Kovacs, 2016).

Molecular Pathological Classification

The most critical step based on this classification is to assess the site and spreading of proteins (Kovacs and Budka, 2010). Extracellular deposits mainly deposit with positive immune reaction for Aβ or PrP. Essentially, sickness related PrP represents a synaptic site of aggregation. Most important proteins that

aggregate intracellular are: tau, α-syn, TDP-43, FUS/FET proteins, and they are related with rare genetic diseases (Walker et al., 2013).

Current studies propose that disease related protein helps as important key role in the start and increase of aggregated proteins in NDs (Walker et al., 2013) investigation in humans showed specific mechanisms by which definite protein pathology might transmit by the central nervous system (CNS) accompanying evidence of the molecular pathways of protein proliferation in AD (tau and Aβ), FTLD-tau, and FTLD-TDP (Brettschneider et al., 2015). Furthermore to building a basis for improving therapeutically policies that stop the spreading of protein deposits, this all ideas have essential effects on categorization and pathological relationship (Kovacs, 2016).

SYNTHESIS OF BIOCHEMISTRY, GENETICS AND MORPHOLOGY

Biochemical considerations revealed variances among the proteins in physiological and in sickness states. These variances can prevent the solubility, and ability of fibril development, or can be toxic. Examples of these interferences between proteins, for instance generation of β-sheet, proteinase-resistant cores, and phosphorylation (Kovacs, 2016). Yet, from a large number of biochemical alterations only some have been turned into the investigative kits like Proteinase K (PK)-resistance for PrP, phosphorylation for tau, isoform alterations for tau, and by products for Aβ. But, the spatial and progressive spreading of the diverse pathologic protein types has not been explained in particulars (Kovacs, 2016).

Anatomical spreading and morphology of pathological changes still control the categorization NDs. Inspection of important gene alterations, besides with biological inspection, has been integrated into the classification strategy (Kovacs, 2016). Concerning the spreading of pathological protein aggregation, there are coinciding properties seen in diverse proteinopathies, like:

1. Discrimination relies on extra- (Aβ, PrP) or intra-cellular (tau, α-syn, TDP-43, FUS) control of protein deposits (Kovacs, 2016);
2. Differentiating neuronal, mixed neuronal-glial, and glial predominant types of proteinopathies (Kovacs, 2016);
3. Estimation of periods is applied in an increasing number of disorders (Kovacs, 2016);
4. Existence of intracellular protein deposits showing primary phases expressing future steps of intracellular protein pathologies (Kovacs, 2016).

Another fact is the common incidence of associated proteinopathies, leading to complications of disease identification. So, additionally to the specific injuries of an ND structure, extra pathological variations can be showed in the similar case (Kovacs, 2016). Aggregation of deferent neurodegeneration linked proteins in conjunction with non neurodegenerative pathologies, is a communal occurrence (Rahimi and Kovacs, 2014; Kovacs et al., 2008). These outcomes might have consequences on therapy techniques directing to specific pathological protein in the brains of old patients with dementia. Accepting the thought of "decreasing" for a medical indication is mandatory for the medical and neuropathological experience. Lastly, it essential be well-known that numerous gene alterations related also with depositions of various proteins not only specific to their gene (Kovacs, 2016).

FEW IMPERIOUS NEURODEGENERATIVE DISORDERS

Alzheimer's Disease

AD is portrayed by the extracellular aggregation of Aβ fibrils and by the intraneuronal aggregation of irregularly phosphorylated tau protein (Duyckaerts et al., 2009). Pr-symptomatic AD can be confirmed *in vivo* depending on the incidence of lab results (Jack et al., 2014) or after death by the incidence of AD-type neuropathological changes although without manifestation of mental weakening throughout lifetime. For tau pathology only neuronal tau immunoreactivity are measured. Aβ-fibrils could be deposited in the parenchyma in the shape of signs and in the vessel walls similar to cerebral amyloid angiopathy (CAA). Parenchymal Aβ aggregations appear different morphologies, like stellate (related to astrocytes), prolix aggregations (further divided into fleecy, lake-like) or focal deposits (with or without a dense core), and further sporadic morphologies similar to cotton-wool plaques (Duyckaerts et al., 2009). Different plaque kinds are associated frequently to their structural spreading (Thal et al., 2015; Kovacs, 2016).

Amyotrophic Lateral Sclerosis

ALS is a deadly motor neuron syndrome that is, manifested by advanced damage of the upper and lower motor neurons (MNs) at the spinal or bulbar level (Rowland and Shneider, 2001). The clearest signs that appear in ALS are muscle weakness, twitching, and cramping, which in time can result in the injury of muscles (Wijesekera and Leigh, 2009). In the most progressive periods, ALS patients will develop signs of dyspnea and dysphagia. Magnetic resonance imaging (MRI) readings of the brain and spinal cord are the most valuable neuroimaging method in ALS principally to exclude disorders that like ALS (Hardiman et al., 2011). For instance, new chromosome 9p-linked FTD-ALS shows a dissimilar form of brain atrophy and neuropathological definition that can help to discriminate from typical ALS (Boxer et al., 2009). Innovative neuroimaging machineries are beneficial research means that may aid to recognize specific ALS related pathologies in a non-invasive way. Neuroimaging is frequently done to aid eliminate differential diagnosis rather than approving the diagnosis of ALS (Hardiman et al., 2011; Zarei et al., 2015).

Batten Disease

Batten disease (BD) is a very infrequent and lethal autosomal recessive neurodegenerative syndrome that begins in childhood. It is the most public form of a group of syndromes termed the neuronal ceroid lipofuscinoses (NCLs). Primary symptoms of the syndrome frequently appear around ages 2 to 10, with steady onset of vision difficulties, or seizures (Weimer et al., 2002). Early signs may be refined personality and behavior alterations, limited education or regression, repetitive speech, or stumbling. There may be decelerating head development in the infantile type, weak circulation in lower extremities, diminished body fat and muscle build, curvature of the spine, hyperventilation, teeth crushing, and constipation (Weimer et al., 2002). By the time, affected children undergo mental weakening, increasing seizures, and progressive loss of vision, speech and mechanical abilities. Together denoted to as BD, the NCLs are responsible for the most of neurodegenerative syndromes that affect children. Precisely, the incidence of this disease is around 1 per 12,500 persons (Weimer et al., 2002). The exact type of NCL is categorized by the age of symptomatic beginning and genetic alteration involved. Recently, it has been found that

alterations in ten genes lead to the growth of BD (Weimer et al., 2002). Urinalysis and blood examining can aid to distinguish aberrations that may point to BD. For instance, increased levels of (dolichol) in urine have been shown in many individuals with NCL. The incidence of vacuolated lymphocytes that include holes or cavities when shared with other results that indicate NCL, is indicative for CLN3 mutations (Weimer et al., 2002). Investigative imaging test let doctors to better imagine the appearance of the brain. MRI uses magnetic and radio waves to any one either help or produce images of the brain. The computerized tomography (CT) is additional type of imaging test that uses X-rays and computers to generate a full image of the brain's tissues and constructions. Both diagnostic imaging tests can help to show brain areas that are damaging in persons with NCL (Weimer et al., 2002).

Creutzfeldt-Jakob Disease

Creutzfeldt-Jakob disease (CJD) is an infrequent, deteriorating, always lethal brain sickness. CJD related to a group of human NDs, recently involving Gerstmann-Straussler-Scheinker disease (GSS), kuru, fatal familial insomnia (FFI), and prion protein cerebral amyloid angiopathy (PrPCAA) and variably protease-sensitive prionopathy (VPSPr) (Head et al., 2012). Neuropathologically, the disorder is manifested by many florid signs in the cerebral and cerebellar cortex and frequent mass plaques, amorphous pericellular and perivascular prion protein aggregations in the same regions. There is a high spongiform modification and perineuronal and axonal prion protein conglomerations in the caudate core and putamen, stamped astrocytosis and neuronal harm in the back thalamus and reticular and perineuronal accumulation in the mind stem (Parchi et al., 1997). First problems over nomenclature having been principally fixed, most of the researchers use a $PrPr^{es}$ typing system in which the two main differentially N-terminally truncated 21 kDa and 19 kDa protease-resistant fragments are called type 1 and type 2 $PrPr^{es}$ respectively (Parchi et al., 1996) using western blotting. $PrPr^{es}$ type and glycoform ratio are measured distinctly in this nomenclature (Head et al., 2012). Glycotypes are best characterized as a proportion (% diglycosylated: % monoglycosylated: % nonglycosylated), however a shorthand has been built up in which illustrations where the diglycosylated band leads are given the postfix B and those in which the monoglycosylated band leads are given the addition A (Parchi et al., 1997; Head et al., 2012).

Corticobasal Degeneration

Corticobasal degeneration (CBD) is a pathologic syndrome (Dickson et al., 2002) resulting from unusual accumulation of hyper-phosphorylated tau isoforms with four preserved rehash arrangements (4R tau). Prior to 2013, CBD analytic standards uncovered just a single displaying phenotype, corticobasal syndrome (CBS), once thought pathognomonic for CBD. CBS is an engine appearance with atypical parkinsonism, dystonia, and myoclonus alongside higher cortical manifestations including apraxia, alien limb phenomena, cortical sensory loss, and cognitive alterations (Armstrong, 2014). It is currently realized that CBS is single one showing phenotype of CBD, revealed in updated clinical research diagnostic principles for CBD (Armstrong et al., 2012). Imaging could be valuable to inspect other origins of presenting signs, like signs of prion disease on MRI (Lee et al., 2011) in cases with CBS and quickly worsening dementia or amyloid imaging to predict causal AD. Voxel based morphometry analysis of MRI weaken forms may be prognostic of underlying pathology in CBS cases (Whitwell et al., 2010; Lee et al., 2011; Armstrong, 2014), but these results cannot yet be practical to daily clinical diagnosis.

Friedreich's Ataxia

Friedreich's ataxia (FRDA) is the furthermost shared genetic ataxia (Harding, 1984). It is the outcome of aggregation of iron in mitochondria causing additional generation of free radicals, which at that time leads to cellular loss and loss (Eder et al., 1998). The principal medical structures are advanced gait and limb ataxia, absent lower limb responses, extensor plantar responses, dysarthria, and decrease in or damage of vibration sense and proprioception (sensory modalities connected by posterior column neurons) (Delatycki et al., 2000). Cardiomyopathy, scoliosis, and foot abnormality are shared but non-important signs (Harding, 1984). The chief locations of pathology in FRDA are the dorsal root ganglia, posterior columns of the spinal cord, corticospinal tracts, and the heart. Macroscopically there is a minor part spinal cord with the posterior and lateral columns mainly exaggerated (Harding, 1984). The nervous system variations seem to be a dying back manner from the margin (Hughes et al., 1968). Declined phospholipid heights have been established in the cerebellar and occipital cortex of brains of patients with FRDA (Eder et al., 1998; Delatycki et al., 2000).

Huntington's Disease

Huntington's disease (HD) is an uncommon NDs of the CNS manifested by unwanted choreatic actions, communicative and psychiatric complaints and dementia. Occurrence in the Caucasian people is expected at 1 from 10000 to 20000. The nuclear indications and signs of HD involve motor, mental and psychiatric disorders. Further less familiar, but predominant and often bad structures of HD includes unintentional weight decline, sleep and circadian rhythm troubles and autonomic nervous system abnormalities. The average age at beginning is between 30 and 50 years, with a variety of 2 to 85 years. The mean period of the sickness is 17 to 20 years. The development of the illness clues to additional needs in regular life and lastly death. The greatest shared reason of death is pneumonia, tailed by suicide (Roos, 2010). HD is an autosomal dominantly hereditary sickness triggered by an extended CAG repeat on the short arm of chromosome 4p16.3 in the huntingtin gene (Trottier et al., 1994). This gene codes for the Huntington's protein and, on exon 1, holds the CAG tract. The worst type contains a CAG repeat, coding for a polyglutamine stretch in the protein at that position in the range 6 to 26 (Trottier et al., 1994). Certain medical demonstration will happen if the quantity of repeats goes beyond 40 (Roos, 2010). The range between 29 and 35, is unbalanced, which means that these isoforms are susceptible to alternate throughout reproduction (Roos, 2010). Repetition the gene can lead to errors and frequently leads to elongation and rarely to restriction. This incidence is mostly seen in the man type of reproduction (Trottier et al., 1994). The analysis is established on the medical indications and symptoms in a patient with a parent with established HD (Roos, 2010). Mainly, it is mandatory to take a full history from the person with symptoms followed by a full family history. When all data has been attained the analysis is not very hard, even though nonspecific medical images can be false. Also when the parent is not known or has died due to another reason at an early age, the medical picture can be hard to distinguish (Roos, 2010). It is often essential to demand old data in the form of medical archives and autopsy information. The present important standard is DNA determination, viewing a CAG-repeat of as a minimum 36 on the huntingtin gene on chromosome 4 (Roos, 2010).

Lewy Body Disease

Lewy body disease (LBD) is now known as a broad term that involves PD, PD dementia (PDD)and dementia with Lewy bodies (DLB) (McKeith et al., 2005; Lippa et al., 2007). Many dementia experts, misinterpret the correlation between LBD and DLB. LBD is defined as, a chronic advanced neuropsychiatric syndrome, which is clinically manifested by parkinson signs of pre-senile or senile, or occasionally younger onset, frequently followed by dementia at the advanced stages (Lippa et al., 2007). Progressive dementia or several kinds of psychiatric signs including distinctive visual hallucination and delusions are the main symptoms, commonly followed by parkinson indications. It is neuropathologically described by numerous Lewy bodies (LBs) and neuritis, and neuronal cell damage in the central and autonomic nervous system. DLBD is manifested clinically by advanced dementia and parkinson signs of pre-senile or senile, or occasionally of younger onset, and neuropathologically by frequent LB and neuronal cell damage in the central and autonomic nervous systems, commonly followed by several degrees of Alzheimer pathology. Certain genetic indicators for the judgment of DLB have also been improved, such as brain single photon emission computed tomography/positron emission tomography (SPECT/PET), dopamine transporter imaging [^{123}I-Fluoropropyl-2-beta-carbomethoxy-3-beta(4-iodophenyl) nortropane (FP-CIT) SPECT] (Walker et al., 2007), and meta-iodobenzylguanidine (MIBG) myocardial scintigraphy (Yoshita et al., 2001). α-syn was found to be the key component of LB. α-syn is a 140 amino acid protein encoded by the *SNCA* gene, found in nuclei and presynaptic parts, but its purpose has not yet been known (Kosaka, 2014). Though, the cerebral type of LBD in which plentiful LB was found in the cerebral cortex even with there being only a little in the brain stem nuclei, proposes the probability that Lewy pathology happens in the cerebral cortex and propagates downward to the brain stem. Lewy pathology may possibly also start from Auerbach's plexus of the lower esophagus or the olfactory bulb (Kosaka, 2014). Recently, the possibility that accumulation of α-syn could spread trans-cellular all over the brain in a prion-like technique has been found (Kosaka, 2014).

Parkinson's Disease

PD is a frequently restricting syndrome seen in individuals from all countries and geographical spots, with medical symptoms developing also in a broad age variety (Lees et al. 2009). Motor symptoms might involve bradykinesia (tardiness of movements with an advanced damage of adequacy or speed amid endeavored quick sporadic developments of body parts), rest tremor (cadenced oscillatory involuntary movement that begins when the influenced body part is relaxed and remained by a surface, accordingly make away from the move of gravitational powers). Notwithstanding unbending nature (a hoisted muscle tone detected through examination by aloof movement of the influenced part, including both flexor and extensor muscle gatherings), and postural and stride disability (Massano and Bhatia, 2012). While, the non-motor symptoms could include neuropsychiatric disorders, dysautonomia, sleep disorders, and sensory dysfunction (Massano and Bhatia, 2012). Brain anatomical scanning, whichever by CT or MRI should continuously be done; but the latter is chosen, since certain constructive results infrequently expose other investigative things (Sitburana and Ondo 2009). Dopamine functional scanning might be measured to approve that progressive parkinsonism is the source of signs. Positron emission tomography (PET) with fluorodopa is one of the techniques presented, but the prices and inadequate availability make it hard for using it. So, dopamine transporter (DAT) imaging with single-photon emission CT (DAT-SPECT) is a very valuable method, because it is delicate for the revealing of presynaptic dopaminergic neuron

damage in the striatum (Kagi et al., 2010). Nowadays, MRI is chosen over CT, and family report is not considered as a prohibiting principle.

Posterior Cortical Atrophy

Posterior cortical atrophy (PCA) is a neurodegenerative disease that is manifested by an advanced decrease in visuospatial, visuoperceptual, literacy and praxis abilities (Lehmann et al., 2011). The advanced neurodegeneration damaging parietal, occipital and occipito-temporal cortices which cause PCA is referred to AD in the most of cases. Though, other causal etiologies counting DLB, CBD and prion syndrome have also stood recognized, and not all PCA cases have deteriorated on medical examination (Lehmann et al., 2011). Cross-sectional voxel-based morphometry (VBM) has shown extensive grey matter changes between PCA cases and normal people, with the maximum important decreases established in sections of the occipital and parietal lobes, trailed by sections in the temporal lobe (Lehmann et al., 2011). Direct assessment between PCA and typical AD by both VBM and cortical thickness methods have confirmed more right parietal and less left medial temporal and hippocampal degeneration in PCA (Migliaccio et al., 2012). It must be well-known that a quantity of readings report asymmetric atrophy patterns in PCA (right > lift), but these changes may reproduce choice preferences in the diagnosis and staffing of cases with noticeable visual impairment. Incomplete diffusion tensor imaging (DTI) records also propose PCA decreases the integrity of white matter tracts in posterior brain regions (Migliaccio et al., 2012). Records from practical imaging readings using single photon emission computed tomography (SPECT) and fluorodeoxyglucose positron emission tomography (FDG-PET) are mainly reliable with anatomical alterations in parieto-occipital parts (Gardini et al., 2011).

Progressive Supranuclear Palsy

PSP is a widespread subcortical neurofibrillary deterioration mostly originate in the globus pallidus, subthalamic nucleus, substantia nigra and cerebellar dentate nucleus were manifested as the pathological substrates of the clinic-pathologic entity of progressive supranuclear palsy (PSP), also recognized as Steele-Richardson-Olszewski syndrome (Ling, 2016). Medical subtypes of PSP-parkinsonism (PSP-P) and PSP-pure akinesia with gait freezing (PSP-PAGF) have a further benign growth with a survival period of 10 years or more. Also, both subclasses have a general tau burden fewer than those in PSP-RS and the spreading of irregular tau is comparatively limited to the brain stem (Williams et al., 2007). Clinical signs could involve primary postural instability and/or falls, eye movement irregularities, cognitive weakening, frontal behavior, non-fluent aphasia and/or apraxia of speech, limb dystonia, pyramidal and Babinski's signs, levodopa response, and dysautonomia (Ling, 2016). Conventional MRI of the brain is valuable to eliminate extensive cerebrovascular disease, leukodystrophy, regular pressure hydrocephalus, structural midbrain lesions and, infrequently, manganese poisoning which can all pretense as PSP (Ling, 2016). Laboratory investigations for syphilis and human immunodeficiency virus (HIV) serology, autoimmune disorders, paraneoplastic disease autoantibodies, antibodies for stiff-person syndrome and Niemann Pick type C may be measured (Ling, 2016). Dopamine transporter single photon emission computed tomography (SPECT) imaging displays diminished tracer uptake in the striatum which is a helpful finding to discriminate PSP from other diseases such as cerebrovascular disease and normal pressure hydrocephalus (Kagi et al., 2010). PET imaging with tau ligand is a favorable radiologic method for investigative and check-up of PSP (Kepe et al., 2013).

Pick's Disease

Pick's disease (PiD) is well-defined pathologically by the occurrence of neuronal presence bodies (Pick bodies) immune-reactive to tau and ubiquitin inside cerebral cortical neurons and inflated achromatic neurons (Pick cells) inside the cerebral cortex (Neary et al., 1998). Depending on the site of the cortical degeneration dissimilar medical patterns have stood illustrated in PiD (Neary et al., 1993). Cases with noticeable medial temporal lobe pathology, particularly deteriorating the amygdala, can have a Klüver-Bucy syndrome (Cummings and Duchen, 1983). Cases with extra damaged frontal lobe pathology usually have FLS (Dickson, 1998). As is pure from this information of this syndrome, the neuropathology of FLS is varied; only a lesser percent have classical PiD. In regions with extreme pathology, the cortex has nearly widespread damage of big pyramidal neurons with the breakdown of the parenchyma, diffuse spongiosis and dense gliosis (Dickson, 1998). The cytoarchitectural properties of the cortex turn into cover. In initial phases or zones with less severe pathology, adequate vacuolation of the neuropil is existing in the upper cortex. Swollen neurons (also denoted to as Pick cells) are existing in the central and lower cortical layers. Functional imaging readings such as PET or SPECT can show bifrontal shortages. This outline compares with the biparietal shortages representative of AD and the irregular superior frontal or para-central deficits of CBD (Dickson, 1998).

Primary Progressive Aphasia

Primary progressive aphasia (PPA) is a medical condition distinguished by the instant beginning and advanced ending of language abilities (Mesulam, 2003). While further mental signs may arise far along in the progression of disease, shortages must be totally restricted to the extent of verbal for at minimum 2 years to accomplish the measures for an identification of PPA. At examination, the most constant conclusion is that of focal deterioration, which is commonly established specially and more strongly in verbal regions, and manifested by neuronal damage, gliosis, and spongiform alterations including the superficial cortical layers (Leger and Johnson, 2007). Cortex could also include infrequent ballooned neurons, named Pick cells. Staining with silver and novel histochemical stains for both the microtubule related protein tau (MAPT or tau) and ubiquitin can expose neuronal and glial insertions in an outline specific to the particular neuropathological development approaching (Leger and Johnson, 2007). Using fMRI (functional MRI) and a grammatically complex sentence comprehension pattern, presented that patients with PPA give fewer initiation within the ventral portion of the inferior frontal cortex, a part suspected to be vital to the handing out of difficult sentences (Cooke et al., 2003). They further assume that this disturbance of a supposed big scale neural system for sentence intellectual capacity forms the source for the difficult grammatical comprehension shortages shown in these cases (Cooke et al 2006).

Spinal Muscular Atrophy

The word spinal muscular atrophy (SMA) is realistic to a varied collection of hereditary syndromes that all distress the spinal MN (Arnold et al., 2015). The diverse types of SMA are related with frequent gene alterations and major phenotypic differences. SMA is generally characterized by distinct faintness (proximal or distal) and manner of inheritance (Arnold et al., 2015). SMN lacking disturbance of other cellular mechanisms could also be significant in the pathogenesis of SMA, and damage of axonal mRNA transportation could also have a key role in SMA (Arnold and Burghes, 2013). Changed transcripts (SMN

deficiency) have been recognized, but a certain relation to the disease pathogenesis has not been established. For instance, the protein Stasimon was recognized lately as a probable disease-associated mark of altered splicing produced by SMN insufficiency (Imlach et al., 2012). Muscle biopsy and electrodiagnostic analysis were typical measures for assessment, but since molecular analysis is offered, these and other analytical examinations (MRI) are not necessary. Electrophysiological methods of electromyography (EMG), compound muscle action potential (CMAP), and motor unit number estimation (MUNE) have shown excellent association with clinical progressing, age, and functional grade (Arnold et al., 2015).

Spinocerebellar Ataxias

The most common congenital ataxias, currently named spinocerebellar ataxias (SCAs). Gradually advanced ataxia along with cerebellar deterioration is frequently hereditary in basis. The previous 5 decades have observed an improvement in our knowledge of the reasons of dominantly hereditary ataxias, now acknowledged as the spinocerebellar ataxias SCAs (Paulson, 2009). SCA is a deficit of coordination, mainly of gait. So, when a doctor examines patient with ataxia, it normally is someone with gait inequity related with limb incoordination counting difficulties with gross and fine motor control (Paulson, 2009). The detection over 10 years ago that polyQ sickness brain comprises intracellular presences of the disease protein recommended that the development enhances misfolding of the disease protein, causing in accumulation. The principal advantage of investigative hereditary analysis is that it could deliver an exact and accurate diagnosis (Paulson, 2009). SCA gene test in a case whose signs are constant with a hereditary form of ataxia, but whose family report is indefinite or lacking, can approve the medical analysis with efficacy, cost, and inevitability. In an ataxic case, gene investigations are accurate and precise, whereas brain MRI is not. In SCA gene analysis can agree an identification from between a collection of clinically comparable chromosomal situations (Paulson, 2009).

CONCLUSION

This chapter targets to condense recent thoughts of disease categorization with a concentration on the molecular pathological features for neurodegenerative situations of the old age where microscopically noticeable protein aggregations have stood defined. Misrepresentation of infection gathering with the point of creating treatments for whatever number people as could be allowed indicating comparable clinical highlights has not prompted huge achievement. Characterizing novel groups of patients with NDs for stratified helpful methodologies, in light of consistent, careful, orchestrated, and continually refreshed clinical, neuroimaging, biochemical, and hereditary characterizations with lasting neuropathology-based quality control are by all accounts a superior approach in the time of precise medication.

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Chapter 10
Tau Pathology: A Step Towards Understanding Neurodegenerative Disorders Network Complexity

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ABSTRACT

A number of neurodegenerative disorders (NDs) are usually referred as tauopathies and characterized by the disappearance or disintegration of tau protein from microtubules. Alzheimer's disease (AD), Pick's disease (PiD), Parkinson's disease (PD) are directly or indirectly associated with tauopathy. Tau is a protein which is usually associated with microtubule. Microtubules are the backbone of neurons, and tau provides a support to microtubule stability. Hyperphosphorylation of tau leads to its separation from microtubule, consequently forming neurofibrillary tangles and resulting in a condition of dementia. Therapeutic implication on tauopathy is symptomatic as there is no exact regulation mechanism known till date. This chapter helps in the comprehensive study of biomarkers and pathways involved in tauopathy to decipher the complexity of the system, resulting in candidate drug target for the management of NDs.

INTRODUCTION

NDs like AD and PD are responsible for a notable increase in the proportion of mortality and morbidity in the developed world today (L. E. Hebert, Beckett, Scherr, & Evans, 2001; Liesi E. Hebert, Scherr, Bienias, Bennett, & Evans, 2003). It is due to the result of increase in the life expectancy of individuals and the change in the population demographics like the neurodegenerative movement disorders

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which are more common nowadays, aging of baby boomers as well as the neurodegenerative dementias (Brookmeyer, Gray, & Kawas, 1998; Samii, Nutt, & Ransom, 2004). With the aging of the population will provide an improved perceptive of such diseases and this will provide a vital part in the development of many effective therapies and to combat the shocking costs of such diseases (Ernst, Hay, Fenn, Tinklenberg, & Yesavage, 1997). Unifying pathogenesis theories in ND offers an opportunity for the development of therapeutic strategies with broad range of applications in the prevention of disease and a chance for declining morbidity and mortality due to these disorders in the elderly population (Forman, Trojanowski, & Lee, 2004). The lines of analysis showing convergence have exposed a potential single common pathogenic mechanism that underlies various diverse neurodegenerative disorders (the deposition and aggregation of misfolded proteins). Almost all the major neurodegenerative disease has been characterized pathologically by the insidious buildup of insoluble filamentous aggregates of usually soluble proteins in the central nervous system (CNS) (Irvine, El-Agnaf, Shankar, & Walsh, 2008). Since the filamentous aggregates show the tinctorial and ultrastructural characteristics of amyloid, which are ∼10-nm-wide fibrils with crossed β-pleated sheet structures that stain with Congo red, thioflavin-S, etc; these diseases can together be grouped as brain amyloidosis (Rajamohamedsait& Sigurdsson, 2012).

The main question comes in mind, what is actually responsible for the remarkable phenotypic diversity found in the above mentioned diseases? Every associated brain amyloidosis is differentiated by diverse temporal and regional patterns of aggregates deposition, changing cellular hosts or extracellular locales of the aggregates, and various protein constituents of the aggregates (Guo & Lee, 2014). All of these characters, along with the innate and variable reactions of the patients to the aggregates that might vary the cascade of events which guide to a particular temporal and regional pattern of neuronal dysfunction (Morris, Clark, & Vissel, 2014). This can result in death, revealing as a particular clinical syndrome like dementia in AD or a movement disorder in PD. Therefore, looking from a pathological view point, neurodegenerative entity can be well explained by the nature and pattern of the deposition of amyloid in the brain. Unluckily, the category and pattern of the amyloidosis in the brain does not always relate fine with the experimental clinical phenotype which were observed (Allen, Robinson, Snowden, Davidson, & Mann, 2014). The variability in connections has advanced to a perplexing nosology that at times need clinicians to explain phenotypes with respect to the presumed existence of the pathological lesions like dementia along with Lewy bodies. At times there is a necessity for pathologists to illustrate lesions by means of clinical language despite of the patient's actual clinical presentation as in the case of progressive supranuclear palsy (PSP). One of the right ways to get around this turmoil is by achieving chemical analytes of biological fluids and neuroimaging biomarkers. These biological entities will permit the clinicians to differentiate between brain amyloidosis based on the character and level of the brain pathology along with the particular amyloidogenic proteins caught up in disease pathogenesis (Macedo & Cordeiro, 2017). These NDs share common mechanisms which involves accumulation of CNS misfolded proteins which provides an idea that these disorders might be linked to similar targets for the advancement of diagnostic and therapeutic agents.

In this context, AD, tauopathies (PiD, cortical basal degeneration, and PSP), and the synucleinopathies (dementia with Lewy bodies, PD, and multiple system atrophy) are discussed as models of the brain amyloidosis that are found in many ageing-related neurodegenerative disorders (Hassan, Whitwell, & Josephs, 2011; Levin, Kurz, Arzberger, Giese, & Höglinger, 2016; Tsai & Boxer, 2014). It further deals with mechanistic understanding of the deregulation of neurodegenerative pathways through various signaling cascades. In NDs, the disease spread goes behind disease-specific patterns that look like the structural design of brain connectivity networks. The point which still remains unclear is that, what

makes the disease spread along such networks. Literature survey and all results together may provide support for the hypothesis that the spread of neurodegeneration across neural networks is through a specific cascade. This chapter discusses the role of tau in various forms of dementia and its involvement in molecular pathway. Screening of key biomarkers using various network approaches, understanding of neuronal signaling is simplified in this chapter.

BACKGROUND

The current spreading out of the public interactome databases allow researchers to proceed through various computational methods used for network medicine (Barabási, Gulbahce, & Loscalzo, 2011). The aim of network medicine is to investigate the pathogenic mechanism of a specific disease and additionally to deduce the complex relations of diseases in an organized way. One of the key approaches is the investigation of the human protein-protein interaction (PPI) network to study disease causing genes through their consequent protein's products which are afterwards used to create the disease PPI network (Ideker & Sharan, 2008). Research based on PPI networks for various diseases has achieved remarkable outcomes (Kann, 2007; Navlakha & Kingsford, 2010; Nguyen & Ho, 2012; Nguyen, Liu, & Jordán, 2011; Oti, Snel, Huynen, & Brunner, 2006; Schuster-Böckler & Bateman, 2008). Various on-going and recent studies have analyzed NDs using PPI; though, they generally considered a particular disease, like AD (Goñi et al., 2008; Krauthammer, Kaufmann, Gilliam, & Rzhetsky, 2004; Wang et al., 2016). Another work inferred overlapping regulators of different NDs in various organisms (Chen & Burgoyne, 2012), the direct commonality among NDs in regard to their pathways (Limviphuvadh, Tanaka, Goto, Ueda, & Kanehisa, 2007), or the construction of NDs network which is based on PPI networks, regulatory networks and Boolean networks (Vasaikar, Padhi, Jayaram, & Gomes, 2013). The earlier works which focused upon the construction of PPI networks linked to NDs have still not quantified the topological relations between NDs. Furthermore, the indirect network associations underlying functionality linkages between NDs are still not clear.

AMYLOID BETA ASSOCIATION WITH NEURODEGENERATIVE DISORDERS

Aβ is the protein that forms pathogenic aggregates in the AD brain. The largest aggregates of Aβ are present in extracellular plaques, although data suggest that Aβ aggregates may also form within neurons (Echeverria & Cuello, 2002; Jindal & Bansal, 2016; Oddo et al., 2003). Aβ can be toxic when applied to the targeted proteins, which may accumulate and cause cellular dysfunction and neuronal death (Singh, Srivastav, Yadav, Srikrishna, & Perry, 2016). Aggregation of pathogenic proteins in association with the plasma membrane can impair the function of various transporters (ion-motive adenyl pyrophosphatase or ATPases that catalyze decomposition of ATP into ADP; glucose and glutamate transporters), ion channels, receptors (for neurotransmitters, growth factors, and cell adhesion molecules) and transduction proteins (GTP-binding proteins, adenylate cyclase, phospholipases, kinases) (Mattson, 2004). The protein aggregation that occurs in association with cytoskeleton proteins may disrupt axonal transport and synaptic signaling (Mietelska-Porowska, Wasik, Goras, Filipek, & Niewiadomska, 2014). Alterations in endoplasmic reticulum functions including abnormal stress responses and perturbed calcium regulation have been documented in protein aggregation disorders (A. Kumar & Singh, 2017; Panigrahi

& Singh, 2013). Increasing evidence suggests that intracellular aggregates of α-synuclein, huntingtin and prions impair proteasome-mediated degradation of proteins resulting the accumulation of damaged proteins in neurons (Ciechanover & Kwon, 2015). Mitochondrial dysfunction has been widely documented in patients and experimental models of AD, PD, and Huntington's disease (HD). Aggregation of Aβ, α-synuclein, and expanded polyglutamine proteins might have direct effects on mitochondria or may indirectly compromise mitochondrial function by inducing oxidative stress and disrupting calcium homeostasis. Finally, aggregates of polyglutamine-expanded proteins and other pathogenic proteins can form in the nucleus where they may perturb the transcription of genes (Panigrahi & Singh, 2012).

Aβ aggregation and mutations in tau result in breakage of bond between microtubules which is the skeleton of neuron, ultimately resulting in neuronal damage. The impact of these selected biomarkers can be directly traced and handled until we understand the signaling mechanism in normal and neurodegenerative conditions.

SIGNALING MECHANISMS FOR NEURODEGENERATIVE DISORDERS

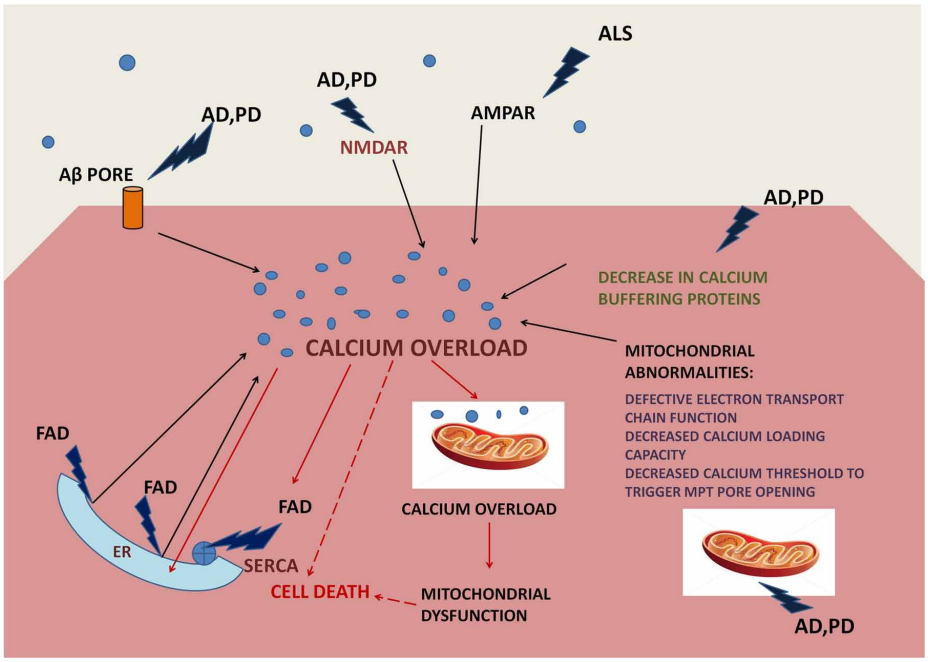
Ca^{2+} Blockers and a Combinational Approach for the Treatment of Neurodegenerative Disorders

The majority of the scientific attempt is paying attention on classification of the major reasons of the mentioned diseases and in the development of the methods to target them. Like, in case of AD, the main reason of disease is believed to be amyloid accumulation (Nilsson et al., 2010). Therefore, the much needed research is headed in the path of searching ways to avoid buildup of amyloid through blocking the fabrication or by the facilitation of its clearance from the brain. The major cause of the disease in the case of HD is the expression of mutant huntingtin protein (Irvine et al., 2008). The effort here is focused on trying to lessen the expression of mutant huntingtin in the brain which can be done with the help of antisense or ribonucleic acid interference knockdown. These approaches have been tricky to decode to the clinic in spite of outstanding scientific rationales. In case of HD clinical trials, already existing hindrance is the advancement of an antisense brain-delivery system which might be helpful in humans. RNAi methodologies might not initiate in HD clinical trials, unless it gets achieved. The clinical trials involving amyloid-binding compound tramiprosate along with tarenflurbil (Flurizan) which is a γ-secretase inhibitor have failed (Lukiw, 2012). Moreover while considering AD, the amyloid-binding monoclonal antibodies have yielded a few restricted benefits in the clinical trials.

Neuronal Ca^{2+}Signaling and Aging

Various studies related to comparative analysis were done over the neurons taken from rodents which show the neuronal calcium ion signaling machinery undergoing major changes which are age-related (Toescu & Verkhratsky, 2007). A model of changes dependent on age in hippocampal calcium ion handling is newly planned (Gant, Sama, Landfield, & Thibault, 2006). The leading modulations in the aging neurons comprise of the amplified release of calcium ions from the intracellular stores via different receptors like inositol (1,4,5)-trisphosphate receptors (InsP3R) and ryanodine receptors (RyanRs) (Núñez-Santana et

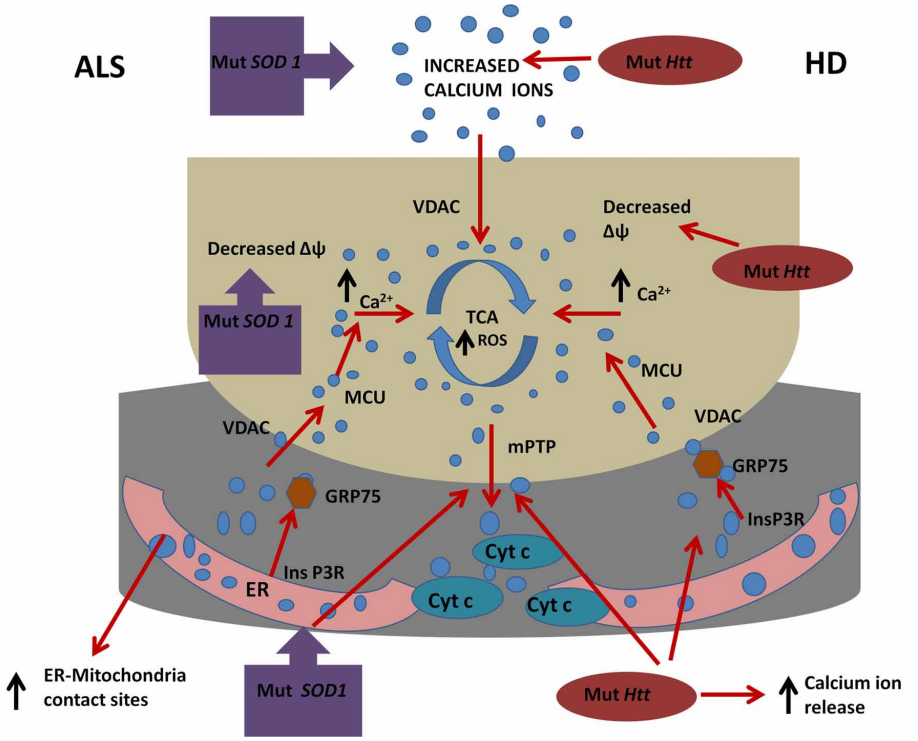
Figure 1. Role of calcium accumulation in neurodegenerative disorders through mitochondrial dysfunction (Berridge, 2010)



al., 2014). Amplified Ca^{2+} influx via L-type voltage-gated calcium channels (VGCCs), amplified slow after-hyperpolarization with the initiation of Ca^{2+}-dependent K^{+} channels, lesser input of N-methyl D-aspartate receptor (NMDAR)-mediated Ca^{2+} influx and condensed cytosolic Ca^{2+} buffering capacity and moreover the induction of calcineurin and calpains (Catterall, 2011). The substantial changes in neuronal Ca^{2+} dynamics further leads to augmented susceptibility to induction of long-term depression (LTD) and an increase in the threshold frequency for initiation of long-term potentiation (LTP) in aging neurons (Foster, 2007). LTD and LTP refer to activity-dependent and constant variations in synaptic strength, which are generally considered to form a basis for formation and then storage of memories in the brain (Foster, 2007).

The pathways accountable for alterations depending on age in neuronal Ca^{2+} signaling mechanism are not clearly understood. The probable clarification is associated to defects induced with the age in the functioning of mitochondria due to cumulative oxidative damage to mitochondria. The depolarization of the mitochondria from aged neurons and lesser proficient in handling Calcium ions load (Toescu & Verkhratsky, 2007). Changes related to age in the transcription of calcium ion signaling genes were practically obtained in microarray studies (Toescu & Verkhratsky, 2007). A few of these alterations are caused directly due to aging and a few are compensatory, on the other hand, the general picture is constant with alterations due to age in neuronal calcium ion signaling at several levels. The modulations in calcium ion signaling which are detected in the NDs such as PD and AD is discussed using calcium signaling route in given Figure 2.

Figure 2. Calcium signaling understanding through mitochondrial route and association with cell death pathway by increase in calcium level (Rizzuto, Stefani, Raffaello, &Mammucari, 2012)



Neuronal Ca^{2+}Signaling and Alzheimer's Disease

Amyloid hypothesis is the most governing representation for pathogenesis in the case AD according to which the amplified production of amyloidogenic Aβ42 peptide or an enhance in Aβ42:Aβ40 ratio is a major reason behind neuronal and synaptic loss (Hardy & Selkoe, 2002). The tentative hold for this hypothesis is drawn from:

1. Buildup of amyloid plaques in the brains of patients suffering from AD, (Arispe, Rojas, & Pollard, 1993)
2. The Familial AD cases that are an outcome of the missense mutations of amyloid-precursor protein (Arispe et al., 1993)
3. The FAD cases that result from the missense mutations in presenilins forming a catalytic subunit of the amyloid precursor protein (APP)-cleaving enzyme γ-secretase (Singh et al., 2016).

The prime focus of AD drug development has been the 'amyloid-targeting' therapies. The latest clinical trial outcomes have suggested that additional targets beyond amyloid have to be considered seriously for the treatment of AD (Seabrook, Ray, Shearman, & Hutton, 2007). Amyloid body of confirmation has also recommended that neuronal Calcium ions dyshomeostasis have an essential role in AD.

One of the potential connections involving AD pathogenesis and calcium ions can be observed from Aβ oligomers that can form Ca^{2+}permeable channels in membranes (Arispe et al., 1993). Presence of

phosphatidylserine (PtdS) on the surface of the cell ordinarily demonstrates the cells under vitality shortage conditions and additionally improves the capacity of relationship of Aβ with the film (G. Lee, Pollard, and Arispe, 2002). Mitochondrial disabilities which are related with the age may bring about the expanded surface PtdS levels in neurons that are influenced and arrange them up for Aβ-intervened pore development, Ca^{2+} attack and cell passing. The neurons with dense cytosolic ATP levels and unmistakable surface PtdS levels are predominantly vulnerable to Aβ poisonous quality (Simakova and Arispe, 2007). The ability of Aβ oligomers to frame channels which demonstrate Ca^{2+} penetrability in neuronal plasma films is steady with most recent in vivo Ca^{2+} imaging tests which are performed utilizing APP transgenic mice (Kuchibhotla et al., 2008). The examinations portrayed the resting levels of Ca^{2+} were extensively conspicuous in about 35% of neurites found in the quick surroundings of Aβ plaques. The conceivable elucidation for these results is restricted convergence of Aβ oligomers in the close-by areas of amyloid plaques which prompts the arrangement of Ca^{2+}porous particle diverts in the neuronal plasma film. The neurites with hoisted Ca^{2+} levels needed spines and demonstrated a unique morphology (Kuchibhotla et al., 2008). These morphological changes in the neurites may get lessened by treatment with the calcineurin (CaN) inhibitor named FK-506 (Kuchibhotla et al., 2008), which proposes that CaN has a critical part to play in obsessive reactions in order to hoist Ca^{2+} levels in the APP transgenic mouse. Moreover, straight impacts of Aβ on plasma layer Ca^{2+} porousness, Aβ oligomers even impact neuronal Ca^{2+} homeostasis by altering the activity of N-methyl-D-aspartate receptor (NMDARs) (De Felice et al., 2007; Shankar et al., 2007), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic corrosive receptors (AMPARs) (Hsieh et al., 2006) and additionally P/Q-sort VGCCs (Nimmrich et al., 2008).

One more likely affiliation associating Ca^{2+} flagging and AD can be comprehended by means of watching different FAD transformations in presenilins impact in irregular Calcium particles flagging. The connection including presenilins and Ca^{2+} flagging was initially uncovered once it was watched that fibroblasts from FAD patients free supranormal measures of Ca^{2+} in response with InsP3 (Ito et al., 1994). Related results were acquired from tries different things with cells communicating FAD mutant presenilins (Leissring, Paul, Parker, Cotman, and LaFerla, 1999) and cortical neurons from FAD presenilin-mutant thump in mice (Stutzmann et al., 2006; Stutzmann, Caccamo, LaFerla, and Parker, 2004). Keeping in mind the end goal to illuminate these results, it is prompted that mutant presenilins impact store-worked Ca^{2+} deluge (Leissring et al., 2000; Yoo et al., 2000), help the movement and in addition the outflow of intracellular Ca^{2+}discharge channels, as RyanR (S. L. Chan, Mayne, Holden, Geiger, and Mattson, 2000; Rybalchenko, Hwang, Rybalchenko, and Koulen, 2008; Yoo et al., 2000) and InsP3R (Cai et al., 2006; Cheung et al., 2008), or change the part of the sarcoplasmic and endoplasmic reticulum calcium ATPase (*SERCA*) ER Ca2+ pump (Green et al., 2008). Presenilins have themselves been seen to work as ER Ca^{2+}spill channels and numerous FAD changes in presenilins prompt the loss of ER Ca^{2+}release work, additionally bringing about ER Ca^{2+} over-burden and supranormal Ca^{2+} discharge from the ER (Nelson et al., 2007; Tu et al., 2006). Even though they vary in the particulars of the expected mechanisms, many of the research work was accomplished with various FAD mutations in presenilins resulting in intense Ca^{2+} release from the ER via InsP3R and RyanR.

Neuronal Ca^{2+}Signaling and Parkinson's Disease

PD fallout due to the selective loss of dopaminergic neurons in the substantia nigra pars compacta (SNc). The majority of the genes involved in familial PD e.g. *PINK1, DJ-1, LRRK2* and *Parkin* which encode proteins that are linked to a few aspects of mitochondrial function, pointing to mitochondria

as an essential locus in PD pathogenesis (Abou-Sleiman, Muqit, & Wood, 2006). The widespread idea of the 'dopamine hypothesis' states that dopamine (DA) which acts as a natural toxin and oxidation of cytosolic DA to 6-hydroxy-DA and other metabolites damages mitochondria and causes cell death of SNc neurons (Sulzer, 2007). Consistent with the continuous oxidative damage, affected SNc neurons accumulate large amounts of neuromelanin (NM), which is a lysosome composed of oxyradical DA derivatives of lipids and proteins. The Food and Drug Administration (FDA) approved treatment for PD is administration of levodopa (L-dopa), which is converted to DA and leads to elevation of DA levels in the cytosol and synaptic vesicles of remaining SNc neurons (Alexander, 2004). In an evident disagreement to the 'dopamine hypothesis', the management of L-dopa does not speed up disease expansion in PD patients in spite of increased levels of DA in their brain (Sulzer, 2007). Moreover, PD has lower level of penetrance and the majority of the people do not build up PD in spite of various similar levels of DA in their SNc neurons. The above mentioned observations hint towards a 'multi-hit' hypothesis of PD, which states that SNc neurons in PD provide a collective outcome of DA-related oxidative stress along with 'factor X' (Sulzer, 2007).

Midbrain dopaminergic neurons that express lifted levels of the calcium restricting protein (CaBP) calbindin are reasonably more secure in PD patients and in addition in creature models (Surmeier, 2007). Calpain actuation has additionally been inspected in sporadic PD and furthermore in creature models. α-synuclein is a principle constituent of Lewy bodies saw in the brains of sporadic PD patients and the changes in α-synuclein prompt autosomal-predominant inherited PD. The conceivable strategy for α-synuclein harmfulness is related with the development of little α-synuclein totals or protofibrils (Lashuel, Overk, Oueslati, and Masliah, 2013). Biophysicians thinks that synucleinprotofibrils deliver particle pores in manufactured lipid films (Volles et al., 2001) and empower Ca^{2+} convergence in neurons (Danzer et al., 2007; Furukawa et al., 2006). The proposed technique for synuclein-intervened Ca^{2+} flood might be similar the one proposed for Aβ oligomer-shaped Ca^{2+} channels. Additionally hold up for the 'Ca^{2+}speculations of PD (Surmeier, 2007) was given by physiological investigations. In actuality, the majority of alternate neurons in the sensory system, the SNc dopaminergic neurons utilize CaV1.3 L-sort Ca^{2+} channels to make imprudent pacemaking development in the scope of 2 to 4 Hz (C. S. Chan et al., 2007). The steady Ca^{2+} deluge prompts an over the top metabolic load on SNc neurons and thus making them overwhelmingly vulnerable to optional abuse on mitochondrial work. The reliance of SNc neurons on L-sort Ca^{2+} channels for the control over pacemaking increments with age and this may illuminate whether why age is such a noteworthy hazard factor for growing PD (C. S. Chan et al., 2007).

Inhibition of pharmacological $Ca_V1.3$ L-type Ca2+ channels having dihydropyridine isradipine by restoring Ca^{2+}free 'juvenile' pacemaking movement in SNc neurons. Subcutaneous release of isradipine considerably sheltered SNc neurons in animal models of PD. In support of this association to PD, a latest demonstration on epidemiological study suggested that the treatment of hypertension with Ca^{2+}channel antagonists considerably reduced the threat of rising PD (Becker, Jick, & Meier, 2008). These interpretations encouraged a restricted clinical trial for isradipine in PD patients.

Neuronal Ca^{2+}Signaling and Huntington's Disease

The disorders [AD, PD and amyotrophic sidelong sclerosis (ALS)] are for the most part unpredictable with uncommon familial structures. A couple of regular point of view that shows up from the investigation of the capacity of neuronal calcium particles motioning in these sporadic issues. These disorders

are 'multi-hit' and will most likely require a blended treatment, with Ca^{2+} inhibitors included as a piece of the treatment regimen. Rather than these clutters, HD is an absolutely hereditary confusion that is caused by a solitary change in CAG rehash (polyglutamine) extension in the huntingtin (*HTT*) quality (Gusella and MacDonald, 2000). The medium prickly striatal neurons (MSNs) are most influenced in HD. Chiefly, specialists concur with mutant *Htt* exp protein securing a 'dangerous pick up of capacity' (Gusella and MacDonald, 2000; Li and Li, 2006). Crumbling of neuronal Ca^{2+} flagging is such dangerous elements of the *Htt* exp protein. Steady changes in the articulation levels of numerous Ca^{2+} flagging proteins were seen in microarray investigations of the brains from HD patients and furthermore from HD mouse models (Kuhn et al., 2007). The proof for a 'Ca^{2+} theory of HD' have been explored already (Bezprozvanny and Hayden, 2004) and are compressed and refreshed quickly here.

Neuronal Ca^{2+}Signaling Association With Amyotrophic Lateral Sclerosis

Sporadic AD, PD and ALS are 'multi-hit' diseases that are activated by a few neurotic components shown to be acting. Some of these variables are normal to all said three issues, while some are 'illness specific' (Bezprozvanny and Hayden, 2004). One of the critical components which are basic to these disarranges is maturing. The 'infection particular' elements result in specificity of neuronal populaces being influenced in these disarranges – hippocampal and cortical neurons in AD, dopaminergic SNc neurons in PD and engine neurons in ALS. The critical 'infection particular' factor for AD is collection of amyloid totals; for ALS, it is incendiary harm prompted by actuated microglia and for PD, it is poisonous quality coming about because of dopamine oxidation. As these disarranges seem to be 'multi-target', combinational treatments can be just unbeaten in treating such infection, with both 'ailment particular' and in addition 'normal' pathways targeted (Alexander, 2004).

Neuronal populaces communicating lifted levels of Ca^{2+}restricting proteins are decently saved in such clutters, yet if there should be an occurrence of neuronal populaces with diminished levels of CaBP are extremely influenced. Decrease in levels of neuronal CaBPs is one of the results of the typical maturing process. Lessened capacity to cradle cytosolic Ca^{2+} is probably going to be one of the components that make maturing neurons defenseless in AD, PD and ALS (Surmeier, 2007).

Enactment of the calpain group of Ca^{2+} subordinate proteases is seen in maturing neurons and in sporadic AD, PD and ALS. The initiation of calpains is caused by raised cytosolic Ca^{2+} levels. Actuated calpains cut an assortment of substrates critical for neuronal capacity, prompting neuronal brokenness and death (Bezprozvanny and Hayden, 2004).

TAUOPATHIES

Tau pathology is not a well-known characteristic of AD, however it is additionally found in an assortment of other related NDs. Actually, PiD, corticobasal degeneration, PSP and frontal temporal dementia alongside parkinsonism identified with chromosome 17 (FTDP-17) are all defined by some specific local and in addition by cell appropriations of strangely collected tau filaments (Wszolek et al., 2006). There is presently an unmistakable affirmation demonstrating the variations from the norm in tau are sufficient to cause NDs. These abnormalities comprise of:

1. The occurrence of causative mutations in the gene for tau in patients with FTDP-17(Clark et al., 1998; Goedert, Crowther, & Spillantini, 1998)
2. The linkage of specific tau haplotypes to PSP and CBD (Houlden et al., 2001)
3. The deficiency of other disease specific neuropathological abnormalities in many tauopathies (Wszolek et al., 2006)
4. The creation of tau transgenic mice that can recapitulate the chief phenotypic hallmark so authentic human neurodegenerative tauopathies (Lee, Kenyon, & Trojanowski, 2005)

Despite the fact that tau dysfunction unaided is adequate to fortify neurodegeneration without other cerebrum amyloids however the recurrence with which tau pathology happens in a wide scope of different NDs. These NDs has prompted the theory that tau capacities in a final, normal pathway that prompts neuronal passing or brokenness however this can be actuated by some other starting occasions. In transgenic mice, communicating tau and co-expression of APP or α-synuclein brings about the accelerating of tau pathology (Morris et al., 2014). This proposes neurodegeneration intervened by tau pathology can likewise get enacted downstream of the pathways of different illness which comes about because of the collections of both Aβ and α synuclein amyloidogenesis. This fits into the elucidations from infection appeared by the patients with APP changes clarifying bounteous Aβ and tauopathology, yet patients with tau mutations demonstrate for the most part tau pathology alone (Morris et al., 2014).

Tau is basically a microtubule-linked protein that binds to microtubules and stabilizes it. At present there are more than 30 different mutations or pathogenic nucleotide substitutions in the gene intended for tau that have been exposed to be the reason behind FTDP-17 in more than 50 different disease related biomarkers (Levy et al., 2005). These mutations might lead to NDs by one or more different mechanisms:

1. Alterations in tau splicing that lead to abnormal patterns of tau-isoform expression (D'Souza et al., 1999).
2. Compromise of tau's capability to combine with and stabilize microtubules (Hasegawa, Smith, & Goedert, 1998; Hong et al., 1998).
3. Enhanced fibrillization of tau (Goedert, Jakes, & Crowther, 1999).

Therefore, it can be said that tau mutations and by analogy tau dysfunction in sporadic disease, can lead to pathogenesis through mechanisms that involve both losses of function i.e., decreased microtubule stabilization and toxic gain of function which is increased fibril formation (Van Dooren, Princen, De Witte, & Griffioen, 2014). Depicting this fundamental dichotomy, therapies which target both the mechanisms are presently in development.

Research on biomarkers on NDs is a hotly debated issue where much work has to be done yet. As we can gain from this examination subject, biomarkers are enabling us to grow the information on the organic and anatomical premise of NDs and to actualize demonstrative methods in clinical practice and clinical trials.

TOPOLOGICAL METHODS FOR NETWORK ANALYSIS

On the basis of the set of curated ND genes, firstly the network of disease proteins associated to the diseases of concern is recognized. In order to evaluate the topological features of the proteins, several

centralities in the network were measured; namely, degree, betweenness centrality, closeness and topological significance. The disease-networks were modeled afterward by calculating the disease linkages in terms of shortest paths among the pairs of disease proteins. Allocation of proteins and connecting proteins were identified as the major requirements to be most likely accountable for disease linkages. The functioning of these connecting proteins was studied by the Gene Ontology (GO) enrichment analysis (Bansal & Srivastava, 2018).

Modeling Interaction Network of Disease Proteins

For the investigation of the NDs from the network view point, firstly the interaction networks of diseases proteins were modeled (Hasegawa et al., 1998; A. Kumar & Bansal, 2017). The expressed proteins of disease genes are the disease proteins that are linked to particular NDs, the list of disease genes related to the top neurodiseases which were obtained from the morbid map published in the Online Mendelian Inheritance in Man (OMIM) database. Sequentially the construction of the protein interaction network related to the top neurodiseases was done and then the disease genes to disease proteins were mapped based on the mapping design of the UniProt which is a database of protein sequences and their functional information (Apweiler et al., 2004; Bansal, Singh, & Chauhan, 2017). The associations of those disease proteins were then derived by validation of the experimental interactions from the Interologous Interaction Database (i2d) database. The homologous predicted protein interactions in the i2d database were expelled to amplify the dependability of protein interaction data. The ultimate interaction network of interest enclosed the disease proteins (nodes) and their direct interacting partners (edges) (V. Kumar, Bansal, & Chauhan, 2017). The network design was not directed and weighted as only the binary interactions were considered (Panigrahi & Singh, 2013).

Modeling Interaction Network of Neurodegenerative Disorders

On the basis of the disease proteins network, the network of NDs with meta-nodes and meta-edges were modeled that represented the diseases and the relations among them, in the same way. A meta-node was reasonable as a group of the ailment proteins related to one disease (Goñiet al., 2008). A meta-edge connecting one illness to the next was characterized as an arrangement of the ways interfacing their infection proteins (Bansal & Ramana, 2015). The meta-edges were weighted by methods for extraordinary score capacities *ri* to uncover the intensity of the association including two infections, similar to the two meta-hubs, called as ALS and spinal solid decay (SMA), included every one of the proteins related to ALS and SMA correspondingly (Bansal & Srivastava, 2018). Each match of proteins (one from ALS and one from SMA), were assembled by figuring their ways interfacing them together to perceive a meta-edge, called ALS-SMA alongside weight computed by *ri*. The meta-edges are just obvious if their score $ri > 0$.

ANALYZING THE NEURODEGENERATIVE DISORDERS NETWORK USING THE NETWORK MINING APPROACH

Computing Topological Properties of Protein Interaction Network

In order to study networks and their participating proteins the centrality of proteins in the network were evaluated. The practical importance of proteins may be observed by understanding their central roles in

the network. As the centrality depicts an exclusive structural characteristic, reliable possibilities of the biological traits can be attained by combinations of the above measures than depending upon a particular index (Azuaje, 2014). Various centralities changing from nearby scale were processed to transitional scale (topological hugeness upto 1 and 3 stages) and in conclusion to worldwide scale (betweenness and closeness). Different centralities have been utilized to portray the systems considered as takes after:

1. Firstly, the degree centrality or connectivity (D) of protein vertices Vi, depicting total number of interactions eij the protein has with other proteins vertices Vj. This is mostly accepted to calculate the local centrality in the network (Navlakha & Kingsford, 2010).
2. Secondly, the betweenness centrality (B) which is a measure of the positional control of proteins in the networks. The betweenness centrality of protein vertices Vi is well explained as the total number of shortest paths p lying between pairs of other proteins that pass through vertices Vi over the total number of shortest paths involving pairs of other proteins (Goñi et al., 2008).
3. Lastly, the closeness centrality (C) which measures whether how close a protein is to other proteins as well as the distant node (Limviphuvadh et al., 2007).

There are various online as well as standalone tools for network analysis like Cytoscape, STRING and GORILLA, BLAST2GO, etc. Network base analysis of molecular pathways will help in efficient prediction of biomarkers for diagnosis and prognosis of different forms of dementia. Moreover, network parameters and graph theory gives new insight to the available information which was earlier hidden in various data layers.

CONCLUSION

This chapter describes of molecular mechanisms occurs during neurodegeneration and helps to give overall view of pathological understanding through various modeling and network perspective. NDs have extended by the various characteristic features of the neuropathological lesions found in the brain. It is known now that these lesions cannot be considered as just biomarkers for NDs like AD and PD, but are tied essentially to their pathogenesis. For each situation of predominantly acquired neurodegeneration, the illness causing changes can be associated unswervingly to amyloid arrangement. These signs have now come into pointed concentration and neurodegenerative properties are enhanced comprehended, and they have given a well-manufactured method of reasoning to the in vitro, in vivo tests, and epidemiological investigations that have gone far towards checking this theory. These tests have established a strong framework for various potential therapeutics that is currently in preclinical and clinical advancement. Over the next few years the effectiveness of a many drugs will be experimentally tested, and there is an increasing assurance of the outcomes of these trials that will confirm current concept of the etiology of NDs.

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Chapter 11
Amyloid Beta:
The Foremost Protagonist in Alzheimer's Disease

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ABSTRACT

Alzheimer's disease (AD), exhibiting accumulation of amyloid beta (Aβ) peptide as a foremost protagonist, is one of the top five causes of deaths. It is a neurodegenerative disorder (ND) that causes a progressive decline in memory and cognitive abilities. It is characterized by deposition of Aβ plaques and neurofibrillary tangles (NFTs) in the neurons, which in turn causes a decline in the brain acetylcholine levels. Aβ hypothesis is the most accepted hypothesis pertaining to the pathogenesis of AD. Amyloid Precursor Protein (APP) is constitutively present in brain and it is cleaved by three proteolytic enzymes (i.e., alpha, beta, and gamma secretases). Beta and gamma secretases cleave APP to form Aβ. Ubiquitin Proteasome System (UPS) is involved in the clearing of Aβ plaques. AD also involves impairment in UPS. The novel disease-modifying approaches involve inhibition of beta and gamma secretases. A number of clinical trials are going on worldwide with moieties targeting beta and gamma secretases. This chapter deals with an overview of APP and its enzymatic cleavage leading to AD.

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INTRODUCTION

Dementia is considered to be an aggregation of symptoms affecting memory, cognition, social abilities on a severe magnitude. These adverse effects affecting the daily activities result from physical changes in brain. Dementia can further be of several types depending upon the underlying pathological condition and symptoms (Anand, Khurana, Chawla, Sharma, & Khurana, 2017). Dementias are progressive in nature. The sufferers may have troubles with short-term memory in the beginning which evolves into a loss of memory altogether. While there are varied symptoms of dementia, impairment in at least two of the following mentioned core mental functions should be there for the condition to be considered as dementia. These include deficit in memory, language and communication, ability to focus, capability to reason and judge and visual perception (Alzheimer's Association, 2017c). AD is the most common form of dementia. Over 47.5 million people globally were estimated to be suffering from dementia in 2016. By 2030, the figure is expected to reach as high as 75.6 million (World Health Organization, 2016). AD generally appears in mid to late adulthood. It is associated with a progressive and rather irreversible decline in memory and various other cognitive capabilities. In AD, there is neuronal destruction and deterioration of neural connections in the cerebral cortex region of the brain along with a substantial loss of brain mass (Perl, 2010). AD is lethal within 5–10 years of its onset (Dwyer et al., 2009). Mortality usually ensues due to complications of the chronic illness.

AD is characterized by the presence of two neuropathological hallmarks i.e. extracellular Aβ plaques and intracellular NFTs. The plaques constitute chiefly of the neurotoxic peptide Aβ, which forms after the sequential cleavage of a large precursor protein i.e. APP by two enzymes, namely, β-secretase (commonly known as BACE1) and γ-secretase (involving four proteins, including presenilin). However, Aβ is not formed if APP is first acted upon and cleaved by the enzyme α-secretase instead of β-secretase. NFTs comprise mainly of the protein tau which is a microtubule associated protein (MAP) i.e. it binds microtubules in cells to facilitate the neuronal transport system. In the development of AD, Tau uncouples from microtubules and aggregates into tangles thereby inhibiting transport and resulting in microtubule disassembly. It also depends on the phosphorylation of Tau (Anand, Patience, Sharma, & Khurana, 2017; Nisbet, Polanco, Ittner, & Götz, 2015).

The actual causes at play behind the development of AD are still not well defined. However, certain factors like anomaly in the phosphorylation of tau protein, alterations in calcium metabolism, oxidative stress, neuro-inflammation, abnormal energy metabolism and protein processing i.e. undesired Aβ formation and aggregation, are considered to be important factors in the pathogenesis of AD (Butterfield et al., 2002; Habibyar, Sharma, & Khurana, 2016; J Hardy & Selkoe, 2002). In the present chapter, role of Aβ formation and aggregation as the foremost protagonist in AD is discussed with special emphasis on APP and enzymes involved in its cleavage along with involvement of UPS in amyloid hypothesis of AD.

BACKGROUND

AD was first described by a German neuropathologist Alois Alzheimer in 1906 (Editors of Encyclopædia Britannica, 2016). AD was recognized as the most prevalent form of dementia among geriatric persons by the commencement of 21st century. It is one of the top five most common causes of mortality in population of the United States (Centers for Disease Control and Prevention, 2017). In rare cases, it may appear in people in their 40s and 50s, but otherwise it is a disease of old age. Based on clinical, population-

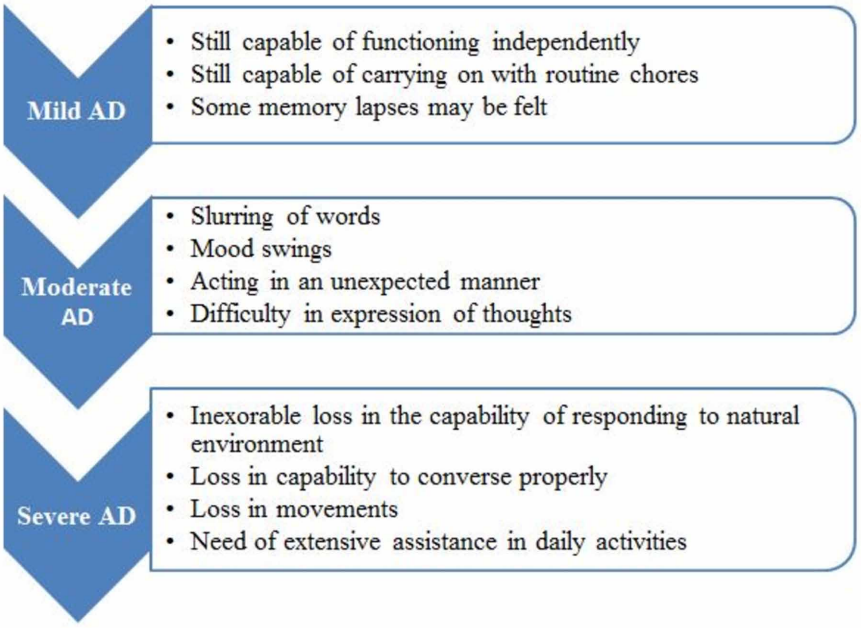
based studies, about 200,000 people under 65 years of age are suffering from AD. In contrast, around 5 million of those over 65 years of age have AD. As per speculations, a new case of AD is expected to be developed every 33 seconds, by 2050 (Alzheimer's Association, 2014).

The symptoms of AD get worse with time, although the pace at which the disease progresses is variable. Alterations in the brain related to AD commence years before any related clinical manifestations emerge. This period, spanning over a few years, is known as preclinical AD. The progression of AD occurs in three stages, namely mild AD (early-stage), moderate AD (middle-stage) and severe AD (late-stage). The symptoms associated with each stage are given in Figure 1.

There are several hypotheses which have been put up by several researchers for pathogenesis of AD out of which cholinergic hypothesis (McGleenon, Dynan, & Passmore, 1999) and Aβ hypothesis (Storey & Cappai, 1999) have been subjected to extensive research. Aβ hypothesis talks more about the actual pathological hallmarks which are visible in the patients' brains during autopsy. Cholinergic hypothesis has generated several acetylcholinesterase inhibitors as therapeutic measures for AD. However, these agents provide mere symptomatic relief (Anand, Patience, et al., 2017). Researchers are foraying more and more into the potential drugs targeting the amyloid pathway as it is considered to be a disease modifying approach.

Evidence exists suggesting involvement of both cholinergic and glutamatergic neurochemical systems in the etiology of AD. Acetylcholine (ACh) is an essential neurotransmitter responsible for cognitive functions and learning. In the brains of patients suffering from AD, it is decreased both in concentration and function. This deficit and other presynaptic cholinergic limitations, like loss of cholinergic neuronal network and reduced acetylcholinesterase activity, validate the cholinergic hypothesis of AD. Another neurochemical hypothesis for development of AD is the N-Methyl d-aspartate (NMDA) mediated glutamatergic hypothesis. Glutamate is an excitatory neurotransmitter which acts on NMDA

Figure 1. Stages and associated symptoms of Alzheimer's disease (Alzheimer's Association, 2017a)



receptors, which are pivotal in learning and memory. However, in some circumstances, over stimulation of NMDA receptors by glutamate causes neuronal damage due to excitotoxicity (Francis, 2005). A relatively recent mitochondrial dysfunction hypothesis for pathogenesis of AD proposes that AD brain mitochondrial dysfunction leads to amyloidosis, cell cycle re-entry, and tau phosphorylation (Swerdlow, Burns, & Khan, 2014).

The appearance of Aβ begins many years before the clinical manifestations of the disease appear, so it could be a reliable biomarker for AD prediction. As indicated, Aβ plays a major role in the formation of both amyloid plaques and NFTs, which gradually leads to AD. Aβ deposition leads to degeneration in synapses which leads to faulty interactions with different types of CNS receptors. Therefore, it disrupts neuronal homeostasis. Moreover, Aβ deposition along the cerebral vessels changes their tonicity and leads to some of the cerebrovascular deficits. Furthermore, its accumulation disrupts intracellular Ca^{2+} homeostasis which ultimately reduces neuronal Ca^{2+} buffering capacity. This, in turn increases excitotoxicity outcomes. Also, Aβ peptides may fold in different ways and show a prion-like pathology in the brain of AD patients (Sadigh-Eteghad et al., 2015).

An evidence base implicates Aβ in the pathogenesis of AD, leading to the formulation of the amyloid cascade hypothesis, i.e., the null hypothesis (John Hardy, 2006). The post mortem observation of the brain tissue of diseased individuals has made it quite obvious why Aβ is the primary suspect in disease pathogenesis. Aβ is the major constituent in two of the most distinctive histopathological hallmarks, namely senile plaques and cerebral amyloid angiopathy (Glenner & Wong, 1984a, 1984b).

The first and foremost argument that Aβ does not inititate AD is that deposition of Aβ into senile plaques is in no way specific to AD patients and is instead a marker of normal aging, i.e. the alternate hypothesis (Davies et al., 1988). Therefore, the strong association of Aβ in AD may simply mean an acceleration of senescence related deterioration. Support for this view can be found with the number of plaques in cognitively normal individuals against those seen in advanced disease (Mann, Jones, South, Snowden, & Neary, 1992; Schmitt et al., 2000). Furthermore, there exists only a weak correlation between the burden of Aβ and neuronal loss or cognitive impairment (Guillozet, Weintraub, Mash, & Mesulam, 2003). The alternate hypothesis is based on the notion that Aβ simply acts as a bystander or a protector rather than the causative factor of AD (H. Lee et al., 2007).

AMYLOID HYPOTHESIS OF ALZHEIMER'S DISEASE

There is an on-going debate about the Aβ hypothesis stating that the early, often initiating factor in development of AD is the imbalance between the production and clearance of Aβ42 and other related Aβ peptides. There are several hypotheses that have been suggested pertaining to the pathogenesis of AD. However, Aβ hypothesis is becoming increasingly popular amongst researchers worldwide (Alzheimer's Association, 2014). The Aβ hypothesis comes with the innate advantage of involving several molecular targets for drug development. Some important molecular targets are – APP, β- secretase 2 (BACE2), Aβ plaques. By efficiently creating structural and/or functional alterations at any of these targets, the progression of AD could be delayed or halted altogether.

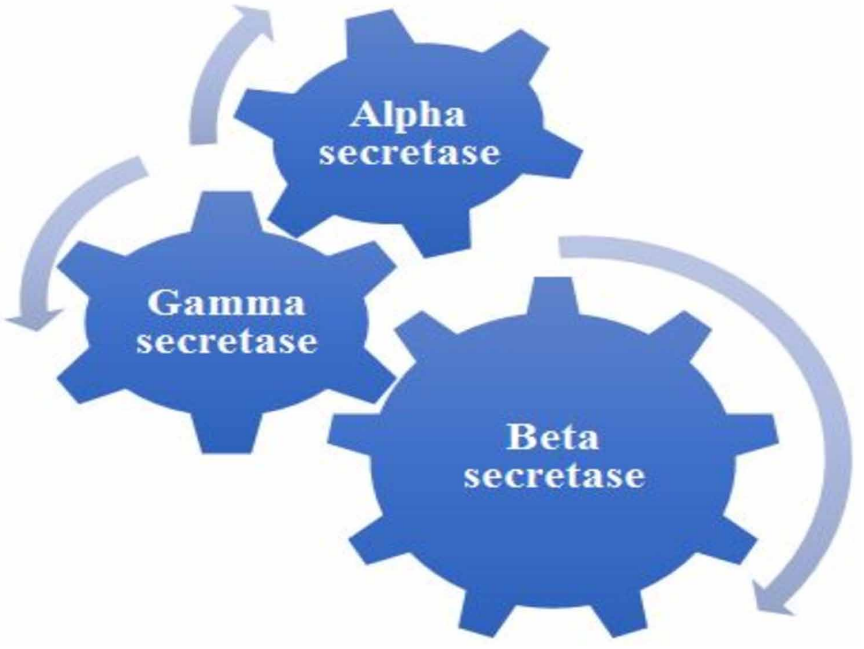
Amyloid Precursor Protein and Its Enzymatic Cleavage

APP belongs to the family of transmembrane and secreted proteins which includes the amyloid precursor-like proteins (APLP1 and APLP2) in mammals. It has several functions, which include regulation of haemostasis and mediation of neuroprotection. It is believed to stimulate neurite outgrowth and synaptogenesis. Also, it has been reported to have a role in stimulation of mitogenesis, G_0 proteins and MAP kinases for regulating cell proliferation, differentiation and survival. It seems to have a neuroprotective effect by altering cyclic guanosine monophosphate (cGMP) levels, Ca^{2+} homeostasis and activation of K^+ channels. It has also been reported to have a protective action against excitotoxicity, hypoglycemia and brain ischemia (Storey & Cappai, 1999).

The neuroprotective activity of APP has been substantiated by *in vivo* studies on mice. In one experiment, APP-transgenic mice were mated with HIV-gp120 transgenic mice and a significant protection was reported against HIV-gp 120 induced neurotoxicity (Mucke et al., 1995).

Although APP is a transmembrane protein that is present on the surface of neurons, the majority of it undergoes degradation within the secretory pathway even before it could reach the cell surface (Caporaso, Gandy, Buxbaum, & Greengard, 1992; Citron, Teplow, & Selkoe, 1995). APP is expressed in great quantities in neurons and undergoes rapid metabolism. Several alternate pathways exist for APP proteolysis. Some of these pathways lead to formation of the Aβ peptide and some of them do not (M. Lee et al., 2000). There are three enzymes which are responsible for proteolytic cleavage of APP (Figure 2).

Figure 2. Enzymes involved in proteolytic cleavage of amyloid precursor protein



Alpha Secretase

Alpha secretase is synonymous with the metalloprotease activity that is believed to have an involvement in the prevention of underlying molecular pathways of AD pathogenesis. Increasing α-secretase associated proteolytic cleavage of APP is thought of as a therapeutic measure for AD (Lichtenthaler, 2012). Neurotoxic Aβ peptides are not formed if APP is first acted upon by α-secretase. α-secretase cleaves APP inside the Aβ sequence. This, in turn, prevents the formation neurotoxic Aβ peptides (Zhang & Saunders, 2007).

After several years of research on α-secretase, the chiefly involved enzymes have been identified as parts of a disintegrin and metalloproteinase (ADAM) family. The family comprises of three membrane proteins i.e. zinc-dependent metalloproteinases. Three members of this family i.e. ADAM 10, ADAM 17 and to some extent ADAM 9 are known to exhibit α-secretase activity. Additionally, some other membrane linked metalloproteinases may play a role in processing of APP (Postina, 2008). Several cellular signalling pathways encompassing phospholipase C (PLC), serine/threonine specific kinases (protein kinases C, MAP kinases) and phosphatidylinositol-3-kinase also contribute to expression of α-secretase. α-secretase dependent processing of APP is also known to be stimulated by direct activation of protein kinase C and activation of distinct G protein coupled receptors (Skovronsky, Moore, Milla, Doms, & Lee, 2000). Therefore, M1 muscarinic cholinergic agonists and 5-HT4/5-HT6 serotonergic agonists are being clinically evaluated for their potential in treatment of AD.

Amongst the ADAM family, ADAM 10 is the constitutive and most physiologically relevant α-secretase for shedding of APP. It partially competes with γ secretase to cleave down a C-terminal fragment generated due to β secretase (Kuhn et al., 2010). A study has reported an 81% decrease in α-secretase and 185% increase in β secretase in temporal cortex of patients of sporadic AD (Tyler, Dawbarn, Wilcock, & Allen, 2002).

α-secretase activators show a potential to become a disease modifying therapeutic approach in the coming times.

Beta Secretase and Gamma Secretase

The most widely accepted hypothesis of AD is the aggregation of Aβ peptide in neurons leading to neurodegeneration. Beta secretase (BACE) is known to be the main culprit involved in the shedding of APP to generate neurotoxic Aβ aggregates in neurons. BACE, chiefly BACE-1, cleaves APP the product of which is further acted upon by gamma secretase to generate Aβ. It was a landmark discovery when BACE-1 (memapsin-2) was identified as a novel class of type 1 transmembrane aspartic protease. BACE-2 was identified soon after but it was revealed subsequently that BACE-1 is essential for majority of neuronal Aβ aggregation (Venugopal, Demos, Rao, Pappolla, & Sambamurti, 2008). BACE-1 causes endoproteolysis of APP to liberate Aβ N-terminal fragment, APPsβ, and a C-terminal fragment, C99. Cleavage of APP by BACE1is a prerequisite for γ-secretase dependent cleavage (Figure 3) (Robert Vassar, 2004). γ-secretase is multi subunit enzyme complex which plays a great role, subsequent to BACE1, in yielding Aβ from APP. It comprises of four principle components i.e. presenilin, nicastrin, anterior pharynx defective 1 and presenilin enhancer 2. These interact in a complex of high molecular weight to execute intramembrane proteolytic cleavage on a number of membrane-bound proteins including APP and Notch (Krishnaswamy, Verdile, Groth, Kanyenda, & Martins, 2009). Notch is a transmembrane receptor that regulates the cell-fate decisions (Barten, Meredith, Zaczek, Houston, & Albright, 2006).

Assembly of these four subunits leads to autoproteolytic breakdown of presenilin to yield two subunits, each of which donates one aspartate to the active site of aspartyl protease. The aspartyl protease bears an initial docking site for substrate where it binds before passing between the two presenilin subunits to the internal active site. Modulators and inhibitors of γ-secretase have been in clinical assessment to evaluate therapeutic benefit in AD. The ultimate goal is to alter the function of γ secretase on APP without interfering with the processing of Notch signalling. The allosteric sites on the protease permit such selective moderation (Wolfe, 2008).

BACE 1 exists abundantly in human brain. The maximum BACE activity is seen in neural tissue while astrocytes exhibit less activity than neurons (R Vassar et al., 1999). BACE mRNA levels are low in resting glial cells. Like other members of pepsin family, BACE 1 comprises of two active site motifs and the mutation of either leads to inactivity (Bennett et al., 2000; Hussain et al., 1999). It is a type 1 membrane protease with a luminal active site which provides the optimal spatial orientation for cleavage of APP (Cole & Vassar, 2008). The gene expression of BACE1 is strictly moderated at the transcriptional level. The promoter of BACE1 comprises of a functional Sp1 response element. The gene expression of BACE gets potentiated by overexpression of transcription factor Sp1. The transcription factor Sp1 has been known to have the major involvement in modulating the BACE1 regulated cleavage of APP (Christensen et al., 2004). However, γ secretase cleavage is imprecise and yields Aβ isoforms of varying C terminus lengths. The longer isoforms are typically linked to AD (Robert Vassar, 2014).

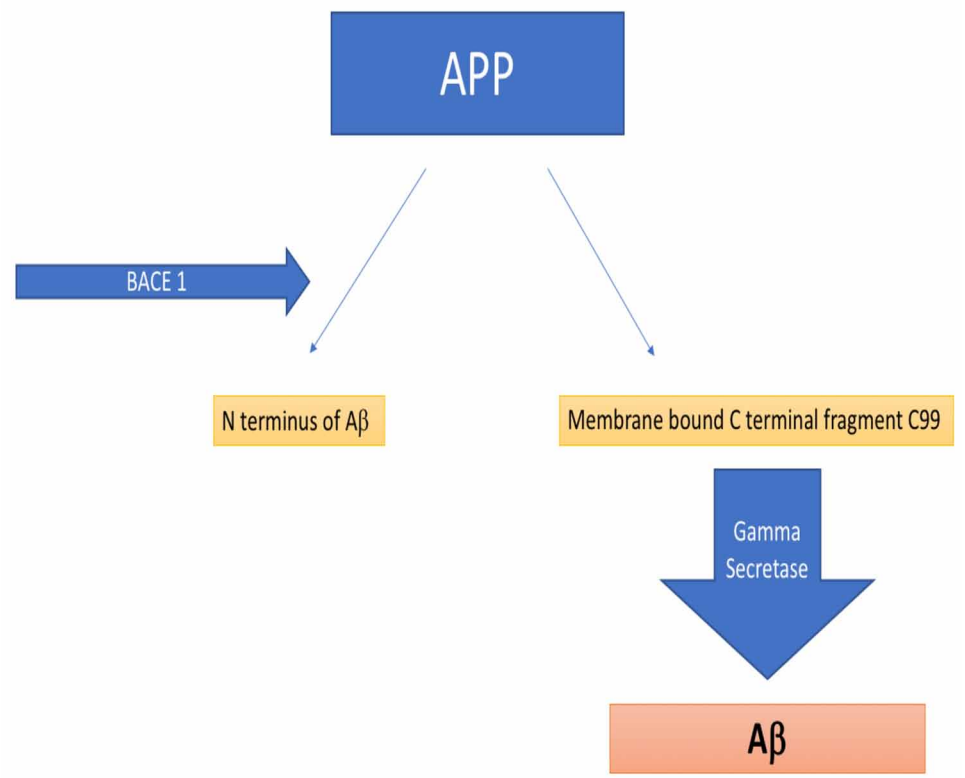
BACE1 is the prime disease modifying therapeutic target for treatment of AD. Inhibition of BACE1 can lead to a substantial decrease in cerebral Aβ levels. Clinical development of BACE1 antagonists is being intensely researched upon. Although, BACE1 antagonism provides high hopes for prevention and treatment of AD, concerns have been rising about the mechanism based potential side effects of these agents (Yan & Vassar, 2014).

Ubiquitin-Proteasome System

Deposition of proteins is a recurring event in several NDs, including AD. Evidence is there suggesting that protein accumulation may be a consequence of an impaired UPS. Indeed, there is clear genetic and biochemical evidence of an involvement of the UPS in AD pathogenesis (Oddo, 2008) . UPS, the major intracellular protein quality control system in eukaryotes, is responsible for the clearance and degradation of Aβ (Hong, Huang, & Jiang, 2014). There is growing evidence showing that there exists a strong relationship between Aβ (Hong et al., 2014) and UPS and this relationship plays an important role in pathogenesis of AD. The disturbance in the UPS contributes to deposition of Aβ in brain. The impairment in the UPS in AD affects the degradation of Aβ and causes an abnormal aggregation of Aβ (Hong et al., 2014). Simultaneously, Aβ inhibits the proteasomal activity and subsequently causes impairment in multivesicular bodies (MVB) sorting pathway, forming an interacting relationship between Aβ and UPS. Mutant ubiquitin and ubiquitin-like ubiquilin-1 are related to Aβ accumulation (Hong et al., 2014). The proteasome is a constitutive multi-catalytic, multi-subunit protease complex which employs homopolymers of ubiquitin as a signal for targeting proteins for degradation in an ATP-dependent pathway (Baranello et al., 2015).

In mammals, the most common form is 26S proteasome comprising of a proteolytic 20S core subunit with two 19S regulatory subunits. The complex is a hollow moiety so as to provide an entrance for proteins to be takeen in and degraded (Thrower, Hoffman, Rechsteiner, & Pickart, 2000). The first event involves adenylation of ubiquitin by the ubiquitin activating enzyme E1. Then, it is transferred to

Figure 3. The interplay of BACE1 and γ secretase in processing of amyloid precursor protein to yield Aβ



the active site cysteine residue of E2- the ubiquitin conjugating enzyme. In the last event, a family of ubiquitin ligases – E3 is involved (Pappolla, Omar, Kim, & Robakis, 1992). It identifies specific targets and catalyses the transfer of ubiquitin from E2 to the target protein (Pappolla et al., 1992). A target protein has to be labelled by at least 4 ubiquitin molecules for it to be able to be recognized for proteolysis.

Despite the inhibitory action of Aβ40 on the proteasome, it does not appear to be a substrate of the UPS. The proteasome can also moderate intracellular concentrations of PS1 and PS2, both, which indirectly influence γ secretase activity (Flood et al., 2005; Perry, Friedman, Shaw, & Chau, 1987).

AMYLOID BETA AND NEUROFIBRILLARY TANGLES: THE INTERPLAY

Apart from Aβ, NFTs are also invariably found in the brains of patients suffering from AD. The first experimental evidence that relates Aβ to tau, functionally, was described in a pair of landmark papers. Together, these studies concluded that increased tau pathology due to Aβ in the absence of any demonstrable effects on Aβ is caused by excess mutant tau. Thus, Aβ was reported to function upstream of tau, albeit by pathways that remained to be defined. (Gotz, Chen, van Dorpe, & Nitsch, 2001; Lewis et al., 2001).

During the past few years, ample evidence has been reported suggesting that the soluble forms of Aβ and tau act in combination, independent of their accumulation into plaques and tangles, to take neurons from healthy state to the diseased state. Also, it has been reported that hallmark toxic properties of Aβ

require tau (Bloom, 2014). The evidence that suggests that Aβ is influenced by tau, together with earlier reports that clearly demonstrated that Aβ clearly functions upstream of tau (Hurtado et al., 2010), creates the chances that Aβ triggers off a pathological feedback events with tau.

A protein that is responsible for a functional connection between Aβ and tau is fyn. It is a nonreceptor tyrosine kinase that causes positive regulation of NMDA receptor activity which was recently reported to be targeted to postsynaptic sites in dendrites by tau (Ittner et al., 2010) which binds fyn directly (G. Lee, Newman, Gard, Band, & Panchamoorthy, 1998). Tau is otherwise highly available in axons as compared to dendrites (Binder, Frankfurter, & Rebhun, 1985) but in response to Aβ, tau undergoes extensive redistribution into the somatodendritic compartment (Delacourte et al., 1990; H. Zempel, Thies, Mandelkow, & Mandelkow, 2010). Acute cytotoxicity is not the only tau-dependent manifestation of Aβ on cultured dissociated neurons or brain slices (Nussbaum et al., 2012; Rapoport, Dawson, Binder, Vitek, & Ferreira, 2002). Aβ oligomers have been reported to bring about tau-dependent microtubule disassembly (King et al., 2006), impaired long-term potentiation (Shipton et al., 2011), dendritic microtubule severing (Hans Zempel et al., 2013), inhibition of mitochondrial transport along microtubules (Vossel et al., 2010), and ectopic cell cycle re-entry of neurons (Seward et al., 2013), which eventually leads to massive neuronal death in AD.

NEW DEVELOPMENTS IN PHARMACOTHERAPEUTICS FOR THE MANAGEMENT OF ALZHEIMER'S DISEASE

The development of new therapeutic interventions for AD is under the threat of chasing the wrong pathology. Because of little concrete evidence base pertaining to a definite underlying pathological mechanism for development of AD, hypotheses based pharmacological interventions are being developed. Earlier, cholinergic hypothesis of development of AD emerged as a potential ground to build research upon. Several compounds were developed to target the acetylcholinesterase enzyme in order to elevate the levels of brain ACh. These agents are still in use but they provide only symptomatic relief. Also, a wide spectrum of side effects is associated with these agents. A few decades later, memantine came into picture as a protectant against glutamate excitotoxicity. However, this drug also could not yield effect better than mere symptomatic relief.

Several new chemical entities claiming to have potential benefits in AD have been developed by researchers all over the globe. However, a lot of them failed in the clinical trials due to different reasons mostly the severe adverse effects and lack of significant efficacy. A major factor that contributes to the increasing failures in development of new therapeutic measures for AD is that the current trial designs are quite nonspecific and blunt. Measure of cognitive abilities is a reductionist approach as the disease is too complex. Most of the pathobiological alterations do not manifest in alterations in cognitive processes and hence these two parameters cannot be correlated. The drug candidates targeting amyloid pathology are often employed at the later stages when Aβ related neurodegeneration has begun. This further adds to the increase in failures of new anti-AD therapeutics. This has not stopped the researchers from creating new possibilities for the treatment of AD (Anand, Patience, et al., 2017). The preclinical screening of novel entities for anti-AD effects is being carried out on a large scale worldwide. It is worth noting that no new drug (excluding nutraceutical products) has been able to obtain FDA's approval for treatment of AD in the last decade (Berk & Sabbagh, 2013). A great attrition has been found, with an

overall failure rate of 99.6% (0.4% success) in the decade spanning from 2002 to 2012 in the field of anti-AD therapeutics. The trial length and magnitude for disease modifying agents is greater than those for symptomatic agents. The success rate of an entity's progression from one phase of clinical trial to the next is low. The number of entities advancing to regulatory review is among the lowest seen in any area of therapeutics (Cummings, Morstorf, & Zhong, 2014).

Due to the limited options for the therapeutic agents, several new molecules have come in the recent years claiming to have a curative potential for AD. The existing pipeline for anti-AD drugs is quite modest in the light of the tremendous challenges associated with AD. Currently, AD is proving to be very expensive to the US economy, even more than cancer and cardiovascular diseases (Hurd, Martorell, Delavande, Mullen, & Langa, 2013).

Entities currently in clinical trials globally (as of 2017) targetting the amyloid pathological pathway of AD (Anand, Patience, et al., 2017) are given in Table 1.

FUTURE RESEARCH DIRECTIONS

Despite the exhaustive research that has happened in delineating the role of amyloid beta in AD, still certain unexplored areas remain in this amyloid hypothesis of AD. Mismatched APP cleavage by three proteolytic enzymes i.e. alpha, beta and gamma secretases, is believed to be the major reason for the production of neurotoxic Aβ peptides. The exact role of amyloid pathway of AD pathogenesis is still gray. There are several assumptions and hypotheses associated with it. An elaborate thrust on research areas intending to more clearly elucidate the intricate molecular mechanisms linked to amyloid pathway of AD pathogenesis needs to see the light of day. Recently unsuccessful antiamyloidogenic trials portray a strong need for an objective reassessment of the much talked about amyloid hypothesis of AD. The existing efforts with focus on Aβ, its deposition and accumulation, and its removal need to be supported by more intensive research in new directions. Once the exact molecular mechanisms, reaction cascades, proteolysis sequences and other associated targets are identified more clearly, effective and safe disease modifying pharmacotherapeutics can be developed.

Table 1. Entities currently in clinical trials for Alzheimer's disease.

Entity	C ompany	Description	Reference
AZD3293	AstraZeneca	Beta secretase inhibitor	Lilly, 2017
BACE inhibitor	Lilly	Beta secretase inhibitor	Lilly, 2017
CNP 520	Amgen	Beta secretase protein inhibitor	Amgen, 2017
E2609	Biogen	Beta secretase inhibitor	Biogen, 2017; Eisai, 2017
LY3314814	Lilly	Beta secretase inhibitor	Lilly, 2017
NGP 555	Neurogenetic Pharmaceuticals	Reported to cross blood brain barrier and effectively reducing the brain biomarkers Aβ42 and Aβ40 (in mice harbouring the human APP) by modulating the gamma secretase complex	NeuroGenetic Pharmaceuticals, 2017

Future research directions may be oriented thereafter towards increasing the expression of alpha secretase as its action on APP does not yield a neurotoxic product (Zhang & Saunders, 2007). Beta secretase and gamma secretase inhibitors are surely to experience an elaborate and tremendous research as they are the key enzymes that are responsible for generation of Aβ plaques which in turn cause neurodegeneration (Venugopal et al., 2008). Also, UPS stabilizers may be developed to halt or delay the impairment in the system thereby ensuring efficient clearance of formed Aβ plaques (Hong et al., 2014).

CONCLUSION

AD being a growing health concern worldwide has received a lot of attention from researchers in the past few decades. Despite enormous research, only symptomatic relief could be provided to the sufferers of AD. Aβ hypothesis of AD is the most widely accepted hypothesis for pathogenesis of AD. It states that the beta and gamma secretase linked cleavage of APP in brain leads to the formation of neurotoxic Aβ plaques. Also, an impairment in UPS system further augments the intensity of AD as there is significantly reduced clearance of Aβ from brain. All these events contribute to the state of loss of neuronal connections in brain and eventually cause a progressive and irreversible loss in memory and cognitive abilities. From developing safer and more effective drug candidates for the existing therapeutic targets (cholinesterase, NMDA glutamate receptors) to developing moieties focusing on newer targets (Aβ, BACE, gamma secretase, α-secretase), the researchers have been contributing their efforts to bring a preventive and/or curative therapy for AD. With an in-depth understanding of the amyloid hypothesis of AD, an effective disease modifying therapy for AD can be developed in the coming years.

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Chapter 12
Parkinson's Disease:
A Progressive Disorder of the Nervous System That Affects Movement

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ABSTRACT

Parkinson's disease (PD) is a neurodegenerative disorder in which a progressive loss of the dopaminergic neurons occurs. The loss of the neurons is most prominent in the substantia nigra region of the brain. The prevalence of PD is much greater among the older patients suggesting the risk of PD increases with the increase of age. The exact cause of the neurodegeneration in PD is not known. In this chapter, the authors introduce PD, demonstrate its history, pathogenesis, neurobiology, sign and symptoms, diagnosis, and pharmacotherapy.

INTRODUCTION

Parkinson's disease (PD) was first introduced by James Parkinson and arises by the progressive death of the dopamine neurons in the midbrain (Dauer & Przedborski, 2003). Neuronal cell death in the SN region in PD gives rise to the deficiency of dopamine in various region of brain including striatum, basal ganglia (BG) and subthalamic nucleus (STN) (Forno, 1996; Hornykiewicz & Kish, 1987). Increase in the age generally above 65 years increased the risk of the PD development; only a small number of individuals develop PD in early ages suggesting aging increased the risk of PD (Olanow & Tatton, 1999; Tanner, 2003). Thus older age individuals are particularly susceptible to PD (Fahn, 2003; Moghal et al,

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1994). The death of the dopaminergic neurons in PD results in the development of the motor symptoms of the PD (Goldenberg et al, 2008). The exact mechanism of the neuronal cell death in PD is not known completely, however it suggested that the mutations in the number of genes linked PD (Mizuno et al, 2001; Van Den Eeden et al, 2003). The prevalence of the familial PD is approx. 5% whereas for sporadic forms it is about 95% (Farrer, 2006; Tanner, 2003). In this chapter authors demonstrate the history, pathogenesis, neurobiology, symptoms, diagnosis and pharmacotherapy of PD.

BACKGROUND

SN region of the brain is rich in the dopamine containing neurons and the neuronal cell death in the SN region increases with the increase in the age and thus increased the risk of PD (Olanow & Tatton, 1999; Tanner, 2003). The death of the dopaminergic neurons in PD results in the development of the motor symptoms of the PD (Goldenberg et al, 2008). The exact mechanism of the neuronal cell death in PD is not known completely. Further it has been reported that besides SN region the neuronal cell death also occurs in the various other regions of the brain responsible for the complexity of the pathogenesis and the variety of the symptoms observed in the patients of the PD. However there are several therapeutics options are present for the pharmacotherapeutics of the PD patients but till date there is no suitable pharmacotherapeutic agent which can stop the neuronal degeneration in the PD. Further the complexity of the symptoms often makes the diagnosis and the therapeutics of the PD patients difficult. The present chapter demonstrates the history, genetics, neuronal degeneration, symptoms and the therapeutics of PD in details

HISTORY OF PARKINSON'S DISEASE

In 1817 James Parkinsons wrote "Essay on the Shaking Palsy" and described features including flexed posture, resting tremor, and shuffling gait in his monograph (Parkinson, 1817). After Parkinson, 50 years later use the term "Parkinson's disease". He demonstrated that the PD patients did not have tremor necessarily. He suggested that PD patients performs all task, but performs the task slowly suggesting the problems lies in the execution. Charcot defines two prototypes of PD, rigid and tremorous PD (Charcot, 1872). William Gowers, suggested that males are more susceptible to PD and described the impairment in the movement of fingers in PD patients (Gowers, 1898). Richer and Meige demonstrated the clinical and morphologic details regarding the various stages of PD (Richer & Meige, 1895). Adams and colleagues first described the degeneration of neurons in the SN region (Adams et al, 1964). Brissaud described the neuronal damage in the SN region as the anatomical seat of PD (Brissaud, 1895). Involvement of midbrain in context of PD were then described (Foix & Nicolesco, 1925; Tretiakoff, 1919). Greenfield & Bosanquet, described the involvement of brainstem in PD (Greenfield & Bosanquet, 1953). Hoehn & Yahr, described the stages to described the clinical progression of the PD (Hoehn &Yahr, 1967). The development of MPTP proves beneficial as it damages SN regions, so that the potential compounds can be tested in the preclinical studies (Langston et al, 1983).

GENETIC MUTATIONS AND PARKINSON'S DISEASE

The sporadic form of the PD is more common as compared to the PD associated with the family history. However 6 genes are targeted in context to PD and the mutations in these genes is responsible for the PD cases. These genes are located on the autosomes and therefore the PD arises from the mutations in these genes can be of 2 types, autosomal recessive and autosomal dominant. Further the autosomal-dominant PD develops due to the mutations in *SNCA* and *LRRK2* genes while autosomal-recessive PD develops due to the mutations in *Parkin, PINK1, DJ-1,* and *ATP13A2* (Klein & Westenberger, 2012).

α-synuclein is a filamentous protein present in LBs and the presence of LBs is the hallmark of PD. α-synuclein performs various functions including synaptic function and vesicular trafficking. It is reported that the overexpression of α-synuclein disrupts the mitochondrial functions, reduces tyrosine hydroxylase activity, and impairs synaptic function. It is reported that the mutation in *SNCA* gene results in the formation of the mutant protein which further contributes to dopamine toxicity by the oxidative stress (Campelo et al, 2017). SNCA gene encodes α-synuclein and *SNCA* gene mutation is responsible for the autosomal-dominant PD with the early onset (Klein & Westenberger, 2012). *SNCA* gene found physiologically has T instead of an A at position 53 of the protein, while the substitution of these amino acids in humans leads to the manifestation of PD. Further the A53T mutation of *SNCA* results in the impairments seen in the patients of the PD (Oczkowska et al., 2013). *PINK1-Parkin* pathway plays a key role in the pathogenesis of the neurodegenerative disorders e.g. PD (Narendra et al, 2008). *PINK1* is located on the outer mitochondrial membrane upon stimulated it is translocated inside the mitochondria where it is partially degraded by presenilin-associated rhomboid like protein (PARL) resulting in the release of the degraded *PINK1* (N terminal degraded) into the cytoplasm and in the cytoplasm it is gain degraded by the ubiquitin proteasome system (UPS). Thus a very low undetectable level of *PINK1* is present inside the mitochondria. Accumulation of the misfolded protein, results in the accumulation of the *PINK1* on the outer mitochondrial membrane suggesting the elimination of that mitochondria (Pickrell & Youle, 2015). *PINK1* localized on the mitochondria recruits *Parkin* to mitochondria from the cytoplasm, followed by the activation of *Parkin* which further results in eliminates the damaged mitochondria (Youle & Narendra 2011). Mutations in *PINK1* gene results in the development of the autosomal recessive form of PD (Klein & Westenberger, 2012).

Parkin was the second identified PD gene in context of PD, and the mutation in *Parkin* is responsible for early onset of the autosomal recessive form of PD (Klein & Westenberger, 2012). *Parkin* is an ubiquitin E3 ligase responsible for the degradation of the altered proteins and prevents the cellular apoptosis (Yoshii et al, 2011; Zhang et al, 2000). *Parkin* maintain the proper functioning of mitochondria and mitochondrial DNA (mtDNA) (Kuroda et al, 2006), inhibits ROS formation (Kuroda et al, 2006; Temme et al., 2009), protects mtDNA from damage from oxidative stress (Rothfuss et al, 2009, Watson et al, 2004), and regulates mitochondrial fission and fusion mechanism (Glauser et al., 2011; Narendra et al., 2008). *PINK1* phosphorylates *Parkin* at Ser65 in the N-terminal UBL domain followed by the activation of the *Parkin* (Truban et al, 2016) which then degrades the accumulated misfolded proteins and thus prevents the cell apoptosis (Yoshii et al, 2011; Zhang et al, 2000). *PINK 1* phosphorylates the mitofusin 2, for the binding of the *Parkin* to the mitochondria (Pickrell & Youle, 2015). *Parkin* thus acts as a protective agent. Thus *Parkin* mediated ubiquitination serve as signal for the degradation of ubiquitinated substance by the ubiquitin proteasome system, suggesting the role of *Parkin* in the formation of inclusion and autophagic clearance of targeted proteins (Dawson & Dawson, 2010). It is reported that the mutation in the gene encodes for *Parkin* accounts for the development of the PD pathology(Miklya et al,

2014; West et al, 2007), α-synuclein aggregation mediated oxidative stress (Bendor et al. 2013; Breydo et al, 2012; Fujiwara et al, 2002; Giasson et al, 2000), structural changes in mitochondria (Botella et al, 2008) reduced complex-I activity of ETC and ROS formation (Devi et al, 2008; Parihar et al, 2008, 2009) increase mitochondrial membrane permeability responsible for the leakage of pro-apoptotic molecules (Bandopadhyay & de Belleroche, 2010) resulting in neuronal cell death.

DJ-1 is a predominantly cytosolic, homodimeric protein, ubiquitously expressed in both brain and provides the neuroprotection by protecting cells against reactive oxygen species (ROS) (Björkblom et al, 2013). *DJ-1* contains 3 cysteine residues of which only C106 is highly susceptible to oxidative damage and it is reported that the alterations in the normal functioning of this residue led to the loss of the DJ1 function completely. *DJ-1* quenches ROS (Ariga et al, 2013) inhibit p53 and stimulates SOD expression (Ariga et al, 2013). Further the activity of the DJ1 decreases with the increase in the age suggesting the risk of the PD increases with the increase in age. Further the *DJ-1* mutations are responsible for the development of autosomal recessive form of PD but found in rare cases (Klein & Westenberger, 2012).

LRRK2 belongs to the Roco family proteins (Bosgraaf & Van Haastert, 2003; Marín et al, 2008; van Egmond & van Haastert, 2010) consisting of 2 domains: Roc and COR domains. Roc domain is essential for the kinase activity (Ito et al, 2007; Xiong et al, 2010; Taymans et al, 2011) while COR domain is essential for the dimerization (Gotthardt et al, 2008). Roc domain of *LRRK2* belongs to family of small G-proteins which become activated when GTP is bound and becomes inactive when GDP is bound (Vetter & Wittinghofer, 2001). *LRRK2* in monomer form is inactivated, dimerization led to the activation (Berger et al, 2010; Greggio et al, 2008; James et al, 2012; Schapansky et al, 2014; Webber et al, 2011). Dimerization led to the activation of GTPase reaction (Gotthardt et al, 2008; Sen et al, 2009) required for the normal biological functioning of the Roco proteins (Webber et al, 2011). In the neurons *LRRK2* colocalizes with Dynamin like protein 1 (DLP1) and its expression induced mitochondrial fragmentation and increased the level of ROS (Niu et al, 2012; West et al, 2005). *LRRK2* is involved in the various cellular functions including vesicular trafficking, proteolysis, regulation of neuritic outgrowth and neuritic morphology (Li et al, 2014). *LRRK2* is a positive regulator of murine microglia (Kim et al, 2012) and therefore its inhibition abolished the inflammatory mediators within the murine microglia cells (Kim et al, 2012; Moehle et al, 2012). *LRRK2* is known to regulate NF-κB activity (Gardet et al, 2010) which is further responsible for the induction of TNF mediated extrinsic pathway of the cell death and the inhibition of this pathway might reduce the neuronal death in the PD (Dauer & Przedborski, 2003; Hayley et al, 2004; McCoy et al, 2006). *LRRK2* gene mutations results in the onset of autosomal dominant PD in the later ages most frequently (Klein & Westenberger, 2012).

ATP13A2 gene encodes for lysosomal P5-type ATPase and it is suggested that the reduced levels of *ATP13A2* or loss-of-function mutations impairs degradation mechanisms due to the inhibition of the lysosomal mediated clearance of the misfolded proteins, resulting in the accumulation of α-synuclein which is responsible for the neurotoxicity (Bento et al, 2016). Mutations of *ATP13A2* is further characterized by early onset, rapid progression, dementia, pyramidal signs and supranuclear gaze palsy (Klein & Westenberger, 2012).

NEURONAL DEGENERATION IN PARKINSON'S DISEASE

SN neurons are under oxidative stress due to the metabolism of dopamine (Bender et al., 2006; Kraytsberg et al., 2006) and the metabolism of dopamine in SN generates a large number of oxidative species

(Sulzer, 2007) that evokes the oxidative stress in SN. Oxidative stress promotes the misfolding, aggregation of α-synuclein protein to form protofibrils resulting in the neurotoxicity (Lotharius & Brundin, 2002) by mitochondrial dysfunction (Ved et al., 2005), membrane disruption (Conway et al., 2001), and inhibition of protein degradation by lysosomes (Martinez-Vicente et al., 2008). Protofibrils themselves raised level of the dopamine in the cytoplasm by modulating vesicular membranes (Lotharius & Brundin, 2002) and the raised levels of the dopamine further interact with the α-synuclein to exert neurotoxic effects (Caudle et al., 2008; Chen et al., 2008; Edwards, 1993; Pardo et al., 1995; Sulzer & Zecca, 2000). The neuronal cell death in the SN region that primarily gives dopaminergic innervation to the striatum results in the marked deficiency of the dopamine in the striatum responsible for the motor dysfunction in PD (Alexander, 2004). Deficiency of the dopamine then results in the decreased activity of direct pathways and increased activity of indirect pathways of BG (Figure 1 and Figure 2), resulting in difficulty in initiating movement and excessive inhibition of movements (Walia et al, 2014) Further the loss of the dopaminergic cells in the retinal cells is responsible for the visual impairments in PD patients.

Basal forebrain consists of the cholinergic neurons (Bohnen & Albin, 2011). It is reported that the cholinergic neurons present in the pedunculopontine nucleus (PPN) and nucleus basalis of Meynert (nBM) is responsible for the maintenance of the gait (Rochester et al, 2012). It is suggested that besides SN region neuronal degeneration and accumulation of the LBs (Braak et al, 2003) also found in the PPN and nBM region (Arendt et al, 1983; Bohnen & Albin, 2011; Candy et al, 1983; Chui et al, 1986; Perry et al, 1985) of the brain resulting in the cognitive impairment (Kehagia et al, 2013) gait disturbance (Bohnen et al, 2012; Rochester et al, 2012) dopamine-resistant akinesia (Bohnen & Albin, 2011). Cholinergic

Figure 1. Direct pathway of basal ganglia. Cortex excites striatum which further receives the excitatory input from SNc region, results in the activation of striatum. Striatum sends inhibitory projections to the globus pallidus interna (GPi) and substantia nigra pars reticulate (SNr). GPi/SNr further exerts an inhibitory control on thalamus. Striatum upon excitation by SNc region, inhibits the GPi/SNr mediated inhibition of thalamus and thus facilitates movements. Therefore the damage to the neurons of direct pathway is responsible for the difficulty in initiating movement.

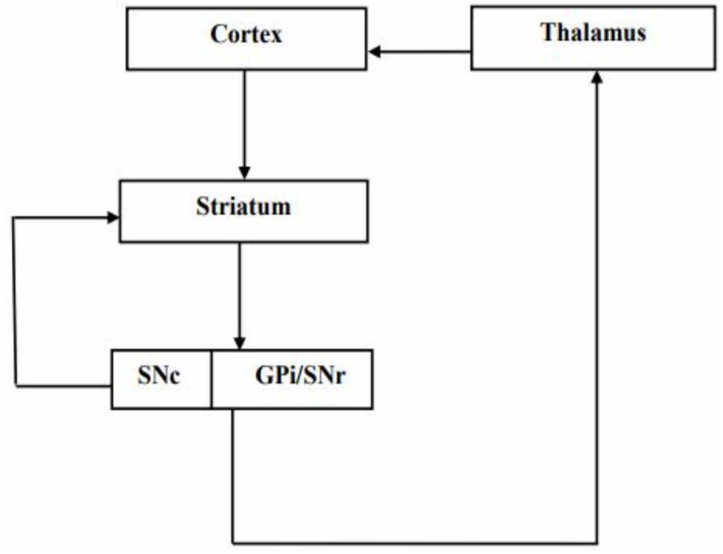
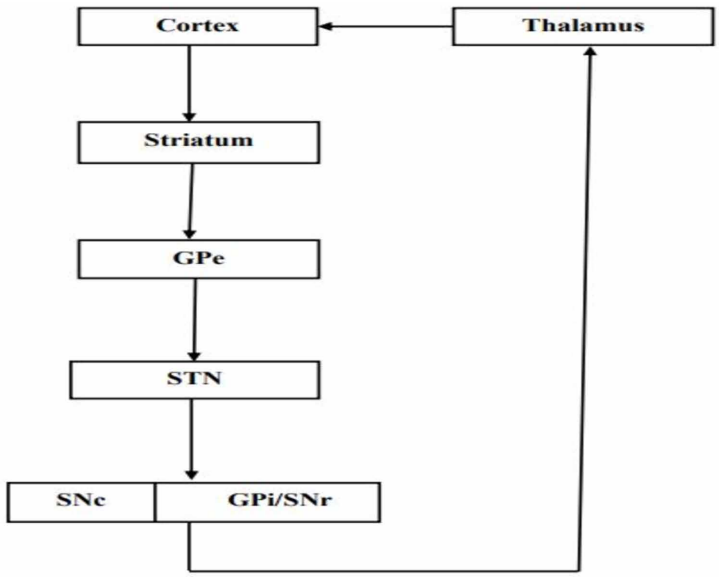


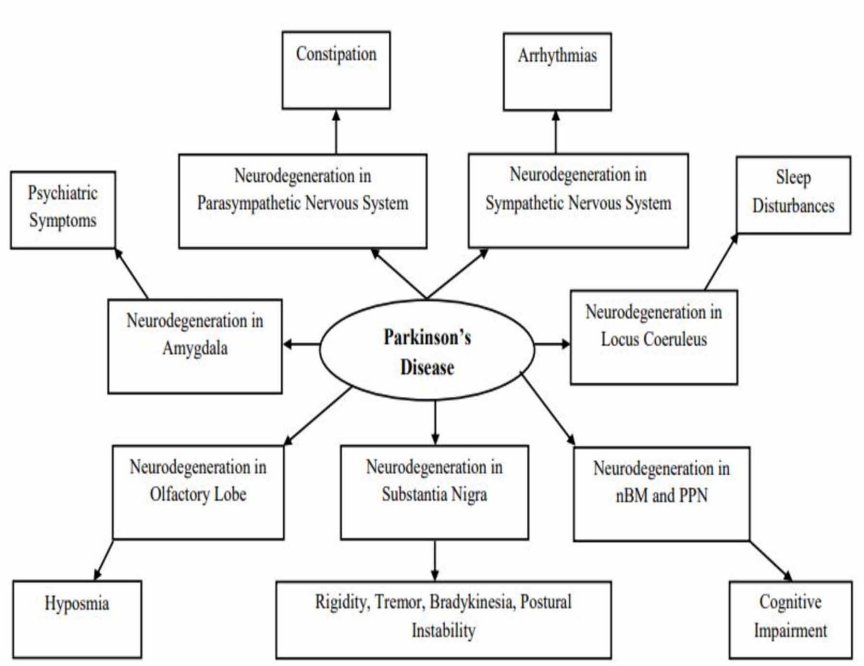
Figure 2. Indirect pathway of basal ganglia. In this pathways cortex send signal to the striatum which then send inhibitory signal to the globus pallidus externa (GPe) and reduced its activity. GPe sends projection to the subthalamic nucleus (STN) to inhibit its activity. STN further sends projections to activate GPi/SNr region resulting in the inhibition of thalamus. The reduced activity of GPe results in the increased activation of STN which is further responsible for the increased activity of GPi/SNr region and excessive inhibition of thalamus. Therefore the greater activation of this area is responsible for the inhibition of movement. In PD the activity of the indirect pathway increases resulting in the excessive inhibition of the movements.



neuronal loss in the PPN region is responsible for REM behavioral disorder in PD and in the nBM is responsible for dementia in PD (Alexander, 2004). Further the neuronal loss in these areas becomes more prominent in the presence of dementia (Candy et al, 1983; Nakano & Hirano, 1984; Rogers et al, 1985; Tagliavini et al, 1984; Whitehouse et al, 1983).

Further the destruction to the noradrenergic neuronal cells of locus coeruleus (LC) resulting in the marked decreased in the level of NA in cerebellum and frontal cortex responsible for the REM behavioral disorder in PD patients (Alexander, 2004). The destruction to the parasympathetic neurons at the preganglionic levels results in difficulty in swallowing in PD patients by the reduced esophageal motility and the destruction to the parasympathetic neurons at the preganglionic levels results in reduced GIT motility and constipation in the patients of PD (Alexander, 2004). Also the neuronal damage in the anterior olfactory nucleus and olfactory bulb is responsible for hyposmia seen in approx. 90% of PD patients (Alexander, 2004). Destruction to the sympathetic neurons at the preganglionic levels results in orthostatic hypotension in PD patients (Alexander, 2004) while at the postganglionic levels results in cardiac dysfunction (Alexander, 2004). BLA is further damaged to the glutamatergic neurons of BLA results in the visual hallucinations in PD patients (Alexander, 2004). Thus the pathogenesis of PD involves the neuronal degeneration in the different regions of the brain giving rise to the complexity and the variety of the symptoms that can be observed in the patients of PD (shown in Figure 3.)

Figure 3. Pathogenesis and symptoms of Parkinson's disease. This disease is accompanied by the neuronal damages in the different region of the brain and the symptom evoke depends on the region in which the damage occurs. Damage to the substantia nigra results in the motor dysfunction, damage to the nucleus basalis Meynert (nBM) and pedunculopontine nucleus (PPN) results in the cognitive impairment, damage in the locus coeruleus and amygdala results in the sleep disturbances and psychiatric symptoms, neuronal damage in the olfactory region is responsible for the loss of olfaction and the damage to the autonomic nervous system i.e. parasympathetic and sympathetic system is responsible for arrhythmia and constipation.



SYMPTOMS OF PARKINSON'S DISEASE

PD symptoms can be of motor and non-motor types. Motor symptoms of the PD includes resting tremor, bradykinesia, rigidity and postural instability (Clarke, 2002). Rest tremor is usually pill rolling type and is least disabling in nature as compared to the other features (DeMaagd & Philip, 2015). Besides rest tremors patients of PD often showed the presence of the various other form of tremor. Resting tremor occurs in 90%, postural tremor occurs in 88-92%, and head tremor occurs in 17% of PD patient (Thenganatt & Louis, 2012). Bradykinesia refers to the slowness of movement, a core motor feature of PD, develops initially or after the tremors (DeMaagd & Philip, 2015) and is the most disabling because of slowness imposed in the daily movements of patients they cannot perform the task quickly (Goldenberg, 2008). Rigidity is defined as the increased resistance offered during movement (Baradaran et al, 2013). Rigidity in PD is described by the term cogwheel rigidity means small jerks occurs while moving passively (DeMaagd & Philip, 2015). All the muscles in body have the opposing muscle such that if a muscle is contracted then its opposing muscles are relaxed. Rigidity occurs when this balance got disturbed. Rigidity can affect different body parts and face and therefore the patients often displayed masked expression

(DeMaagd & Philip, 2015). Postural instability develops in the latter stages (Santamato et al, 2015) and the postural instability in PD patients increased the risk of fall due to the imbalance (DeMaagd & Philip, 2015). The imbalance is due to the change in the posture of the patients (Goldenberg, 2008). Postural instability in PD predisposed the patients to the injuries and increased the incidence of the fractures (Santamato et al, 2015). PD related postural instability might be due to the lesions in nondopaminergic systems (Santamato et al, 2015).

Non motor symptoms suggested the involvement of extra-nigral pathology in PD patients (Braak et al, 2003) and these include autonomic disturbance, olfactory dysfunctions, psychiatric problems and sleep disturbances. Autonomic disturbance presents the multiple system atrophy (MSA) in PD often responsible for the reduced levels of the dopamine, serotonin and noradrenaline (Pellicano et al, 2007). Olfactory dysfunction occurs due to the death of the neurons in the olfactory region of the brain and is responsible for anosmia and hyposmia in PD patients (Pellicano et al, 2007). Psychiatric symptoms frequently occur in the PD patients, patients often suffer from the anxiety attacks and depression (Pellicano et al, 2007). Sleep disturbance develops due to the damage in the brainstem and thalamocortical pathways in PD. Sleep disturbance is characterized by the REM behavioral disturbances further characterized by the violent activities of the patients (Pellicano et al, 2007).

DIAGNOSIS OF PARKINSON'S DISEASE

PD involves the destruction of the dopaminergic neurons and the presence of LBs in the SN region. There is exactly no definite criteria for the diagnosis of PD. However diagnosis of the clinical PD is based on the presence of the symptoms or their combination. The diagnosis should be done in a careful and systematic manner. PD can be definite, possible or probable, however if the clinical symptoms are present then possible and probable PD should be diagnosed however if the neuropathological evidences are present then definite PD should be diagnosed (Gelb et al, 1999). Inquire should be made about the family history, daily life styles, previous medical history, occupation and environmental factors, followed by the anosmia/hyposmia, REM sleep disruption behavior, constipation, dementia, visual hallucinations and psychiatric symptoms. The clinician should check the eye movement, slowness, posture, and movement of body. Thus the careful assessment of the patient history through the questioning is the first step in the diagnosis of PD to rule out the presence of the familial cases of PD or any drug induced PD symptoms. The next step is the assessment of symptoms, clinicians should check the presence of resting tremor or bradykinesia to check whether the PD is tremor dominant or rigid type. Since PD is different from the parkinsonian symptoms because PD progresses asymmetrically and generally affect one side of the body. The careful examination should be done to rule out the presence of any movement disorders, asthenia and dementia. Different types of the parkinsonism have different distinguishing features for e.g. in case of the vascular parkinsonism (or lower body parkinsonism) lower limbs and the gait is affected and resting tremor are uncommon, in case of the drug induced parkinsonism the sign are symmetrical and tremors are present. It should be noted that the essential tremor and resting tremor are two distinct phenomenon such that the essential tremor rarely occurs at the rest and is not accompanied by the PD symptoms and gait disturbances. Dementia occurs in the patients of PD in late stages of the disease. If the dementia develops before or within one year of the PD diagnosis then it is known as Parkinson's disease dementia, however the diagnosis of the dementia prior to the onset of the PD is known as de-

mentia with LB (Massano & Bhatia, 2012). The damage to structure should be confirmed by imaging studies (Massano & Bhatia, 2012).

PHARMACOTHERAPY OF PARKINSON'S DISEASE

There are currently no standard established regarding, which should be initiate first in the treatment of PD patients. However different drugs should be used either as monotherapy or in combination for the therapeutics of PD patients. For e.g. L-dopa should be used for the treatment of the motor features, sildenafil should be used for the treatment of erectile dysfunction; cholinesterase inhibitors should be used for the treatment of the dementia and macrogol should be used for the treatment of constipation (Massano & Bhatia, 2012). The main aim of the pharmacotherapeutics of the PD patients is to reduce the symptoms and prevent progression of dopaminergic neuronal cell death in PD patients. The selection of the therapeutic agents should be on the basis of diagnosis and patient history to avoid the risk of adverse drug effects.

Dopaminergic Agents

L-dopa was introduced in the 1960s and its introduction revolutionized the treatment of PD (Katzenschlager & Lees, 2002). L-dopa when given cross the BBB and transported inside the brain, where it is metabolized by the enzyme aromatic amino acid decarboxylase into dopamine, which is then uptake and stored by the vesicles and released upon the neuronal depolarization (DeMaagd & Philip, 2015). L-dopa metabolized extensively in the gut and only 30% of the L-dopa reaches the systemic circulation (DeMaagd & Philip, 2015), therefore to avoid this extensive metabolism L-dopa is administered in combination carbidopa (Salat & Tolosa, 2013). The addition of the carbidopa increased the bioavailability and improved the tolerability of L-dopa. L-dopa is used as the first choice drug in the treatment of PD (Katzenschlager & Lees, 2002), however the fluctuations, on-off effect, dyskinesia, and psychiatric problems are frequently associated with the use of L-dopa (Katzenschlager & Lees, 2002; Salat & Tolosa, 2013).

Dopamine Agonists

Dopamine receptor agonists results in the activation of postsynaptic dopaminergic receptors present in the BG (Bonuccelli et al, 2009; Perez-Lloret & Rascol, 2010). Dopamine agonists are used in the symptomatic treatment of the PD and are as effective as L-dopa in the reduction of the motor symptoms of PD (Tintner & Jankovic, 2003). Dopamine agonists should be initiated at lower dose to avoid the incidence of adverse effects (Kieburtz, 2011; Hauser et al, 2010; Giladi et al, 2007; Watts et al, 2007). Instead of these facts L-dopa/carbidopa were considered more effective for controlling the motor symptoms of PD patients than the dopamine agonists (Hayes et al, 2010). Dopamine agonists should be used as monotherapy in the early PD because of their L-dopa sparing effects but used as the adjunctive to L-dopa in the advanced cases of the PD (Tan, 2003). Adverse effect includes the risk of nausea, vomiting, headache, narcolepsy, hallucination, somnolence, valvular heart disease (Borovac, 2016). Dopamine agonists are commonly divided into two groups:

Ergoline-Derivatives

Derived from the ergot and have greater risk of cancer, cardiac valve regurgitation and fibrotic changes. Ergoline derivatives include bromocriptine, pergolide, cabergoline, and lisuride. Bromocriptine shows agonism at D_2 receptors, used as monotherapy and adjunct therapy with L-dopa. Adverse effect includes nausea, vomiting, headache, confusion, hypotension, hallucinations, and delusions (Borovac, 2016). Pergolide shows agonism at D_1 and D_2 receptors and 5-HT_1 and 5-HT_2 receptors and used as the monotherapy for early PD. Adverse effect includes somnolence, sedation, and narcolepsy (Borovac, 2016). Cabergoline shows agonism at D_2, D_3, D_4 and 5-HT_2 receptors and antagonism at 5-HT_7 and α_2B receptors. Adverse effects include nausea, vomiting, dizziness, dyspepsia, postural hypotension, peripheral edema, and narcolepsy (Borovac, 2016). Lisuride shows agonism at D_2, D_3, and D_4 receptor agonist. It used as an adjunct to the L-dopa therapy used in the treatment of the PD. Adverse effects include nausea, dry mouth, headache, and postural hypotension (Borovac, 2016).

Non-Ergoline-Derivatives

These dopamine agonists have better safety profile and free from the risk of the cardiac toxicity. Non-ergoline derivatives include pramipexole, ropinirole, apomorphine, piribedil. Pramipexole shows agonism at D_2 and D_3 receptors and evokes beneficial effect in the early stages of PD. Adverse effects includes weight gain, constipation, and hallucinations (Borovac, 2016). Ropinirole shows agonism at D_2, D_3 and D_4 receptors. It is used for the pharmacotherapeutics of the PD patients in the early stages of the PD. Adverse effects include nausea, vomiting, constipation, dizziness, somnolence, confusion, hallucinations, and orthostatic hypotension (Borovac, 2016). Apomorphine is a strong non-ergoline D_1 and D_2 class receptor agonist. It is used for the treatment of the L-dopa induce dyskinesia. Adverse effects includes nausea, vomiting, headache, psychiatric problems, postural instability and injection site reactions (Borovac, 2016). Piribedil shows agonism at D_2 and D_3 receptors and antagonism at α2 receptors and produce marked vasodilatation. Adverse effect includes syncope and orthostatic hypotension (Borovac, 2016).

Catechol-*O*-Methyltransferase Inhibitors

Catechol-*O*-methyltransferase (COMT) inhibitors act by extending the duration of action of L-dopa and thus used in conjunction with levodopa (Waters, 2000) and increased its (Antonini et al, 2008). COMT-inhibitors including tolcapone and entacapone reduces the incidence of the wearing off associated with L-dopa/carbidopa therapy in the PD patients (Kurth et al, 1997). Adverse effect includes headache, dizziness, mental confusion, nausea and vomiting, dyskinesia, etc (Antonini et al, 2008).

Monoamine Oxidase Inhibitors

Monoamine oxidase (MAO) exists in 2 isoforms. MAO-A presents inside the presynaptic neurons and outside the neurons, accounts for about 20% of MAO activity in BG while MAO-B is localized in the extra-neuronal region (Sieradzan et al, 1995). MAO inhibition inhibits the metabolism of the dopamine and increased the levels of the dopamine (Sieradzan et al, 1995). MAO-A inhibitors i.e. Moclobemide has shown the symptomatic benefit in PD, safe to use and shown efficacy in the patients prescribed with L-dopa/carbidopa. However the major limitation is the incidence of cheese reaction on the consumption

of products rich in tyramine (Youdim & Bakhle, 2006). MAO-B inhibitors i.e. selegiline and rasagiline inhibit the enzyme MAO-B irreversibly, used either as the monotherapy or the adjunctive treatment to L-dopa in the therapeutics of the PD. Adverse effect includes sleeplessness, nausea, vomiting, dizziness, dry mouth, orthostatic hypotension, headache, confusion, and anxiety (Riederer & Laux, 2011).

Anticholinergic Drugs

Anticholinergic drugs are effective in the symptomatic treatments of the resting tremor seen in the patients of PD. These drugs can be used as the monotherapy or as adjunctive to L-dopa or helpful in reducing the dose of L-dopa in the advanced PD (Brocks, 1999). Anticholinergics used in the treatment of the PD are the competitive antagonists of muscarinic receptors and corrects the imbalance between the dopamine and acetylcholine as seen in the patients of PD. Adverse effects includes dryness of mouth, blurred vision urinary retention, blurred vision, tachycardia, mental confusion, constipation, and blurred vision (Brocks, 1999; Goldenberg, 2008)

CHALLENGES IN THE TREATMENT AND RESEARCH IN PARKINSON'S DISEASE

The greatest challenge is to find the reason and the mechanism of the neuronal cell death in the PD which is still unknown. Also the site of the neurodegeneration is not fixed, since multiple site of the neurodegeneration has been investigated though the stress on SN region is given primarily. The late diagnosis of the PD also promotes the progression of the disease and worsening of the symptoms in PD patients. PD is characterized by the presence of the LBs in the brainstem nuclei and the various other regions of the brain. However LBs have been noticed in the brain of the patients showing no clinical symptoms of PD and signs of dopaminergic neuronal degeneration representing a unique condition. Since PD occurs in the late phase of life which is often accompanied by the presence of the some other pathologies, further hampers the treatment of the PD. L-dopa (the main therapeutic agent reduces the motor symptoms in PD patients), itself produce dopamine and dopamine itself produces oxidative stress and exerts neurotoxicity. Further currently there is no drug available that can stop the neurodegeneration in the PD patients.

FUTURE RESEARCH DIRECTIONS

The neuronal cell death in the SN region of the midbrain might be due to the excessive release of glutamate which is known to interfere with the normal functioning of BG (Marino et al, 2003). Glutamate is the well known excitatory neurotransmitter of the CNS, produces its action by binding its receptors (Pettorruso e al, 2014). NMDA receptors have been found to be responsible for the glutamate mediated excitotoxicity and therefore the blockade of these receptors is responsible for the beneficial effect in PD. NMDA antagonists including traxoprodil and ifenprodil inhibit the glutamate mediated excitotoxicity, reduces the motor symptoms, potentiate the effect of L-dopa and reduce L-dopa induced dyskinesia associated with the L-dopa therapy. However the antiviral drug, amantadine exerts beneficial effects in the PD by its antiglutamatergic and NMDA blockade action (Johnson et al, 2009).

Coenzyme Q10 is a unique molecule, synthesized endogenously, involved in the transfer of the electrons in the mitochondrial electron transport chain and exerts the antioxidant activity. Further CoQ10 provides protection against the ROS mediated damage and abolished oxidative stress mediated neuronal cell death (Mancuso et al, 2009). Thus this unique molecule exerts the neuroprotective effect and therefore might be a good therapeutic option used for the treatment of PD.

Another new target which can be explored in context of PD is the enzyme GSK-3, which is the target of the neurotrophic factors, i.e. BDNF. Inhibition of GSK-3 provides protection against MPTP toxicity. α-synuclein, acts a substrate and activator for GSK-3 and the activation of this enzyme results in the reduced neurogenesis and neuronal damage (Lei et al, 2011). BDNF deficiency might be responsible for the hyperactive GSK3 (Beurel et al, 2015) and therefore GSK3 inhibitors counteracts neuronal loss in PD and GSK-3 inhibitors should be explored in context of PD.

CONCLUSION

The present chapter address about the various aspects including symptoms, diagnosis, treatment and challenges related to PD. However the exact cause of the death of the dopaminergic neurons in the brain is still unknown. Therefore the future work should be focus on the elucidation of the mechanism responsible for the death of dopaminergic neurons in brain. Further there is none of therapeutic agent available today which can prevent the death of dopaminergic neurons in the brain or stop the progression of disease further. Thus future work should focus on these aspects so as to provide better therapeutic options for the treatment of PD.

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Chapter 13
Alpha-Synucleinopathies: Parkinson's Disease, Dementia With Lewy Bodies, and Multiple System Atrophy

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ABSTRACT

Alpha-synuclein is a protein that forms a major component of abnormal neuronal aggregates known as Lewy bodies. A particular group of neurodegenerative disorders (NDs) is characterized by the abnormal accumulation of α-synuclein; termed the α-synucleinopathies, this group includes Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). Lysosomal storage diseases have also been linked to α-synuclein toxicity. Several therapeutic targets have been chosen among steps of metabolism of α-synuclein. Reducing α-synuclein synthesis or expression and increasing the clearance can be achieved in many ways. The development of immunotherapeutic approaches targeting α-synuclein has received considerable attention in recent years. The aim of this chapter is to present the α-synucleinopathies, as well as to present the most recent researches about treatment of synucleinopathies based on knowledge of the pathophysiology of α-synuclein pathways.

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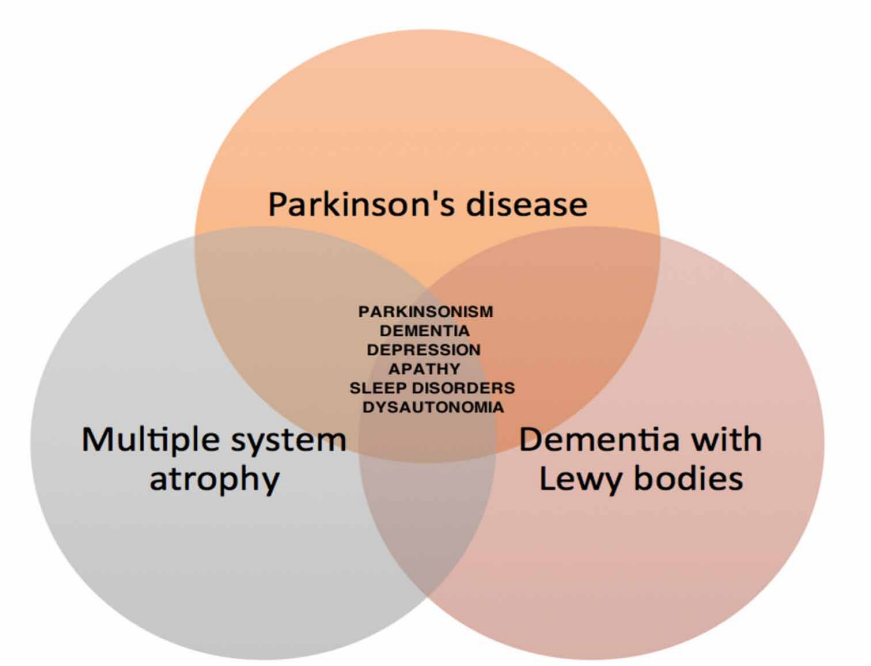
INTRODUCTION

A common feature among a number of neurological disorders is the abnormal aggregation of a protein as observed with amyloid beta in Alzheimer's disease (Selkoe et al., 1990) and huntingtin protein in Huntington's disease (Vonsattel et al., 2011). In 1912, Frederick Lewy first described the cytoplasmic inclusions now known as Lewy bodies in the substantia nigra in PD Cortical Lewy bodies were first reported in association with dementia in 1961 (Okazaki et al., 1961) but they were felt to be a relatively rare finding until the 1980s, when first ubiquitin and later α-synuclein immunostains made it easier to see them (Spillantini et al., 1997) and demonstrated that Lewy bodies were a common neuropathologic finding in dementia (Gomperts, 2016). α-Synucleinopathies is a particular group of NDs characterized by the abnormal accumulation of α-synuclein (Gomperts, 2016; Kahle, 2008) (Figure 1). Lysosomal storage diseases have also been linked to α-synuclein toxicity (Wong and Krainc, 2017). There are new treatments being researched based on the pathophysiology of alpha-synuclein, and immunology. The aim of this chapter is to present the α-synucleinopathies, as well as to present the most recent researches about treatment of synucleinopathies based on knowledge of the pathophysiology of α-synuclein pathways.

BACKGROUND

Despite the early knowledge of the involvement of α-synuclein in several neurodegenerative disorders, only recently has there been, as a Holy Grail, a search for the cause and cure of these diseases through α-synuclein cellular and extracellular mechanisms and pathways. A heated discussion on this topic was

Figure 1. Main common features among α-synucleinopathies



triggered after studies suggesting a prion-like role of α-synuclein in parkinsonisms (Brundin et al., 2016). After that, studies suggested the shaping of prions from gut sharing to central nervous system. Finaly, gut microbiota changes in PD patients increased discussions and interest in this subject (Scheperjans et al., 2015).

These are not the only controversies related to synucleinopathies. Neurologists have not always contented the term synucleinopathies, a clustering of various diseases that have the Lewy bodies and alpha synuclein as the center of pathophysiology. However, this chapter will try to demonstrate after describing the differences and similarities between these diseases, new findings on the pathophysiology of α-synuclein have helped to understand the clinical differences and, therefore, generating new researches for general treatments of synucleinopathies and also specific for them.

ALPHA SYNUCLEIN

There are different strains of α-synuclein, defined as conformational variants of α-synuclein — that exhibit distinct properties such as differences in structure and toxicity and ability to seed, propagate and cross-seed tau fibrillization. α-synuclein is able to transition between multiple different conformations, including monomers, tetramers, higher-level oligomers (soluble conformations), fibrils (highly ordered insoluble conformations characterized by β-sheet conformation) and aggregates. In addition, differences in α-synuclein strains also exist between synucleinopathies, such as PD and MSA (Bendor et al., 2013; Wong and Krainc, 2017).

The presynaptic location of α-synuclein has been recognized since its original identification as a protein associated with synaptic vesicles (Maroteaux et al., 1988). The protein is relatively specific to the nervous system (Iwai et al., 1995). In addition, α-synuclein is widely expressed by many neuronal populations within both central and peripheral nervous systems, suggesting a general role in neuronal function. However, α-synuclein appears to be one of the last proteins that localizes to developing synapses, arriving after integral membrane proteins of the synaptic vesicle and the peripheral membrane synapsin proteins (Withers et al., 1997).

ALPHA SYNUCLEINOPATHIES

Parkinson's Disease

PD is a neurodegenerative disorder, characterized by movement disorders and non-motors symptoms (Salat et al., 2016), associated mainly with dopaminergic neurons death in the substantia nigra, the progressive depletion of dopaminergic nigrostriatal and mesocorticolimbic neurons (Callesen et al., 2013), abnormal deposition of α-synuclein in remaining cells and gliosis in specific areas of the nervous system (Lees et al., 2009; Salat et al., 2016). However, the changes are not restricted to these brain regions and can be found in other nuclei of the brainstem, in the cerebral cortex and even in peripheral neurons, such as those in the myenteric plexus. The presence of degenerative processes in the dopaminergic system and in different brain areas, for example the frontal lobe, can explain a series of non-motor signs and symptoms such as cognitive impairment and dementia (Lees et al., 2009). Non-dopaminergic pathways are

also involved, including the serotoninergic and cholinergic neurons at, in addition to the spinal cord and peripheral nervous system, correlating with the main non-motor symptoms of the disease (Poewe, 2008).

PD was for a long time characterized by its motor symptoms and signs (Parkinson, 1817). In the International Parkinson's Disease and Movement Disorders Society 2015 Criteria for PD (MDS-PD criteria), the centrality of the motor syndrome remains the core feature by which clinical PD is defined. The prerequisite to apply the MDS-PD criteria is the diagnosis of parkinsonism, which is based on three cardinal motor manifestations. Parkinsonism is defined as bradykinesia, in combination with either rest tremor, rigidity, or both. These features must be clearly demonstrable and not attributable to confounding factors. Having established that the patient has parkinsonism, the MDS-PD criteria will be applied to determine whether the patient meets criteria for PD as the cause of this parkinsonism. The diagnosis of clinically established PD requires: absence of absolute exclusion criteria (e.g. cerebellar abnormalities), at least two supportive criteria (e.g., marked improvement with dopaminergic therapy), no red flags (e.g. rapid progression of gait impairment) (Table 1) (Postuma et al., 2015).

However, over the years the non-motor manifestations became better characterized and can now be identified in most, if not all, patients (Seppi et al., 2011: Simuni et al., 2013). The non-motor manifestations of PD involve autonomic, neuropsychiatric dysfunctions, changes in sleep-wakefulness and in pain perception (Goldman and Weintraub, 2015; Poewe, 2008). The most common neuropsychiatric phenomena include dementia, visual hallucinations, apathy and depression (Aarsland et al., 2009; Lieberman, 2006).

In recent decades various sensory abnormalities have been identified as a result of more effective diagnosis and improved treatment strategies (Hughes et al., 1992). Pain is present in around 60% of PD patients and occurs two to three times more frequently in this population than in age-matched individuals

Table 1. Summary of Parkinson's disease Movement Disorders Society criteria 2015 (Postuma et al., 2015).

Supportive Criteria	1. Response to dopaminergic therapy 2. Presence of levodopa-induced dyskinesia 3. Rest tremor of a limb 4. Positive results from at least one ancillary diagnostic test a. Olfactory loss b. Scintigraphy clearly documenting cardiac sympathetic denervation
Absolute Exclusion Criteria The presence of any of these features rules out PD	1. Unequivocal cerebellar abnormalities on examination 2. Downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades 3. Diagnosis of probable behavioral variant frontotemporal dementia within the first 5 y of disease 4. Parkinsonian features restricted to the lower limbs for more than 3 y 5. Drug-induced parkinsonism 6. Absence of observable response to high-dose levodopa 7. Unequivocal cortical sensory loss, clear limb ideomotor apraxia, or progressive aphasia 8. Normal functional neuroimaging of the presynaptic dopaminergic system 9. Documentation of an alternative condition known to produce parkinsonism
Red Flags	1. Rapid progression of gait impairment requiring regular use of wheelchair within 5 y of onset 2. A complete absence of progression of motor symptoms or signs over 5 or more years 3. Early bulbar dysfunction 4. Inspiratory respiratory dysfunction 5. Severe autonomic failure in the first 5 y of disease. 6. Recurrent (>1/y) falls because of impaired balance within 3 y of onset. 7. The presence of disproportionate anterocollis (dystonic in nature) or contractures of hand or feet within the first 10 y. 8. Absence of any of the common nonmotor features of disease despite 5 y disease duration. 9. Otherwise unexplained pyramidal tract signs 10. Bilateral symmetric parkinsonism throughout the disease course

without PD (Beiske et al., 2009; Defazio et al., 2008; Nègre-Pagès et al., 2008). It is an early symptom and can precede motor symptoms by several years (Kim et al., 2013; Lin et al., 2013; Pont-Sunyer et al., 2015). In the case of smell, which appears to be the sense that is involved the earliest, the prevalence of dysfunction can reach 90% (Doty et al., 1988).

The initial pathological description of PD changed drastically after functional and neuropathological studies showed the extensive involvement of extranigral pathways (Rajput et al., 1991). In addition, following studies like that by Braak et al. (2003), who showed that Lewy bodies are found throughout the nervous system and affect even the peripheral nervous system, a search began for nonmotor clinical findings and pathophysiological responses in PD, particularly dysautonomias, olfactory dysfunctions and sleep disorders (Jellinger, 2009).

Hereditary Parkinson's Disease

In 1997, mutations responsible for the disease were identified in the α-synuclein gene (*SNCA*) (Polimeroloulos et al., 1997). Understanding the monogenic forms of PD provides insight more broadly into the genetic architecture of this disease, and as described later, there appears to be overlap in the genes that contain disease causing mutations and those that contain risk variants (Table 2). Mutations in three genes, *SNCA* (*PARK1*; encoding α-synuclein), *LRRK2* (*PARK8*; encoding dardarin) and *VPS35* (encoding vacuolar protein sorting 35) have been shown to cause autosomal dominant forms of PD. Mutations in six other genes, *PINK1* (*PARK6*; PTEN induced kinase-1), *DJ-1* (*PARK7*), *Parkin* (*PARK2*), *ATP13A2* (*PARK9*), *FBXO7* and *PLA2GB* have been shown to cause autosomal recessive parkinsonism. All known monogenic forms of PD combined explain only about 30% of familial and 3–5% of sporadic cases (Hernandez et al., 2016; Kumar et al., 2011).

Following the discovery of *SNCA* mutations causing a rare familial form of PD, Spillantini et al. (1997) determined that α-synuclein was a major constituent of Lewy bodies, the pathological hallmark of PD. In addition to *SNCA*, autosomal-dominant PD-causing mutations have been found in the gene encoding Leucine-rich repeat kinase 2 *(LRRK2).* Mutations in *LRRK2* are the most common known genetic cause of late-onset PD and are found in both autosomal dominant and sporadic cases (Hernandez et al., 2016). *LRRK2* encodes a large the ROCO protein family, dardarin (Beilina et al., 2014; Greggio et al., 2009; Li et al., 2009), widely expressed in brain tissue.

During recent years several susceptibility genes and numerous risk loci associated with PD have been identified. While success in this regard has been driven by largely unbiased genome wide studies, some limited success was achieved through candidate gene-based assessments in three genes: *SNCA*, *LRRK2* and *GBA (*Hernandez et al., 2016).

Lewy Bodies Dementias

DLB and dementia that arises in PD (ie, Parkinson disease dementia [PDD]) together comprise the Lewy body dementias. Despite the different temporal sequences of motor and cognitive deficits, PDD and DLB show remarkably convergent neuropathologic changes at autopsy. These changes include widespread limbic and cortical Lewy bodies and Lewy neurites composed of aggregates of α-synuclein that involve the brainstem as well as limbic and neocortical regions (referred to as Lewy body disease), loss of midbrain dopamine cells, and loss of cholinergic neurons in ventral forebrain nuclei. Neuritic

Table 2. Monogenic forms of hereditary Parkinson's disease (Funayama et al., 2015; Hernandez et al., 2016; Kalinderi et al., 2016; Lesage et al., 2016).

Locus	Gene	Protein	Model
Park1	*SNCA*	α-Synuclein	Autosomal Dominant
Park2	*PARK2*	Parkin	Autosomal Recessive
Park3	*unknown*	unknown	Autosomal Dominant
Park4	*SNCA*	α-Synuclein	Autosomal Dominant
Park5	*UCHL1*	Ubiquitin c terminal hydrolase	Autosomal Dominant
Park6	*PINK1*	Pten-induced putative kinase 1	Autosomal Recessive
Park7	*PARK7*	DJ-1	Autosomal Recessive
Park8	*LRRK2*	Leucine rich repeat kinase 2 (dardarin)	Autosomal Dominant
Park9	*ATP13A2*	lysosomal type 5 ATPase	Autosomal Recessive
Park10	*unknown*	unknown	Risk Locus
Park11	*GIGYF2*	GRB interacting GYF protein 2	Autosomal Dominant
Park12	*unknown*	unknown	X-Linked
Park13	*HTRA2*	HTRA serine peptidase 2	Autosomal Dominant
Park14	*PLA2G6*	Phospholipase A2	Autosomal Recessive
Park15	*FBXO7*	F-box only protein 7	Autosomal Recessive
Park17	*VPS35*	Vacuolar protein sorting 35	Autosomal Dominant
Park18	*EIF4G1*	Eukaryotic translation initiation factor 4 gamma 1	Autosomal Dominant
Park19	*DNAJC6*	DNAJ/HSP40 homolog subfamily C member 6	Autosomal Recessive
Park20	*SYNJ1*	SYNJ1	Autosomal Recessive
Park21	*DNAJC13*	DNAJ/HSP40 homolog subfamily C member 13	Autosomal Dominant
Park22	*CHCHD2*	CHCHD2	Autosomal Dominant
Park23	*VPS13C*	Vacuolar protein sorting 13C	Autosomal Recessive
-	*SNCA*	α-Synuclein	Risk Locus
-	*LRRK2*	Leucine rich repeat kinase 2	Risk Locus
-	*GBA1*	Glucocerebrocidase	Risk Locus

plaques that contain amyloid and neurofibrillary tangles are found in the majority of cases of DLB and are common in PD (Gomperts, 2016).

A related Lewy body disease is PD, in which dementia may ensue and thereby, shares many clinical and cognitive features with DLB (Emre et al, 2007; Goldman et al., 2014). At early stages, DLB and PDD are easy to differentiate by the predominance of dementia in DLB and of parkinsonian motor features in PD. Nevertheless, in some patients, dementia and motor signs occur in close succession, provoking debate about their nosology. For research purposes, the "one-year" rule regarding timing of dementia and parkinsonian features is used (Emre et al, 2007; Goldman et al., 2014; McKeith et al., 2005). In clinical practice, however, a diagnosis is made based on the relative prominence of the clinical features. The separation between DLB and PDD is considered by some to be artificial, since it implies that the two clinical syndromes have different pathophysiologies (Aarsland et al., 2004; Goldman et al., 2014).

DLB is the second most common form of degenerative dementia after Alzheimer's disease, with prevalence rates of up to 5% in the elderly and up to 30% of all dementia cases (McKeith et al., 2005; Zaccai et al., 2005). PDD affects about 40% to 80% (Poewe, 2008; Pigott et al., 2015) of individuals with PD during the course of the disease. It is believed that 3% to 4% of cases of dementia in the general population are related to PD, and the estimated prevalence of PDD in the general population aged over 65 years is 0.2 to 0.5% (Aarsland et al., 2007). Mild cognitive impairment in PD (MCI-PD) has been shown to be a symptom that can progress to PDD. PDD has an insidious onset and progressive evolution (Goetz et al., 2008), being a major cause of the increase in the need of care at the old people's home, higher costs in healthcare and increased mortality (de Lau et al, 2005; Poewe e Mahlknecht, 2009). When dementia becomes clinically significant, the average survival of patients drops to 5 years (Poewe e Mahlknecht, 2009). However, cognitive decline is not limited to PD advanced stages and has been identified in 20 to 35% of patients recently diagnosed with PD or in the initial stages of the disease. This high prevalence and the major impact the condition has on the patient and family members make it essential to detect and diagnose cognitive changes in PD patients as early as possible (de Lau et al, 2005; Poewe e Mahlknecht, 2009).

The characteristic features of DLB are spontaneous parkinsonism, recurrent visual hallucinations, fluctuating cognition, rapid eye movement sleep behaviour disorder (RBD), severe sensitivity to antipsychotic medications and reduction in striatal dopamine transporters on single photon emission computed tomography (SPECT) or positron emission tomography (PET) (Donaghy e McKeith, 2014). The cognitive domains affected in patients with Lewy body dementia are: attention, memory, executive function, construction and apraxia, visuospatial function and language (Goetz et al., 2008). However, Lewy body dementia is mainly a dysexecutive syndrome characterized by impaired planning, a deficit in executive function (including organization of goal-directed activities), dyspraxia, bradyphrenia, reduced problem-solving ability, learning difficulty and short-term memory loss. Most patients also present concomitantly fluctuations in attention, mood and personality, as well as hallucinations and psychoses (Emre et al., 2007; Aarsland et al., 2010). This cognitive impairment is sufficient to compromise the ability to perform activities of daily living and planning, organizational, executive, visuospatial and language abilities (Aarsland et al., 2007).

PDD and DLB are associated with dopamine loss in dopaminergic pathways to the prefrontal cortex, and, to a lesser extent, the ventral tegmental area. In PDD, the appearance of Lewy bodies, which normally occurs in the advanced stages of PD, contributes to the development of severe dementia (Aarsland et al., 2009; de la Fuente-Fernández, 2012). As PD and PDD, the main pathological lesions seen in DLB are Lewy bodies and Lewy neurites, both containing α-synuclein. The pattern of distribution of Lewy bodies pathology in DLB, PD and PDD as seen at end stage is very similar, although cortical involvement may occur earlier in DLB and brainstem involvement may be minimal (Donaghy e McKeith, 2014).

There has been shown to be an association between hypofunction in the pathways involving the dorsal caudate nucleus and the orbitofrontal cortex (including connections with the amygdala), the same circuits that have been associated with the onset of PD, when PDD is less prevalent. This may explain the finding that depression is more correlated to less severe cognitive changes (den Brok et al., 2015; Remy et al., 2005). As the disease progresses, hypofunction of the circuit involving the anterior cingulate cortex and nucleus accumbens (including connections with the amygdala) occurs in patients with apathy, followed by changes in the pathways involving the ventral caudate nucleus and orbitofrontal cortex (Monchi et al., 2007; Remy et al., 2005; Reijnders et al., 2010). In the advanced stages of PD, patients have dopamine depletion in the corpus striatum (putamen, globus pallidus and caudate nucleus) as well as the frontal

cortex, increasing the prevalence and severity of apathy as dementia and Lewy bodies' progresses (Emre et al., 2007; Reijnders et al., 2010), in agreement with the findings of the present study. Apathy, rather than depression, therefore has the strongest association with more severe cognitive dysfunction in PD (Emre et al., 2007; Reijnders et al., 2010; Seppi et al., 2011). The good effect caused by levodopa in motor PD treatment was not observed in the assessment of neuropsychiatric dysfunctions. The explanation for this paradox is that levodopa does not cause significant changes in the activity of dopaminergic projections to the frontal cortex, as they are mediated largely by D1 dopamine receptors, but stimulates mainly D2 receptors, which predominate in the corpus striatum. Levodopa therapy is therefore not expected to lead to fluctuations in non-motor disturbances in PD (de la Fuente-Fernández, 2012; Remy et al., 2005).

Multiple System Atrophy

The term multiple system atrophy (MSA) was coined in 1969 to encompass three previously distinct neurodegenerative disorders, striatonigral degeneration, olivopontocerebellar ataxia, and "Shy-Drager syndrome" (Graham and Oppenheimer, 1969).

While in recent years considerable effort has been devoted at understanding the pathogenesis of PD, less is known about MSA, which is a rapidly progressive and fatal ND characterized by parkinsonism, dysautonomia (Dickson et al., 1999; Wenning et al., 2001) and α-synuclein accumulation within oligodendroglial and neurons. This accumulation is accompanied by neuroinflammation, demyelination and neurodegeneration (Valera et al., 2016). Additionally, MSA patients can develop pyramidal and behavioral alterations such as depression and executive dysfunction that suggest frontal lobe impairment (Dujardin et al., 2003; Ubhi et al., 2011). The autonomic dysfunctions most commonly are urogenital, gastrointestinal and cardiovascular dysfunction in the form of orthostatic hypotension (Pfeiffer, 2007).

Parkinsonian features reflecting striato-nigral neurodegeneration predominate in 80% of MSA patients (MSA-P subtype), while the major motor feature in 20% of patients is cerebellar ataxia due to olivopontocerebellar atrophy (MSA-C subtype) (Gilman et al., 2008). However, epidemiological studies in North America (Gilman et al., 2008) and Japan (Yabe et al., 2006) have suggested an ethnic variation with regards to the incidence rates of MSA-P or MSA-C. The North American Study reported 60% of their patients as having MSA-P and 13% exhibiting MSA-C (Gilman et al., 2008). In contrast, the Japanese study reported a much higher percentage of patients (83.8%) exhibiting MSA-C features with only 16.2% of patients being categorized as MSA-P (Yabe et al., 2006). The underlying cause of this variability remains undetermined but may involve genetic or environmental factors, or a combination thereof (Ubhi et al., 2011).

Clinically, the rapid progression, the lack of response to levodopa (Wenning et al., 1994), and pathologically the extensive accumulation of α-synuclein within oligodendrocytes differentiates MSA from other synucleinopathies (Dickson et al., 1999b; Valera et al., 2016). However, the mechanisms through which α-synuclein accumulates within oligodendroglial cells in MSA are not completely understood. One possibility is that α-synuclein is produced by oligodendroglial cells, which in turn over-express or fail to intrinsically clear α-synuclein; the other is that α-synuclein propagates from neurons to oligodendrocytes due to neurons over-expressing and/or displaying defects in the physiological mechanisms of α-synuclein clearance (Valera et al., 2016).

STORAGE DISEASES ASSOCIATED WITH ALPHA SYNUCLEIN TOXICITY

α-Synuclein has been implicated in several diseases, and lysosomal storage diseases have also been linked to α-synuclein toxicity.

Gaucher's Disease

Gaucher's disease (GD) is a rare, autosomal recessive lysosomal storage disorder that results from loss-of-function mutations in glucocerebrosidase (GCase) (Brady et al., 1965).

Three types of GD have been described, based on the rate of clinical progression and involvement of the nervous system (Grabowski, 2008). Type I GD is classically defined as non-neuronopathic and is typically characterized by visceral and hematopoietic abnormalities. Types II and III are differentiated from type I by neurodegeneration with either rapid (type II) or chronic progression (type III). A common feature is accumulation of GlcCer in the affected tissues, but the reasons for variability of GD are not known (Bultron et al, 2010).

A subgroup of type I GD with parkinsonism suggest a possible link between the two disorders (Neudorfer et al., 1996). Neuropathology revealed α-synuclein-positive Lewy bodies (Wong et al., 2004), suggesting the involvement of α-synuclein aggregation. Several genetic studies in large patient cohorts demonstrated that patients with parkinsonism have an increased incidence of *GBA1* mutations (Sidransky et al., 2009), making *GBA1* the most common known genetic risk factor for PD to date.

GBA1 mutations have also been identified in patients with the diagnosis of DLB (Goker-Alpan et al., 2006). The complete mechanism of the linkage between GlcCer and α-synuclein has not been explained.

Metabolism of GlcCer and α-synuclein show a reverse control, with the elevation of α-synuclein contributing to a pathogenic cycle by inhibiting the maturation of normal GCase and the GlcCer accumulation providing α-synuclein oligomer formation (Mazzulli et al., 2011).

It's not completely clear why patients carrying one *GBA1* mutation have increased risk of PD, although many of these patients have well above 50% of control GCase activity.

Thus, it is quite likely that multiple factors, many of which are impacted by the aging process, play a role with deficient GCase to cause parkinsonism (Aflaki et al., 2017).

Additional Lysosomal Storage Disorders

Mucopolysaccharidoses

In the mucopolysaccharidoses (MPS), glycosaminoglycans (mucopolysaccharides) accumulate as a result of impaired function of any of 11 lysosomal enzymes that degrade the glycosaminoglycans (Vitner et al., 2010).

In human MPS IIIB brain tissue, neuronal loss was observed only in the SN, but no Lewy Body-like inclusions were detected. In both MPS IIIB and MPS II brains, α-synuclein was phosphorylated mainly in neurons containing high levels of storage materials (Hamano et al., 2008). In an MPS IIIA mouse model the block in autophagy can lead to accumulation of polyubiquitinated proteins and mutant α-synuclein (Settembre et al., 2008).

Tay-Sachs and Sandhoff Diseases

The GM2 gangliosidosis (including Tay–Sachs and Sandhoff diseases) are caused by defective b-hexosaminidase activity (Vitner et al., 2010) with numerous case reports linking with PD. Adults patients with GM2 gangliosidosis can present various parkinsonian symptoms including bradykinesia, rigidity, bilateral tremor and resting tremor (Argov and Navon, 1984).

Immunohistochemical analyses in neurons of a Sandhoff disease mouse model demonstrated accumulation of α-synuclein and b-synuclein in striatal terminals and in the SN. Neurons that accumulated α-synuclein were negative for ubiquitin, suggesting a different form from that in classical Lewy bodies' disease (Suzuki et al., 2003). α-Synuclein is also observed in the cerebrum, cerebellum, and brain stem of both Sandhoff and Tay–Sachs disease human patients (as young as 2–3 years old) (Suzuki et al., 2007).

A biochemical association between GM2 gangliosidosis and PD has been demonstrated through the reduced levels of UCH-L1 in cultured fibroblasts from brain extracts from a Sandhoff disease mouse model, as seen in PD (Leroy et al., 1998; Liu et al., 2002).

Niemann-Pick Type C

Niemann–Pick C (NPC) disease is caused by the defective activity of either NPC1 or NPC2, resulting in cholesterol and sphingolipid accumulation (Vitner et al., 2010).

α-Synuclein was observed in the midbrain and amygdala, and classical Lewy bodies were found in the SN of NPC patients (Shachar et al., 2011).

Anecdotal reports linked NPC to sporadic parkinsonian syndrome in younger patients (Coleman et al., 1998).

Neurodegeneration With Brain Iron Accumulation

Neurodegeneration with brain iron accumulation (NBIA) is a group of ND characterized by iron accumulation in the basal ganglia, specifically in the globus pallidus (GP) and the substantia nigra (SN) and can be visualized with MRI. The cortex and the cerebellum can be affected, and cerebellar involvement correlates with the most severe NBIA subtypes (Wray et al, 2016).

α-Synuclein pathology is not usual in this class. Authors presented the NBIA forms with α-synuclein presentation, described at Table 3.

PLA2G6-Associated Neurodegeneration

PLA2G6-associated neurodegeneration (PLAN) is the second core NBIA syndrome (NBIA type II, OMIM 256600 and 610217) and is associated to mutations in the PLA2G6 gene (Morgan et al., 2006). It can present as infantile neuroaxonal dystrophy (classic INAD) and as atypical neuroaxonal dystrophy (atypical lNAD). INAD has an early onset presentation, usually with psychomotor regression and has a rapid progression with severe neurological deterioration.

The atypical INAD has a later onset and a less homogeneous presentation with gait problems, ataxia or speech difficulties being the most common symptoms (Gregory et al., 2008). The progression of the disease usually allows a longer life span than classic INAD.

Table 3. Human forms of neurodegeneration with brain iron accumulation, genes and presence of α-synuclein pathology (Adapted from Wray et al., 2016).

Human Disorder	MRI	Symptomatology	Gene	α-Syn Pathology
Pantothenate kinase-associated neurodegeneration (PKAN) (NBIA1)	Hypointensity with central hyperintensity of the GP, referred to as 'eye of the tiger'	Dystonia, spasticity and parkinsonism cognition often spared	*PANK2*	No
COASY protein associated neurodegeneration (CoPAN)	Hypointensity with central hyperintensity of the GP	Spasticity, dystonia, dysarthria, parkinsonism and cognitive decline	*COASY*	Unknown
Mitochondrial membrane-associated neurodegeneration (MPAN) (NBIA4)	Hypointensity of the GP and SN plus hyperintensity in the GP	Spasticity, dystonia, dysarthria, parkinsonism and cognitive decline	*C19orf12*	Severe Lewy bodies and Lewy neuritis GP, SN, cortex, striatum
PLA2G6-associated neurodegeneration (PLAN) (NBIA2)	Hypointensity of the GP in a subset of patients Cerebellar atrophy. Some cortical atrophy	Hypotonia, spasticity, dystonia, parkinsonism and cerebellar ataxia Motor and mental retardation	*PLA2G6*	Severe, Lewy bodies and Lewy neurites Ubq, α-syn SNc, cortex
FA2H-associated neurodegeneration (FAHN)	Hypointensity of the GP Cerebellar and cortical atrophy	Spasticity, ataxia and dystonia	*FA2H*	Unknown
β-propeller-associated neurodegeneration (BPAN)	Hypointensity of the GP/SN with central hyperintense line Cerebral and cerebellar atrophy	Parkinsonism, dystonia and dementia, developmental delay, cognitive disturbances	*WDR45*	No
Kufor-Rakeb syndrome	General atrophy and hypointensity in the basal ganglia/caudo-putamen	Parkinsonism, dementia and some pyramidal signs	*ATP13A2*	Unknown
Woodhouse Sakati syndrome	Hypointensity of the GP and SN	Diabetes, alopecia, hypogonadism, deafness	*DCAF17*	Unknown
Aceruloplasminemia	Hypointense striatum, thalamus and dentate	Dystonia, dyskinesia and cerebellar ataxia, cognitive impairment	*CP*	Unknown
Neuroferritinopathy (NBIA3)	Hypointensity in basal ganglia, especially GP and SN. Also motor cortex	Dystonia, spasticity, rigidity and parkinsonism. Some cognitive impairment	*FTL*	Unknown

The PLA2G6 gene encodes an 806 amino acid protein with predicted size of 88 kDa. (Mak et al., 2011). PLA2G6 has been shown to be expressed with protective function in the mitochondria (Saito et al, 2000).

Autosomal recessive mutations are found throughout PLA2G6 and lead to reduced enzyme activity, with the magnitude of enzymatic effect correlating with the disease severity (Morris et al., 1992).

PLA2G6 is classified as a PD gene (PARK14), and also, a reduction in PLA2G6 protein levels has been shown in the brains of Alzheimer's patients (Kupsch et al., 2003).

Pathology

The major pathological hallmark of PLAN is the presence of axonal swellings throughout the cortex, GP, striatum, cerebellum, brain stem and spinal cord. These are also present throughout the peripheral nervous system and can be diagnostic via peripheral nerve biopsies. There is evidence for PLA2G6 mutation-associated PLAN without spheroids (Morris et al., 1992). Peripheral spheroids are not observed in dystonia-parkinsonism subset of PLAN patients (Eidelberg et al., 1987).

α-Synuclein positive Lewy bodies are found throughout the degenerating brain areas to a very high degree, and a proportion of the axonal swellings also stained positive for α-synuclein (Williams et al., 2012; Lee et al., 2006).

Atrophy is evident in the cortex, GP, white matter and cerebellar cells and was shown to be associated with gliosis in the cortex and the striatum (Lee and Andersen, 2006). Excess iron deposition was specifically observed in the GP and the SN pars reticulata and there is extensive cortical involvement in disease with Lewy bodies seen in all cases whereas tau deposition is rarer.

Mitochondrial Membrane-Associated Neurodegeneration

Mutations in the *C19orf12* gene are associated with mitochondrial membrane-associated neurodegeneration (MPAN), an autosomal recessive disorder that represents between 5 and 30% of NBIA cases (Hartig et al., 2011; Hogarth et al., 2013; Panteghini et al., 2012). These patients are characterized by pyramidal and extrapyramidal signs, cognitive decline, neuropsychiatric changes, optic atrophy, and upper and lower motor neuron signs (Hartig et al., 2011; Hogarth et al., 2013).

Great variability is present in disease onset (between 3 and 30 years) and progression. Gait instability or visual impairment are often the initial symptoms, then followed by muscular weakness and atrophy, dystonia and dysarthria. Almost constant is the cognitive decline leading to dementia as well as the appearance of neuropsychiatric symptoms (Arber et al, 2016).

Brain iron accumulation is the most significant sign at MRI. It involves both the GP and the substantia nigra; it can be accompanied by cortical and cerebellar atrophy. Neuropathologic assessment performed in two cases showed very similar results with iron accumulation, axonal spheroids, tau and Lewy pathology in basal ganglia, the archicortex, the neocortex, and the spinal cord. Iron was evident in the GP and the substantia nigra and associated with neuronal loss and gliosis. Eosinophilic axonal spheroids were evident and were strongly immunoreactive for ubiquitin, and less positive for tau or APP staining (Hogarth et al, 2013).

Lewy pathology was present in many brain regions. In one case the overall burden was greater than that observed in cases of sporadic Lewy body disease (Hogarth et al., 2013).

The *C19orf12* gene consists of three exons and codes for two alternative mRNA isoforms (NM_001031726.3 and NM_031448.4) and proteins that differ for the presence of a stretch of 11aminoacids at the N-terminus of the longer form (Arber et al, 2016). Different types of mutation have been identified and many of them lead to truncated, non-functional proteins. The missense mutation c.32C>T is the most common and affects tyrosine 11, exclusively present in the longer form. The protein has a hydrophobic domain that could represent a transmembrane region. Its expression appears to be involved with CoA and lipid metabolism and mitochondria. No other information is available to explain the connection between the protein function, the neurodegenerative process, and iron accumulation in the brain. Recently, a *Drosophila* model with impaired expression of the two orthologs of human *C19orf12*, was

obtained (Iuso et al., 2014); those flies showed reduced life span, signs of neurodegeneration (vacuoles) but not of iron accumulation (negative Prussian blue staining) (Arber et al, 2016).

THERAPEUTIC POSSIBILITIES

Reducing α-Synuclein Synthesis

Given that increased α-synuclein uclein expression causes familial PD, several studies have aimed to decrease its synthesis by using siRNA that targets α-synuclein mRNA. In mice, direct siRNA infusion decreases hippocampal and cortical α-synuclein levels for a week after infusion (Lewis et al, 2008), whereas in mice expressing a human form of α-synuclein, injecting siRNA-containing exosomes decreases protein aggregation in the SNc (Cooper et al, 2014).

Given that antisense oligonucleotide (ASO)-mediated therapies are being tested in clinical trials currently as potential therapeutics for other ND, ASO targeting of α-synuclein may also be effective.

Increasing α-Synuclein Degradation

Increasing the clearance could be achieved in many ways but basically consists of restoring the autophagy-lysosomal pathways that are impaired in PD. Overexpression of the lysosomal transcription factor EB (TFEB), which was reported to coordinate cellular clearance via macroautophagy and exocytosis, in rats expressing α-synuclein decreases α-synuclein oligomer levels and prevents lysosomal dysfunction decline and neurodegeneration. In addition, alteration in TFEB activity was reported in induced pluripotent stem cell-derived neurons from GD patients who present α-synuclein pathology. In parallel, academic and industrial laboratories are screening for clinically approved drugs that can enhance TFEB function (Dehay et al., 2016; Wong and Krainc, 2017).

In addition to attempting to boost lysosomal biogenesis, acidic NPs (aNPs) of poly DL-lactide-*co*-glycolide (PLGA), which are FDA approved, have been reported to traffic to lysosomes and to act on lysosomal pH. However, whether PLGA-aNPs can acidify sick lysosomes and restore lysosomal/autophagic function in pathological conditions remains to be determined. Reacidification of defective lysosomes following PLGA-aNP treatment restores lysosomal function in different pathological contexts (Dehay et al., 2016). An alternate protective strategy could be to prevent endosomal uptake of pathological α-synuclein into cells increased expression of other lysosomal proteins, including LIMP2 and ATP13A2, also promote α-synuclein degradation in various models, presenting additional targets for the acceleration of α-synuclein degradation (Wong and Krainc, 2017).

Reducing α-Synuclein Agregation

Given that α-synuclein oligomers and fibrils are implicated in α-synuclein toxicity, several strategies have been attempted to reduce their formation. The porphyrin phthalocyanine tetrasulfonate binds and stabilizes vesicle-associated α-synuclein, which thus delays its misfolding and aggregation (Fonseca-Ornelas et al., 2014).

Passive immunization using a protofibril-selective antibody decreases soluble and membrane-bound α-synuclein protofibrils in the spinal cord and decreases motor dysfunction in mice expressing PD-

associated mutant A30P α-synuclein (Lindstrom et al., 2014). In addition, if native α-synuclein exists predominantly as a tetramer, compounds that stabilize α-synuclein in this conformation—as has been applied for transthyretin, which misfolds in the multisystem disorder transthyretin-related amyloidosis—might be effective at combating α-synuclein toxicity (Dettmer et al., 2015).

Several clinical trials are currently using small molecules (Schneeberber et al., 2016) to inhibit either α-synuclein aggregation (glycerol phenylbutyrate (University of Colorado, Denver); nilotinib (Georgetown University) or α-synuclein oligomer formation (EGCG (University of Munich).

Blocking α-Synuclein Propagation

Because α-synuclein propagation may contribute to the spreading of α-synuclein toxicity, passive immunization studies to block spreading have also been performed. Antibodies against C-terminal truncated α-synuclein decrease its propagation in vitro and rescue motor and memory impairments in an α-synuclein mouse model (Games et al., 2014), and monoclonal α-synuclein antibodies prevent propagation and uptake of α-synuclein and rescue dopaminergic neuron loss and motor deficits in mice injected with α-synuclein pffs (Tran et al., 2014).

Importantly, understanding the role of propagation in disease will help to clarify whether these therapies will be successful for patients.

Passive and Active Immunization

The development of immunotherapeutic approaches targeting α-synuclein has received considerable attention in recent years. In this sense, both humoral (active and passive) and T-cell-based approaches have been explored. While active immunization stimulates the immune system to produce antibodies against target proteins (the response takes days/weeks to develop but may be long lasting—even lifelong), passive immunization consists in directly administering IgG antibodies that confer temporary protection against the disease (several weeks to few months) (Valera et al., 2016-b). Monoclonal antibodies against α-synuclein can regulate inflammation and facilitate the clearance of target protein via autophagy or microglia (Valera et al., 2016-b).

Immunotherapy has been shown to induce a physiological microglial response (M2 type) and reduce the production of proinflammatory cytokines, thus exerting an anti-inflammatory effect in neurodegenerative disorders (Valera et al., 2016-b). Among the cell types that can internalize α-synuclein aggregates, microglia exhibit the most rapid clearance of these proteins. Microglia became better scavengers for extracellular α-synuclein aggregates in the presence of specific antibodies against α-synuclein. Antibody-α-synuclein immune complexes entered microglia through the Fcγ receptors, which led to efficient delivery of these immune complexes to lysosomes, hence resulting in fast degradation. By clearing extracellular α-synuclein, antibody treatment significantly reduced the extent of cell-to-cell transmission of the protein in mouse models. Furthermore, clinical advantages might be expected if extracellular α-synuclein is selectively targeted by immunotherapy with the intraneuronal α-synuclein being left intact (Lee and Lee, 2016).

The first study vaccinated transgenic LBD-mice using full human α-synuclein, which cleared α-synuclein aggregates, potentially via lysosomal pathways (Maliash et al., 2005). These results suggested that α-synuclein vaccination is effective in reducing neuronal accumulation of α-synuclein aggregates and that further development of this approach might have a potential role in the treatment of synucle-

inopathies (Valera et al., 2016-b). Other active immunization approaches using a next-generation active vaccination technology with small peptides, or AFFITOPEs® (AFFiRiS AG) (Mandler et al., 2014). AFFITOPEs® that mimic the C-terminal region of α-synuclein are able to elicit an immune response specific to α-synuclein oligomers. Vaccination with one of these AFFITOPEs® (AFF 1) resulted in high antibody titers against α-synuclein aggregates, decreased accumulation of α-synuclein oligomers. When administered to a transgenic model of MSA, AFF 1 also induced a reduction in neurodegeneration and demyelination in neocortex, striatum, and corpus callosum. The clearance of α-synuclein induced by AFF 1 involved activation of microglia, increased anti-inflammatory cytokine production, and reduced spreading of α-synuclein to astroglial cells (Mandler et al., 2014).

Passive immunization approaches using antibodies against α-synuclein are also being actively pursued. Studies observed that antibodies that recognize an epitope in the C-terminal of α-synuclein are more effective at ameliorating the pathology in transgenic mouse models of PD, as they clear intracellular aggregates, inhibit α-synuclein propagation, and prevent C-terminal cleavage of the protein, which may lead to increased aggregation. The reports support the value of immunotherapy with monoclonal antibodies directed against α-synuclein for PD, and in this sense the C-terminal antibody PRX002 (Prothena, South San Francisco, CA, USA) and the antibody BIIB054 (Biogen, Cambridge, MA, USA) are currently being tested in phase I clinical trials (Valera et al., 2016; Schenk et al., 2017).

FUTURE RESEARCH DIRECTIONS

The main future expectations are related to the progress of treatments based on pathophysiology, mainly in the α-synuclein:

- Researchers and pharmaceutical companies are starting studies with immunotherapy for PD and MSA (Valera et al., 2016-b; Schenk et al., 2017). There is great expectation regarding immunological treatments for α-synucleinopathies.
- The knowledge of aggregation and clearance of α-synuclein will be the source of much research for many years towards better treatments for α-synucleinopathies (Schneeberber et al, 2016).
- The action of the gut and gut's flora on the pathophysiology of PD, as well as the involvement of the vagus nerve in the propagation of α-synuclein like the prions, will remain in the target of the scientists in the next years (Lee et al., 2011). It is hoped that new treatments may emerge from research in this area.

CONCLUSION

The studies to date have demonstrated the important participation of α-synuclein and Lewy bodies in the pathophysiology of several ND. However, a long road of discovery and understanding still awaits us. Research into the production of new drugs for the treatment of α-synucleinopathies has developed a lot, demonstrating new ways and unexpected and very interesting solutions. Regarding new treatments, the knowledge of recent years has brought many doors that need to be opened.

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Chapter 14
Lewy Body Disease:
Point Towards Progressive Dementia

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ABSTRACT

Fritz Heinrich Lewy described the intracytoplasmic inclusions found in the neurons for the very first time. In 1919 these inclusions were termed as "LBs" by Tretiakoff. LBs were found in the brain of the patients suffering from Lewy body disease (LBD). LBD is characterized by the presence of Parkinsonian symptoms in the earlier stages and dementia in the later stages of the disease. LBs were classified on the basis of the region of the brain in which they are distributed and so is the case of the LBD means the type of the LBD depends on the anatomical areas of the brain involved. LBD is not a single disorder. It is a spectrum of disorders. This chapter addresses the entire profile of LBs, types, composition, formation, and various LB pathologies as well as diagnostic criteria and pharmacotherapy.

INTRODUCTION

Lewy bodies (LBs) are the eosinophilic intracytoplasmic inclusions found in the brain of the patients of Parkinson's disease (PD) and were first described by Fritz Heinrich Lewy. These inclusions were later called "LBs" by Tretiakoff in 1919 (Wakabayashi et al, 2007). The presence of LBs in the brain of PD patients suggesting the possible involvement of LBs in the process of neurodegeneration, but the recent reports suggested that the LBs formation is a response evoked by the body to scavenge or degrade the neurotoxic substances that is responsible for neuronal degeneration (Sathiyamoorthy et al., 2014). LBs occur in context of various distinct pathologies known as Lewy body disease (LBD) characterized by the presence of the parkinsonian symptoms in earlier stages and dementia in the later stages of disease. Various symptoms of LBD include parkinsonism, hallucination, cognitive impairment, fluctuations in mental status, and dementia. Different types of LBD shares some common characteristics however the marked symptomatic difference found in these pathologies is mainly due to the difference in anatomi-

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cal region of the brain involved (in which the LBs formation occurs) (Kosaka, 2014). Further each of these pathologies is characterized by the presence of LBs, therefore the symptoms appears very similar and sometimes overlaps making the exact pathology difficult to diagnose. Thus the exact pathology so involved sometimes remains undiagnosed and often misdiagnosed (Galvin & Balasubramaniam, 2013) which often becomes troublesome to the patients and caregivers (Galvin et al, 2010). Therefore very precise diagnostic criteria's is required to avoid the false diagnosis and the wrong prescription that may prove fatal later. The difference in diagnosis largely depends on the order of symptomatic presentation such that if only the movement deficits are present then the person is said to be suffering from PD, the development of dementia one year after the onset of the PD is referred as dementia associated with PD (PDD) and if the dementia develops before the onset of the PD or within one year of the PD then it is referred as dementia with LBs (DLB) (Galvin & Balasubramaniam, 2013). In the present chapter authors demonstrate LBD with their similar and differentiating characteristics and provides several recommendations that will prove beneficial in the diagnosis and the pharmacotherapeutics of such pathologies.

BACKGROUND

LBs are the intracytoplasmic inclusions found in the neurons of the patients suffering from LBD, however the exact type of the LBD which a patients exactly suffers from depends upon the region of brain in which the LBs were found predominantly (Kalra et al, 1996). Brainstem nuclei involvement is almost universal in the LBD while the involvement of limbic region and neocortex suggested the progression of disease (Braak et al, 2003). Further it is suggested that the brainstem is involved in the early stages of LBs pathologies whereas the different region of brain also involved when the disease progresses or in the later stages of the disease (Adler et al, 2010). LBs pathologies or the LBD represent a family of the disease that involved three distinct pathologies including PD, PDD and DLB. Before going in to the depth involved in the pathogenesis of these pathologies it remains of interest how LBs occurs and what is the reason of LBs formation. Recent reports suggested that the dopaminergic neurons isolated from the healthy individuals when implanted in the brain of the PD patients form LBs (Kordower et al, 2008; Li et al, 2008) suggesting LBs formations occurs to counteract the pathological insult. Thus LBs formation represents an epiphenomenon, or the scars of neurodegeneration (Popescu et al, 2004). In the present work authors demonstrate the different types of LBs, their formation and composition and the occurrence of LBs in various LBD.

CLASSIFICATION OF LEWY BODIES

LBs can be classified on the basis of their distribution in the different regions of brain.

Type 1 Lewy Bodies

Type 1 LBs are also known as brainstem LBs because of the predominant involvement of the brainstem nuclei (Braak & Braak, 2000; Dickson et al, 1987; 1996; Kosaka et al, 1984). Type 1 LBs are spherical in shape containing eosinophilic cores, lamellar bands and pale halos (Campbell et al, 2001).

Type 2 Lewy Bodies

Type 2 LBs are also known as cortical LBs and characterized by the major involvement of limbic and temporal region and lesser involvement of frontal and posterior cortical region of brain (Braak & Braak, 2000; Braak et al, 2003; Kosaka, 1990; Kosaka et al, 1984). Type 2 LBs are less eosinophilic and less circumscribed (Dickson et al, 1987) and typically lack pale halos (Gomez-Tortosa et al, 2000).

COMPOSITION OF LEWY BODIES

Alpha-synuclein (α-syn) is the major component of LBs (Spillantini et al, 1997). α-syn is a small acidic protein comprises of three domains: N-terminal lipid-binding domain, responsible for the helical structure and the interaction of α-syn with the lipid membranes (Sode et al, 2007); Amyloid-binding central domain (NAC), responsible for the aggregation of α-syn (Rajagopalan & Andersen, 2001) and C-terminal acidic tail, this domain inhibit the aggregation of α-syn (Kim et al, 2004). It has been reported that the mutations in the SNCA gene increase the chances of α-syn aggregation (Minton, 2005) and the aggregation of α-syn is responsible α-synucleinopathies (Spillantini et al, 1997). Aggregation of α-syn monomers leads to the formation of oligomers (Walsh et al, 1997) responsible for neuroinflammation, and neurodegeneration (Wolozin & Behl, 2000) by disrupting proteostasis (Hinault et al, 2010); opening of "mitochondrial permeability transition pore" (mPTP) (Luth et al, 2014) and disrupting mitochondrial respiration (Nakamura, 2013). Oligomers also acts a seeds to promote seeding in which the soluble oligomers acts as the nucleus and form the large insoluble aggregates form known as amyloid fibrils (Eichner & Radford, 2011) that further promotes neuronal death (Jucker & Walker, 2011).

GENESIS OF LEWY BODIES

The precise sequence of events involved in the formation of LBs is completely not known. But it is reported that the process of LBs formation begin with the aggregation of α-syn (Campbell et al, 2001) followed by the incorporation of pale bodies (Gomez-Tortosa et al, 2000) further followed by the incorporation of ubiquitin (Engelender, 2008) and the accumulation of additional proteins (Kuusisto et al, 2003; Orosz et al, 2004). It is reported that LBs distortion often followed by the reduced immunoreactivity (Katsuse et al, 2003).

LEWY BODY DISEASE: PARKINSON'S DISEASE, PARKINSON'S DISEASE DEMENTIA AND DEMENTIA WITH LEWY BODIES

LBD often involves three distinct pathologies including PD, PDD and DLB suggesting LBD a generic term (Figure 1). LBD can be classified into three types (Type A, Type B, and Type C) according to the regional distributional of different LBs in the different regions of brain (Kosaka et al, 1984). Type A referred as brain stem type LBD; Type B referred as transitional type LBD and Type C referred as diffuse type LBD. In brainstem type, LBs occurs in the brainstem nuclei and diencephalon, this is often seen in the PD pathologies (Braak et al, 2003). In DLBD type, LBs are found in the cerebral cortex and

amygdale showing the rarely presence of LBs in brainstem and diencephalon nuclei thus the mesocortical dopaminergic system remains intact and dementia precedes parkinsonism as seen in DLBD (Kosaka et al, 1996). Further DLBD is a neurodegenerative disorder that occur either in common form (cognitive impairment followed by parkinsonism) or pure form (parkinsonism followed by dementia) (Kosaka, 2014); characterized by the symptoms including dementia, cognitive impairments, hallucinations, and parkinsonism (Zesiewicz et al, 2001). Transitional type is the transitional between brainstem type and diffuse LBD.

However besides these three forms of LBD there is another form of LBD which is known as incidental LBD (iLBD). LBs have been found in the patients suffering from the PD. However recent findings suggested LBs were found to be present in the brain of approx. 10% of the normal individuals above the age of 60 years, presenting a unique condition known as ILBD (Dickson et al, 2008). ILBD thus represents a condition either prior to or an early/intermediate stage leading to PD or DLB (Adler et al, 2010). Since the distribution of LBs in the brain in ILBD is similar to the PD, but the differentiating feature is that in case of ILBD there is no damage or loss of dopaminergic neurons. ILBD is thus considered as preclinical PD (Frigerio et al, 2011) but it remains to be clarified whether ILBD is pre-symptomatic PD or it is an age-related change which is unrelated to PD (Dickson et al, 2008).

LBD is not a distinct disorder but a continuum of disorders including disturbances of movement, cognition, behavior, sleep and autonomic function (Figure 2). PD, PDD and DLB, these pathologies are

Figure 1. The family of the Lewy body disease

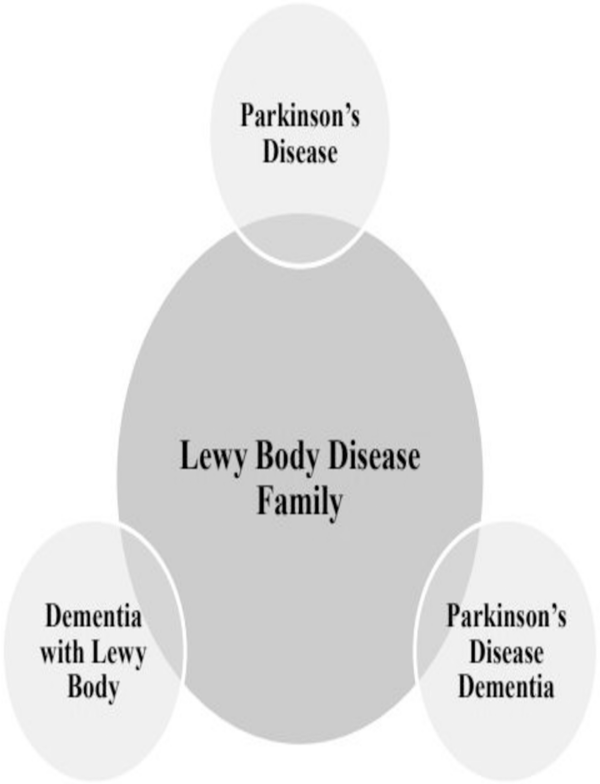
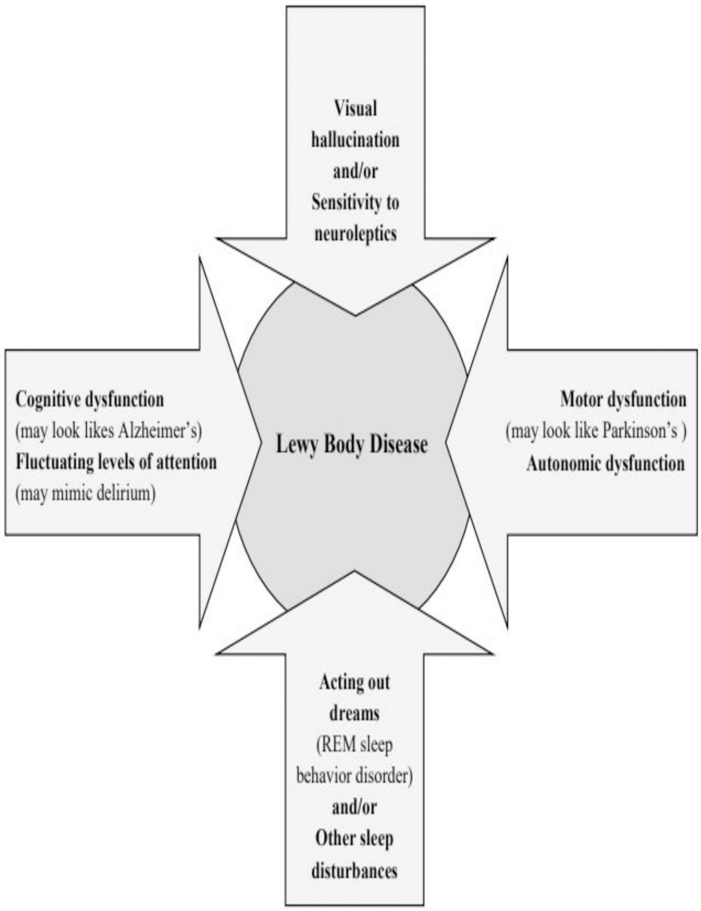


Figure 2. The spectrum of Lewy body disease



distinct actually but their symptoms overlap each other. In this section we describe each pathology and its characteristics in detail (Table 1).

Parkinson's Disease

The death of the dopaminergic neurons in the substantia nigra (SN) region of brain results in the pathology known as Parkinson's disease (PD). Since PD is characterized by the degeneration or the death or the damage of the dopaminergic neurons, however what is exact reason behind the damage of these neurons in the PD still remains unknown (Walia et al., 2014). The death of the dopaminergic neurons in the SN region give rise to the deficiency of the dopamine that further results in the motor symptoms of PD. Several genes have been targeted in context of the PD and these includes SNCA gene (Chartier-Harlin et al, 2004; Forno, 1996; Kruger et al, 1998; Nishioka et al, 2006; Polymeropoulos et al, 1997; Polymeropoulos et al, 1997; Singleton et al, 2003; Zarranz et al, 2004), ubiquitin C-terminal hydrolase L1 (UCH-L1), leucine-rich kinase 2 (LRRK 2), HtrA2/Omi DJ-1, PTEN-induced putative kinase 1

Table 1. Differences amid Parkinson's disease, Parkinson's disease dementia and dementia with Lewy bodies

S. No.	Parkinson's Disease	Parkinson's Disease Dementia	Dementia with Lewy Bodies
1	PD results in the motor dysfunction.	PDD results in the motor and cognitive dysfunction.	DLB results in the motor and cognitive dysfunctions
2	Dementia may or may not be present in PD.	In PDD dementia develops more than one year after the diagnosis of PD.	In DLB dementia develops before or within one year of the PD diagnosis.
3	Executive difficulties in occurs in PD.	Visuospatial functioning and semantic memory deficits occurs in PDD.	Attentional deficits, executive and visuospatial deficits occur in DLB.
6	Resting tremor and rigidity are common.	Non-tremor dominant motor symptoms are present in PDD.	Resting tremor is uncommon, facial masking and axial rigidity occur in DLB.

(PINK1) and parkin (PRKN) (Gosal et al, 2006; Hattori & Mizuno, 2004; Hedrich et al, 2004; Hernandez et al, 2005; Maraganore et al, 2004; Marx et al, 2003; Nishikawa et al, 2003; Strauss et al, 2005). It is suggested that the mutation in the SNCA gene results in the aggregation of the α-syn, which is the main component of the LBs. LBs formation has been reported in the brain of the PD patients. It is suggested that the LBs remain confined to the brainstem nuclei in the stage 1-2, progresses to the SN region in stage 3-4 and finally reaches to neocortex in the latter stages of PD or Stages 5-6 (for detail please refer Braak et al, 2002; 2003). It is suggested that the presence of LBs in the brain of PD patients represents the sign of neuronal degeneration but do not tell anything about the exact sequence of degenerative events, however the LBs formation nowadays is considered as the response of the body to counteracts the neuronal insults (Popescu et al, 2004).

Parkinson's Disease Dementia

The development of dementia more than one year after the PD onset is known as Parkinson's disease dementia (PDD) (McKeith et al, 2006) characterized by the presence of LBs in the cortical and limbic region of the brain (Irwin et al, 2012). Thus PDD presents the condition in which the motor symptom develops one year before the cognitive impairments (Kurtz & Kaufer, 2011). The prevalence rate for PDD in the population above 65 years is about 0.2%-0.5% (Aarsland et al, 2005a; 2007), suggesting aging accelerates the development of dementia, cognitive deficits and increase the severity of motor disturbances (Levy et al, 2002). The presence of PD further increased the risk of developing dementia (Aarsland et al, 2003; Emre et al, 2007; Levy et al, 2002; Williams-Gray et al, 2009) and about 80% of the patients suffering from PD pathology develops dementia (Aarsland et al, 2003; Halliday et al, 2008; Hely et al, 2008). The main difference between PD and PDD is that the PD is characterized by the resting tremor greatly, while PDD is non-tremor-dominant motor subtype (Aarsland et al, 2003; Jankovic et al, 1990; Jellinger et al, 2002; Selikhova et al, 2009). Presence of the cognitive impairment often worsens the motor dysfunction associated with PD (Braak et al, 2005) and increase the disability, morbidity and mortality in the PD patients (Lo et al, 2009; Rosenthal et al, 2010). Also the patients with PDD did not represents the intrinsic core language deficit (Emre et al, 2007) but the difficulties encounters by the patients might be due to the executive dysfunctioning (Grossman et al, 2012).

Dementia With Lewy Bodies

DLB is a neurodegenerative disorder arises due to cortical and subcortical impairments that results in the development of attentional, executive and visuospatial dysfunction (Manning, 2004). The core features include dementia, parkinsonism, fluctuating cognition and hallucinations. Fluctuating cognition includes excessive daytime drowsiness, marked confusion and disorganized speech. Parkinsonism is usually bilateral, resting tremor is uncommon, while axial rigidity and facial masking is often more prominent in DLB. Visual hallucinations in DLB are often powerful, strong, bright, clear and repetitive (McKeith et al, 2005). The recurrent hallucination in DLB might be due to the burden of LBs in the anterior and temporal region of the brain (Harding et al, 2002). Rapid eye movement (REM) disturbance, a suggestive clinical feature of DLB often precedes cognitive or motor symptoms. REM sleep behavioral disturbances are characterized by the intense dreams that might harm the patients since the dream carries the destructive elements, the patients often starts screaming or fighting while sleeping that might results in the injuries (Ferman et al, 2002). Additional supportive features include repeated falls, syncope, unconsciousness, hallucinations, delusions and autonomic dysfunction (McKeith et al, 2005). In DLB, LBs formation has been noticed in the different regions of the brain including brainstem, limbic, neocortex and brain stem (Jellinger, 2009) however why limbic areas are selectively vulnerable to LBs pathology still remains unclear (Rezaie et al, 1996).

PATHOGENESIS OF LEWY BODY DISEASE

PD is disease associated with the defects in the various regions of basal ganglia (BG) resulting in movement deficits (Rubin et al, 2012). Striatum is the receptive nucleus of BG that receives afferent projections from neocortex, thalamus and SNc (Rubin et al, 2012) and sends inhibitory projection to direct pathway and indirect pathway. In direct pathway striatum send projections to globus pallidus interna (GPi)/SN which in turn send projection to thalamus and in indirect pathway striatum send projections to GPe, which then send projection to STN, which further send projection to GPi/SNr. Direct pathway of BG initiate movement and the indirect pathway of BG suppress movements (Kreitzer & Malenka, 2008). The balance between direct and indirect pathways is essential for the normal movements and functioning (Sperlagh & Vizi, 2011). Direct pathway is modulated by D_1 receptors while indirect pathway is modulated by D_2 receptors (Fuentes et al, 2010). Since PD characterized by the death of the dopaminergic neurons often resulting in the dopaminergic deficits and the alteration in the functioning of direct and indirect pathway. It is reported that in PD patients the activity of direct pathway decreases while the activity of indirect pathway increases (Gerfen & Surmeier, 2011; Kreitzer & Malenka, 2008) resulting in the difficulty in initiating movement and excessive inhibition of movement in PD.

The occurrence of LBs in the brainstem nuclei is the characteristic feature of PD (Braak et al, 2003). In PD, LBs has also been found in the different cranial nerve nuclei including premotor oculomotor, precerebellar and vestibular brainstem nuclei (Seidel et al, 2015). Further the presence of LBs in the cortical region is the characteristics of dementia (Duda et al, 2002; Tsuboi et al, 2007). PPN is a brainstem locomotor center, maintain balance and therefore damage to it results in the impaired gait and posture control. In PD about 50% population of the cholinergic neurons of PPN degenerate (Gai et al, 1991; Hirsch et al, 1987; Jellinger, 1988; Karachi et al, 2010; Zweig et al, 1989) resulting in the impaired postural control and gait and DA-resistant akinesia in PD (Stein, 2009).

Since PD involves the degeneration of dopaminergic neurons in the brain but Frederic Lewy first identified LBs in the nbM (Holdorff, 2006). nbM is an open nucleus of basal forebrain characterized by extensive neuronal loss in PD pathology (Arendt et al, 1983; Candy et al, 1983; Chui et al, 1986; Perry et al, 1985) suggesting cholinergic deficits results in the cognitive impairment observed in the patients of PD (Kehagia et al, 2013). This cholinergic neuronal loss even become more prominent in the presence of dementia (Candy et al, 1983; Nakano and Hirano, 1984; Rogers et al, 1985; Tagliavini et al, 1984; Whitehouse et al, 1983) suggesting a greater impairment in the PDD patients. Further the dopaminergic neuronal destruction in the PD occurs concurrently with accumulation of α-syn in the cholinergic neurons of forebrain (BF) (Braak et al, 2003). It is reported that the denervation of cholinergic neurons of forebrain is a possible marker of slowing of gait observed in the patients of PD (Bohnen et al, 2012) that might be due to the possible decrease in the cognitive processing abilities during ambulation (Woollacott & Shumway-Cook, 2002).

PDD refers to the development of dementia more than one year after the onset of PD pathology (Emre et al, 2007). The cognitive picture of PDD is commonly considered as a "subcortical" type and patients typically presents executive dysfunctions (Chui et al, 1986; Darvesh & Freedman, 1996). Both PDD and DLB involved the loss of cholinergic neurons (Klein et al, 2010; Shimada et al, 2009) resulting in the severe cortical acetylcholine deficits (Rolinski et al, 2012). LBs pathologies exist in brains of PDD and DLB (Jellinger & Attems, 2015).Approx. 78% patients suffering from PD develops dementia (Aarsland et al, 2003) which is similar to DLB (Aarsland et al, 2003; Ballard et al, 2002; Emre, 2003). Further pure DLB appear similar to PDD (Emre et al, 2007) and both of these pathologies involved narcolepsy and REM sleep behavior disorder (Kurtz and Kaufer, 2011).

DLB is the condition refers to the onset of the dementia before the onset of PD or with one year of PD onset (McKeith et al, 2006). The DLB and PDD distinguished on the basis of cognitive and motor symptoms (McKeith et al 1996). Cortical cholinergic loss is greater in DLB (Bohnen et al, 2012; Bohnen et al, 2009), while the dopaminergic neuronal loss is more severe in PDD than DLB (Tsuboi & Dickson, 2005). Thus nigrostriatal pathological changes occur in PD, subcortical pathological changes in PDD and the cortical changes occur in DLB (Petrova et al, 2015). Bilateral frontal atrophy occurs in PDD while parietal and occipital atrophy occurs in DLB (Borroni et al, 2015). Further PDD tends to affect younger patients than does DLB (Horimoto et al, 2003; Richard et al, 2002) and this might be due to its specific topography so involved (Revuelta & Lippa, 2009). These findings present the similarities and the dissimilarities in the PD, PDD and DLB.

DIAGNOSTIC CRITERIA FOR LEWY BODY DISEASE

Diagnosis of Parkinson's Disease

The degeneration of dopaminergic neurons in the SN and the presence of LBs in the brainstem nuclei of brain are the main characteristics of PD (Lees et al, 2009; Marsden, 1994). The careful assessment of patient history is very important and therefore thorough questioning should be performed and, inquiry should be made about the presence of premotor symptoms (Massano & Bhatia, 2012). The clinician should note resting tremor, rigidity, postural instability, and akinesia and further should perform CT scan and MRI scan (Massano et al, 2008; Sitburana & Ondo, 2009) the former is used to identify the calcium deposits while the later is used to confirm degeneration (Kagi et al, 2010).

Diagnosis of Parkinson's Disease Dementia

Dementia is the primary feature of the PDD patients (Dubois et al, 2007; Emre et al, 2007). For PDD diagnosis, two core features must be present: first is the presence of PD and second is, PD developed prior to the onset of dementia. Associated clinical features of PDD include deficits in the cognition and behavioral impairments (Dubois et al, 2007; Emre et al, 2007). A patient is said to be suffering from the probable PDD if the impairment is noted in atleast two of the four cognitive domains supported by the presence of atleast one behavioral symptom. A patient is said to be suffer from the possible PDD, if dementia and PD exist together, however the associated clinical features are not considered typical (Dubois et al, 2007; Emre et al, 2007).

Diagnosis of Dementia With Lewy Bodies

According to McKeith et al. DLB is characterized by the presence of central, core, suggestive, and supportive features (McKeith et al, 2005). Like the PDD, central feature of the DLB is dementia, however the early prominent symptoms that can be seen in the patients suffering from DLB includes attention deficits, visual and executive dysfunction. Fluctuating cognition, recurrent visual hallucinations and spontaneous Parkinsonism, represent the core features, REM sleep disorder, severe neuroleptic sensitivity and low dopamine transporter uptake in BG represents the suggestive features and repeated falls, syncope, unexplained loss of consciousness; severe autonomic dysfunction, and non-visual hallucinations constitute the supportive features of DLB. Presence of one core feature with the presence of a suggestive feature suggests the probable DLB while the absence of any core features with the presence of a suggestive feature suggests possible DLB (McKeith et al, 2005).

PHARMACOTHERAPEUTICS OF LEWY BODY DISEASE

Various pharmacotherapeutics agents have been used in the symptomatic treatment of the LBD. Following section defines the selection, benefits, and restrictions of the different pharmacotherapeutics agents for the symptomatic treatment of PD.

Treatment of Cognitive Symptoms

Cognitive symptoms of LBD should be treated with cholinesterase inhibitors (Aarsland et al, 2004; McKeith et al, 2000; Mori et al, 2012; Samuel et al, 2000; Wild et al, 2003). However cholinesterase inhibitors can exacerbate parkinsonism, and increase tremor in the prescribed patients (McKeith et al, 2000).

Treatment of Motor Symptoms

Levodopa/carbidopa might prove beneficial (Goldman et al, 2008). But the efficacy is lesser in DLB than in PD and the risk of development of psychosis increases (Lucetti et al, 2010; Molloy et al, 2005). Further the administration of oral dopamine agonists frequently increases the incidence of hallucinations, abnormal repetitive behaviors (Hassan et al, 2011) and compulsive behavior (Wesnes et al, 2005).

Treatment of Neuropsychiatric Symptoms

SSRIs and SNRIs might prove beneficial (McKeith et al, 2005). However SSRIs increased the risk of suicidality in the prescribed patients (Walia, 2017).

Treatment of Hallucinations and Delusions

Hallucinations and delusions should left untreated if possible (McKeith et al, 2000). DLB patients have increased risk of antipsychotics toxicity (Aarsland et al, 2005b) and a single dose of antipsychotics in these patients increased sedation, confusion, parkinsonism, rigidity, dysautonomia, and mortality (Aarsland et al, 2005b; Hassan et al, 2011; Rochon et al, 2005).

Treatment of Sleep Dysfunction

The presence of sleep dysfunction should be confirmed by polysomnography (Boeve et al, 2013). Treatment with caffeine is useful (Malhotra & Avidan, 2012) while the other therapeutic options may include methylphenidate, dextroamphetamine, and modafinil (Hogl et al, 2002; Seppi et al, 2011).

Treatment of Agitation and Behavioral Disturbance

Pain is often a trigger for agitation and therefore acetaminophen might prove beneficial (Husebo et al, 2011). The incidence of agitation and behavioral disturbances occurs generally in the later stages of disease (Husebo et al, 2011). Agitation and behavioral disturbance can often be treated by the simple measures that include and increased social interaction, training to the caregiver and removal of fear triggers (Rhodes-Kropf et al, 2011).

Treatment of Restless Leg Syndrome

Levodopa/carbidopa, clonazepam, and other GABA analogues might prove beneficial for the treatment of these symptoms (Hening et al, 2004).

Treatment of Autonomic Dysfunction

Autonomic dysfunction includes constipation or diarrhea. (Jost, 1997; Lawrence et al, 2013) as a consequence of DLB (Boot et al, 2013; Postuma et al, 2013; Savica et al, 2010) treatment should include high-fiber diet, exercise, stool softeners, psyllium (Ashraf et al, 1997) and polyethylene glycol (Zangaglia et al, 2007).

ISSUES AND PROBLEMS RELATED TO LEWY BODY DISEASE

LBD are characterized by the presence of LBs in various cortical and subcortical regions (Jellinger, 2009). Presence of LBs in the cortical and limbic regions of the brain correlates dementia in patients with PD or PDD (Irwin et al, 2012). Further the pathological assessment of DLB reveals the presence

of LBs primarily in limbic, and secondly in neocortical regions (Rezaie et al, 1996). The complexity of full spectrum of LBD symptoms (Galvin et al, 2008) and the similarities in clinical features, and neuropathology of LBD, make the diagnosis and management becomes so difficult (Gomperts, 2016) that sometimes clinicians made the wrong diagnosis (Zweig & Galvin, 2014). Also the clinicians view all dementias as the dementia develops due to AD pathology (Galvin et al, 2008). However there are some questions that remains still unresolved in context of LBD includes why the limbic region is more vulnerable to the LBs formation in DLB (Rezaie et al, 1996); why DLB and PDD have similar symptoms despite the fact they are distinct pathologies (Berg et al, 2014) and why the discrimination of DLB from other types of dementia is difficult (Sakamoto et al, 2014).

FUTURE RESEARCH DIRECTIONS

LBD imposed a great burden worldwide. The major limitation is that, till now the complete pathophysiology and the mechanism implicated in the pathogenesis of the LBD is not known completely. Further LBD is often misdiagnosed or underdiagnosed (Zweig & Galvin, 2014) resulting either in the delay in the pharmacotherapeutics of the disease or the wrong prescription that may prove fatal. Epidemiological studies should be done to provide the better understanding and prevalence of LBD (Galvin et al, 2008). Further the development of mouse models and an appropriate biomarker for LBD might prove beneficial in the area of the drug development for LBD (Galvin et al, 2008). Also newer diagnostic techniques and methods should be developed to avoid the incidence of misdiagnosis and under diagnosis that further worsens the conditions of patients (Zweig & Galvin, 2014).

CONCLUSION

It is concluded that the LBD put a great burden worldwide and is responsible for the disability. The greatest problem is that the symptoms are very similar and often led to wrong diagnosis. Therefore a great care should be taken while diagnosing and treating LBD because wrong treatment may further worsens the condition. Since the key step involved in the formation of LBs is the aggregation of α-syn. Therefore the interventional strategy might include the agents that interfere with α-syn aggregation. Further the interfering in either the process of α-syn secretion or neuronal uptake of α-syn might prove beneficial.

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Chapter 15
Amyotrophic Lateral Sclerosis:
A Predominant Form of Degenerative Disease of the Motor Neuron System

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder (ND) that primarily comprises the neurons responsible for controlling voluntary muscle movement. The unique neuropathologic findings include anterior horn cell degeneration producing muscle atrophy or amyotrophy, degeneration, and sclerosis of the corticospinal tracts. It is a common neuromuscular disease worldwide and has been identified in people of all races. There seems to be neither identified risk factors nor family history associated with most of the documented ALS cases. There exists no treatment for ALS that can prevent neither its progression nor reverse its development. However, there are treatments available that can help control symptoms, prevent unnecessary complications, and make living with the disease easier. This chapter extensively discusses this neurodegenerative disorder based on the currently available knowledge on the condition.

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INTRODUCTION

ALS, also known as Charcot's or Lou Gehrig's disease, is a progressive and deadly neurodegenerative disorder (ND) which greatly impacts on patient's quality of life and results in death 2-5 years after diagnosis (Pasinelli & Brown, 2006). From its underlying pathophysiology, the disease was named, that is "amyotrophic" referring to atrophy or death of muscle fibers and "lateral sclerosis" referring to stiffness or hardness of the lateral column of the spinal cord as fibrous astrocytes replace degenerated axons of the upper motor neuron (Armon & Lorenzo, 2017). The disease is associated with the loss of motor neurons that regulate voluntary muscle activities which include walking, breathing, chewing, talking etc. Most importantly, neurons of the spinal cord, brainstem and those present in the motor cortex (Stamenkovic et al, 2017). The effect on the motor neurons accounts for it being also called motor neuron disease (MND).

Clinically, the hallmark of ALS is the presence of upper motor neuron (UMN) and lower motor neuron (LMN) features involving the brainstem and multiple spinal cord regions of innervation. Patients with ALS can present either with bulbar-onset disease (about 25%), limb-onset disease (about 70%), or initial trunk or respiratory involvement (5%), which subsequently spreads to involve other regions (Vucic et al, 2007). Atypical modes of presentation may include weight loss, which is indicative of poor prognosis, cramps and fasciculations in the absence of muscle weakness, emotional lability, and frontal lobe-type cognitive dysfunction (Ferguson & Elman, 2007).

Currently, there is no defined diagnostic test or biomarker for ALS hence experts only rely on its clinical presentation to diagnose. Henceforth, research to establish a novel biomarker that accurately assesses the progression of the condition is of paramount interest in improving therapeutic trial design while also decreasing cost of clinical trials. Lately, it is being progressively identified that population registries are important additions to improved clinical assessment techniques. These collaborative activities will certainly lead to a better understanding of ALS and its often random development, and will lead to the establishment of guidelines for better care of patients (Kiernan et al, 2011).

It is believed that ALS may differ based on clinical phenotype with longer survival reported in ALS without cognitive impairment (Montuschi et al, 2015). The chapter therefore discusses ALS as informed by currently available knowledge on this ND.

BACKGROUND

ALS is a clinically and genetically heterogeneous, devastating, rapidly progressive neurodegenerative motor disorder with cognitive and behavioral impairments as core features (Schmidt et al, 2016). Alongside behavioral features, executive dysfunction is present in up to 50% of ALS patients (Beeldman et al, 2016). Anatomical connectivity studies have revealed clear white matter impairments, mostly affecting tracts directly linked to the motor cortex (Schmidt et al, 2014).

Improvements in our knowledge of the glutamate neurotransmitter system coupled with the detection of causal genes associated with the progression of familial ALS (fALS) have inspired research interest (Kiernan et al, 2011). Whereas these research findings allow for vital comprehensions regarding the ultimate consequences of ALS on the brain, the causal pathogenic mechanism of ALS remains largely unknown (Schmidt et al, 2016).

Cronin et al (2007) reported that there is a low incidence of ALS in people with mixed ancestral origin than in people of Spanish origin. About 5–10% of ALS is familial, with a Mendelian pattern of inheritance. The remaining 90% of the ALS population is identified as having sporadic disease for which results from family aggregation studies have realized a connection between ALS and common NDs, indicative of the presence of susceptibility genes that might elevate the overall risk of neurodegeneration among relatives (Fallis & Hardiman, 2009). As such, attempts to identify susceptibility genes have had little influence on the establishment of a complex genetic basis for sporadic ALS.

SIGNS AND SYMPTOMS OF AMYOTROPHIC LATERAL SCLEROSIS

Muscle weakness and stiffness are the symptoms seen in the early stages of the disease which gradually affect muscles under voluntary control as the disease progresses (Javier & Rojas-garc, 2016).

UMN and LMN signs are observable on neurological examination due to the concomitant association of these neurons in the disease progression. Babinski sign is identified with UMN, as well as, spasticity and hyperreflexia while signs of LMN include cramps, muscle atrophy and fasciculation (Javier & Rojas-garc, 2016). These signs are seen in more advanced stages of the disease.

Bulbar onset ALS usually commences with symptoms such as slurred speech, croakiness or reduced speech volume as well as choking or aspiration during meals which later progresses to the development of strained, strangled vocal quality and eventual speech loss as well as swallowing difficulties and drooling (Armon & Lorenzo, 2017).

Some ALS patients may also experience symptoms such as depression, impaired executive function, maladaptive social behavior and involuntary laughing or crying due to emotional and special cognitive complications (Murphy et al, 2007). Due to atrophy of respiratory muscles, patients with ALS also suffer difficulty in breathing and eventually inability to breath, thereby depending on a ventilator. There is also an accelerated risk of pneumonia as well as painful neuropathy in these patients as the disease progresses (Oliveira & Pereira, 2009).

PATHOPHYSIOLOGICAL MECHANISMS OF MOTOR NEURON DEGENERATION IN AMYOTROPHIC LATERAL SCLEROSIS

There is a multifactorial pathophysiological mechanism underlying the development of ALS-associated motor neuron degeneration despite its exact molecular pathway not being known (Cozzolino et al, 2008; Vucic & Kiernan, 2009; Pasinelli & Brown, 2006). A probable primary mechanism is due to mutation in super oxide dismutase 1 (SOD1), such as anomalous protein aggregation, disorganization of intermediate filaments and glutamate-mediated excitotoxicity, and other abnormalities of intracellular calcium regulation in a process that may involve mitochondrial abnormalities and apoptosis (Rowland & Shneider, 2001). In addition to these, dysfunction of the sodium/potassium ion pump, autophagy and disrupted axonal transport systems have all been associated with the pathogenesis of ALS (Lederer et al, 2007; Ellis et al, 2003; Sasaki & Iwata, 1996)

Genetics

The discoveries of gene mutations causing familial forms of ALS and frontotemporal lobar dementia (FTLD) (microtubule-associated protein tau [*MAPT*]) in combination with neuropathological findings have provided crucial directions in initial research. The discovery that the first genetic causes identified for ALS (mutations in *SOD1*) and FTLD (Rosen et al, 1993, Hutton et al, 1998), each causes exclusively either ALS or FTLD was partially responsible for the delayed recognition of a linkage between ALS and FTLD (Polymenidou & Cleveland, 2017). The identification of a growing list of genetic ALS and FTLD causes and risk factors has led to the realization that errors in RNA metabolism and protein degradation are pivotal in disease initiation. Genetics and pathology of ALS and FTLD subdivide disease into *SOD1*, *TDP-43*, *FUS*, and *TDP-43/DPR* proteinopathies (Polymenidou & Cleveland, 2017).

Superoxide Dismutase 1

Discovery, Prevalence and Clinical Presentation

Superoxide dismutase 1 (SOD1) is an enzyme that in humans is encoded by the *SOD1* gene, located on chromosome 21. Mutations in *SOD1* were the first genetic causes identified in ALS (Rosen et al, 1993), and account for almost 20% of familial (Ling et al, 2013) and rare sporadic (Chio et al, 2008) ALS cases. The clinical presentation of *SOD1* mutation carriers is that of classical ALS (Hardiman et al, 2011), and although rare cases of ALS with cognitive dysfunction have been reported (Stewart et al, 2006), *SOD1*-linked ALS is typically not associated with FTLD symptoms (Wicks et al, 2009).

Mutation Distribution and Effect

More than 170 ALS-linked missense mutations spanning the entirety of the SOD1 polypeptide have been reported (Ling et al, 2013), with each mutation disrupting the physiological conformation of at least a proportion of the mutant subunits, thereby leading to the misfolding and buildup of aberrant forms. Although the misfolded protein is ubiquitinated, and thus directed for degradation (Basso et al, 2006), most mutant SOD1 escape rapid proteolysis, resulting in the development of ubiquitin-positive cytoplasmic inclusions (Kerman et al, 2010), the pathological hallmark of ALS.

Pathogenic Mechanism

Although some ALS-linked mutations decrease the enzymatic activity of SOD1, others do not (Borchelt et al, 1994, 1995). In combination with the observation that loss of SOD1 in knockout mice does not lead to motor neuron degeneration (Reaume et al, 1996) and that disease from a transgene-encoded, dismutase-inactive mutation is unaffected by reduction or elimination of endogenous SOD1 (Bruijn et al, 1998), the evidence argues strongly against a loss-of-function mechanism in SOD1-linked ALS. In contrast, expression of mutant SOD1 in transgenic mice (Gurney et al, 1994; Bruijn et al, 1997) and rats (Howland et al, 2002), or naturally occurring in dogs with canine degenerative myopathy (Crisp et al, 2013), leads to late-onset, progressive paralysis with gliosis and ubiquitinated misfolded SOD1 buildup.

TAR-DNA Binding Protein of 43 kDa

Discovery, Prevalence and Clinical Presentation

In sporadic ALS, histology has established the involvement of phosphorylated 43 kDa TAR DNA-binding protein aggregates in the disease pathology (Brettschneider et al, 2012, 2014; Neumann et al, 2006). The discovery of TDP-43 as the principal composition of the ubiquitin-positive cytoplasmic inclusions, which is in high levels in patients with sporadic ALS (Neumann et al, 2006), was a significant breakthrough. Mutations in *TARDBP* gene (encoding the TAR-DNA binding protein TDP-43) located on chromosome 1p36.22 have been associated with familial and sporadic ALS with the mutation found to cause ALS in 5% of familial cases (Gitcho et al, 2008; Van Deerlin et al, 2008; Yokoseki et al, 2008; Sreedharan et al, 2008). In most patients with TDP-43 mutations, there is a classical ALS phenotype marked by the absence of cognitive deficit, with some unevenness within families on the site of onset and age at which condition starts to develop. Although early studies were unsuccessful in establishing the existence of mutations in TDP-43 in FTLD patients, rare TDP-43 mutations in patients displaying FTLD, with or without motor neuron disease, were reported in 2009 (Benajiba et al, 2009; Borroni et al, 2009; Kovacs et al, 2009).

Mutation Distribution and Effect

The bulk of ALS-associated missense mutations in TDP-43 are restricted to the C-terminal, a glycine-rich domain (Lagier-Tourenne et al, 2010; Ling et al, 2013), which contains a glutamine/asparagine-rich low complexity or prion-like domain that shares similarities with yeast prions (Fuentealba et al, 2010). The latter are proteins showing systematic, self-perpetuating aggregation, which are transmissible from an affected cell to its progeny (Chien et al, 2004; Shorter & Lindquist, 2005). It has been identified that, ALS-associated point mutations expressively increase the aggregation tendency of the already aggregation-prone prion-like domain of TDP-43 (Johnson et al, 2009; Guo et al, 2011; Molliex et al, 2015), indicating a causative link between TDP-43 aggregation and the development of ALS. However, expression of ALS-linked TDP-43 mutants in transgenic mice (Wegorzewska et al, 2009; Zhou et al, 2010; Huang et al, 2012; Arnold et al, 2013) has largely failed to reproduce the characteristic TDP-43 pathology seen in ALS patients, and although these mice develop various aberrations with aspects of motor neuron disease, they do not fully replicate the spectrum of ALS symptoms. Notwithstanding prior reports that mutant TDP-43 displays regular activity in controlling splicing of a reporter gene (D'Ambrogio et al, 2009), genome- wide analysis of mice expressing mutant TDP-43 showed broad aberrant splicing events (Arnold et al, 2013). The TDP-43 mutants moreover show defective transport of their RNA cargo across neuronal axons (Alami et al, 2014).

Pathogenic Mechanism

Two mechanisms have been implicated in TDP-43 induced toxicity. First is the loss of TDP-43 normal function following the redistribution and aggregation of the protein in the cytoplasm (Neumann et al, 2006). Secondly, it is thought that the misfolded protein assemblies in the cytoplasm are toxic to the motor neuron (Tai & Schuman, 2008). However, the relative input of each of these mechanisms is still not fully implicit. However, these two mechanisms are not independent of each other and likely cause

motor neuron degeneration in amalgamation (Lagier-Tourenne et al, 2010; Polymenidou et al, 2012; Ling et al, 2013). After an initiation phase, the formation of TDP-43 pre-inclusions assumes a dual effect in cells (Polymenidou & Cleveland, 2017).

Fused in Sarcoma/Translocated in Liposarcoma

Discovery and Prevalence

FUS or translocated in liposarcoma is a nuclear DNA/RNA binding protein that controls various stages of gene expression, including transcription, splicing and messenger RNA transport (Dormann & Haass, 2013; Vance et al, 2009). *FUS* has been associated with the progression of neurodegeneration since missense and nonsense mutations in the *FUS* gene contribute to approximately 4% of fALS cases and rare sporadic cases (Vance et al, 2009). In the absence of mutations, pathologic accumulations of wild type *FUS* occur in 10% of FTLD cases (Neumann et al, 2009).

Mutation Distribution and Effect

Majority of the ALS-linked *FUS* mutations are localized in the nuclear localization signal sequence (Lagier-Tourenne et al, 2010; Ling et al, 2013) and do not influence aggregation per se (Dormann et al, 2010) but instead enhance redistribution of *FUS* to the cytoplasm (Dormann et al, 2010; Ito et al, 2011), which consequently may initiate its aggregation and confer toxicity. Unlike TDP-43, *FUS* aggregation and toxicity require not just a prion-like domain but also other determinants in the RGG domain (Acton, 2012).

Pathogenic Mechanism

Mutations in the C-terminal domain affect the cytoplasmic localization of *FUS* and disrupts RNA processing and transport. The binding of a single strand DNA to the C-terminus of *FUS* is important for direct binding of *FUS* to promoters of target genes (Bronisz et al, 2014; Tan et al, 2012). The functional and structural parallels of TDP-43 and *FUS* (Lagier-Tourenne et al, 2010) indicate that the two proteins trigger ALS by an independent instigating actions, but likely via common downstream pathways, one of which involves their common RNA targets. Certainly, while TDP-43 and *FUS* bind a distinct spectrum of RNAs, they have high specificity for mRNAs produced from genes with very long introns (Polymenidou et al, 2011; Lagier-Tourenne et al, 2012). The high brain levels of these long intronic genes, tightly bound to both TDP-43 and *FUS* (Ameur et al, 2011; Polymenidou et al, 2011), presents a likely description for why neurons are typically prone to ALS pathogenic processes (Polymenidou & Cleveland, 2017).

Intronic Hexanucleotide Repeats in C9orf72

Discovery and Prevalence

Mutations in the *C9orf72* gene are the commonly associated factor for the development of amyotrophic lateral sclerosis and frontotemporal dementia (Jovicic et al, 2015). The identification of intronic hexanucleotide repeat expansions in the *C9orf72* gene of ALS patients was a significant advance in the study of ALS. These dipeptide repeat proteins (DPRs) fashioned from unusual translation of *C9orf72*

repeat expansions are now identified as the most common genetic cause of ALS and FTLD, accounting for 40% of fALS and 30% of familial FTLD (fFTLD) cases (Renton et al, 2011; Gijselinck et al, 2012; Majounie et al, 2012). It has been identified that up to 90% of families with concurrent ALS and FTLD have the hexanucleotide repeat expansions in their *C9orf72* genes (Majounie et al, 2012; Rademakers & van Blitterswijk, 2013; Renton et al, 2014). However, the *C9orf72* hexanucleotide repeat expansions have also been found in approximately 7% or 5% of apparent sporadic ALS or FTLD cases, respectively, suggesting that the fraction of ALS and FTLD cases with genetic origin may be bigger than predicted (Polymenidou & Cleveland, 2017).

Mutation Distribution and Effect

In normal healthy controls, the intronic GGGGCC repeat in the *C9orf72* gene is smaller than 25 units, whereas in ALS or FTLD patients, it can increase up to 800–4400 units (Gijselinck et al, 2012), with deleterious effects such as neurodegeneration (Majounie et al, 2012; Rademakers & van Blitterswijk, 2013; Renton et al, 2014). First these large intronic expansions interfere with transcription of *C9orf72* RNA, thereby decreasing its levels (Gijselinck et al, 2012). In addition, the repeat RNA accumulates in the nuclear foci (Lagier- Tourenne et al, 2013; Zu et al, 2013; Haeusler et al, 2014) where they can be translated via the repeat-associated non-ATG (RAN) translation (Ash et al, 2013; Zu et al, 2013), resulting in the synthesis and accumulation of anomalous dipeptide proteins.

Pathogenic Mechanism

Despite several descriptions of the cytotoxic mechanisms of *C9orf72* hexanucleotide repeat expansions, their relative influence to the pathogenesis of ALS is yet to be established (Polymenidou & Cleveland, 2017). Firstly, patients with *C9orf72* expansions show typical TDP-43 cytoplasmic additions with nuclear clearance (Gijselinck et al, 2012), which suggests that all of the mechanisms described above for TDP-43 are relevant for the pathogenesis of this specific ALS phenotype. As a result of inactivation of the repeat-containing allele via promoter hypermethylation (Xi et al, 2013), or transcriptional termination of repeat RNAs (Haeusler et al, 2014), patients carrying hexanucleotide repeat expansions produce decreased levels of *C9orf72* RNA (Gijselinck et al, 2012) and, by extension, protein, which may reduce the protein's normal role, a mechanism referred to as haploinsufficiency (Polymenidou & Cleveland, 2017). In contrast, the lack of an ALS/FTLD-like phenotype in mice with heterozygous (Panda et al, 2013; Suzuki et al, 2013) or homozygous (Koppers et al, 2015) disruption of the mouse *C9orf72* homolog strongly argues against the role of haploinsufficiency in *C9orf72*-ALS/FTLD pathogenesis.

However, conflicting reports have proposed that poly-GP, a DPR, is present in UMN and LMN (Zu et al, 2013), which was subsequently shown to be in the cerebrospinal fluid of *C9orf72* patients (Su et al, 2014). On another hand, following exogenous application of the relatively short synthetic sense poly-GR and antisense poly-PR DPRs to cultured human astrocytes, these DPRs enter the nucleus where they bind to the nucleoli and induces cell destruction (Kwon et al, 2014). Lastly, expression of "protein-only" poly-GR and poly-PR constructs in *Drosophila* has been linked with progressive neuronal death *in vivo*, possibly due to the basic nature or a shared structural motif of these DPRs (Mizielinska et al, 2014). In addition to already described mechanisms, the toxic effect of these aberrant proteins can also be mediated via the compromise of the nucleocytoplasmic transport probably by interacting with karyopherin proteins or directly with the nuclear pore (Freibaum et al, 2015; Jovicic et al, 2015).

Impaired Axonal Transport

In addition to glutamate-induced excitotoxicity, mitochondrial dysfunction and oxidative stress, disrupted axonal transport systems have also been implicated in the pathogenesis of ALS (Sasaki & Iwata, 1996). Motor neuron axons may reach up to one meter in length in humans, and rely on effective intracellular transport systems which consist of anterograde (slow and fast) and retrograde transport systems. These systems depend on molecular 'motors', the kinesin complex of proteins (for anterograde) and the dynein-dynactin complex (for retrograde) (Grierson & Miller, 2006). Studies in SOD1 transgenic mouse models of ALS have yielded proof of slowed anterograde transport and retrograde transport in motor neurons (Williamson & Cleveland, 1999). Though no such observations have been realized in humans with ALS, mutations in the kinesin genes are known to cause neurodegenerative motor nerve diseases in humans which include hereditary spastic paraplegia and Type 2A Charcot-Marie-Tooth disease (Reid et al, 2002). Olney et al (2003) has reported that mutations in the dynactin complex cause a LMN disorder with vocal cord paralysis in humans.

DIAGNOSIS OF AMYOTROPHIC LATERAL SCLEROSIS

The diagnosis of ALS depends on distinct clinical findings together with examinations to discount "ALS-mimic" syndromes for example multifocal motor neuropathy, inclusion body myositis, conus lesions and lumbo-sacral radiculopathy (Davenport et al, 1996, Traynor et al, 2000). ALS is implicated when cerebrospinal fluid or serological studies or electrophysiological imaging reveals signs of concomitant UMN and LMN which cannot be linked with any other disease in addition to disease progression compatible with motor neuron degeneration. Isolated investigation result is therefore inadequate to arrive at a diagnosis and hence should be considered together with patient history and other clinical findings (Wijesekera & Leigh 2009).

In 1994, the World Federation of Neurology (WFN) Research Group on Motor Neuron Diseases developed the El Escorial diagnostic criteria (Maurer 2011), to help in diagnosis and classifying patients for research purposes and clinical trials (Wijesekera & Leigh 2009). However, this diagnostic criterion had several limitations which compromised its usefulness (Wilbourn 1998). The El Escorial standards can have poor sensitivity, especially in the early stages of ALS when patients are most likely to profit from therapeutic intervention (Traynor et al, 2000). Because of these drawbacks, the criteria have been revised (Table 1) to benefit early diagnosis (Ross et al, 1998) and in the clinical trial setting, improve levels of diagnostic confidence (Beghi et al, 2002).

MANAGEMENT OF AMYOTROPHIC LATERAL SCLEROSIS

The management of ALS has significantly transformed over the years, with current accent on coordinated multidisciplinary care between specialists, community based therapists and palliative care teams (Kiernan et al, 2011). This extent of survival amongst ALS patients has been found to be greater for management of patients in specialized multidisciplinary ALS clinics than in other settings (Traynor et al, 2003). In spite of the fact that ALS cannot be cured, its associated symptoms can be treated to help improve the quality of life of the patient. Advanced directives on end of life care, respiratory and nutri-

Table 1. A revised El Escorial research diagnostic criteria for ALS (Adapted from Brooks et al., 2000)

The diagnosis of ALS requires: • Evidence of LMN degeneration by clinical, electrophysiological or neuropathological examination; • Evidence of UMN degeneration by clinical examination, and • Progressive spread of symptoms or signs within a region or to other regions, as determined by history or examination,
Together with the absence of: • Electrophysiological and pathological evidence of other disease that might explain the signs of LMN and/or UMN degeneration, and • Neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiological signs
Categories of clinical diagnostic certainty on clinical criteria alone Definite ALS • UMN signs and LMN signs in 3 regions Probable ALS • UMN signs and LMN signs in 2 regions with at least some UMN signs rostral to LMN signs Probable ALS – Laboratory supported • UMN signs in 1 or more regions and LMN signs defined by EMG in at least 2 regions Possible ALS • UMN signs and LMN signs in 1 region (together), or • UMN signs in 2 or more regions • UMN and LMN signs in 2 regions with no UMN signs rostral to LMN signs UMN signs: clonus, Babinski sign, absent abdominal skin reflexes, hypertonia, loss of dexterity. LMN signs: atrophy, weakness. If only fasciculation: search with EMG for active denervation. Regions reflect neuronal pools: bulbar, cervical, thoracic and lumbosacral.

tional management during late stages of life are important issues, and should be discussed with patients and relatives at the earliest opportunity that they are willing to do this (Kiernan et al, 2011). Associated with ALS is psychological and emotional difficulties for the sufferer and their families (Averill et al, 2007; Wicks et al, 2007), which makes it important to offer psychological support and early palliative care to the patients and their families alike (Mitsumoto & Rabkin, 2007).

Pharmacotherapy

Riluzole

Was originally advanced as an antiepileptic drug, riluzole, currently is the only drug approved for use in slowing the progression of ALS (Bensimon et al, 1994; Kiernan et al, 2011). Although the exact mechanism of action of riluzole in modifying disease progression is not entirely elucidated, it is believed to have effect on N-methyl-D-aspartate (NMDA) receptor-mediated responses, stabilization of the inactivated state of voltage-dependent sodium channels, inhibition of glutamate release from pre-synaptic terminals, and elevating extracellular glutamate uptake (Distad et al, 2008). In two therapeutic trials, riluzole prolonged survival by three to six months (Bensimon et al, 1994; Lacomblez et al, 1996).

Lithium Carbonate

A trial of lithium carbonate in ALS compared 16 patients treated with riluzole and lithium carbonate with 28 patients treated with riluzole alone (Class III) (Fornai et al, 2008). Mortality was reduced and disease progression was curtailed in treated patients. Nonetheless, small sample size, lack of adequate blinding, and other design issues compromised the evidence provided by the trial.

Cytidine-5-Diphosphocholine

Cytidine-5-diphosphocholine (citicoline) is an endogenous nucleoside that has neuroprotective roles in certain central nervous system (CNS) injury models (Cakir et al, 2005; de Carvalho, 2008). The neuroprotective function of CDP-choline seems to be linked to its action on glutamate-mediated cell death. Citicoline might lower the extracellular level of glutamate by blockade of neuronal glutamate efflux and elevating astrocytic glutamate uptake. Matyja et al (2008) reports that the neuroprotective role of this compound is related to the blockade of the glutamate-induced apoptotic pathway of cell injury.

Erythropoietin

Erythropoietin (EPO) is believed to be one of the compounds that might play a potential neuroprotective role in ALS. There are many data supporting EPO's protective function of neurons exposed to damaging agents. As a neuroprotective agent, erythropoietin; antagonizes glutamate cytotoxic action, enhances antioxidant enzyme expression, lowers the free radical production rate and affects neurotransmitter release. EPO exerts a neuroprotective effect in the investigated model of chronic excitotoxicity mainly through inhibition of apoptotic neuronal alterations. Results from work by Nagańska et al (2010), Grasso et al (2007) and Liu et al (2008) show that EPO may be an important therapeutic drug in various neurological diseases, including ALS.

Nutrition

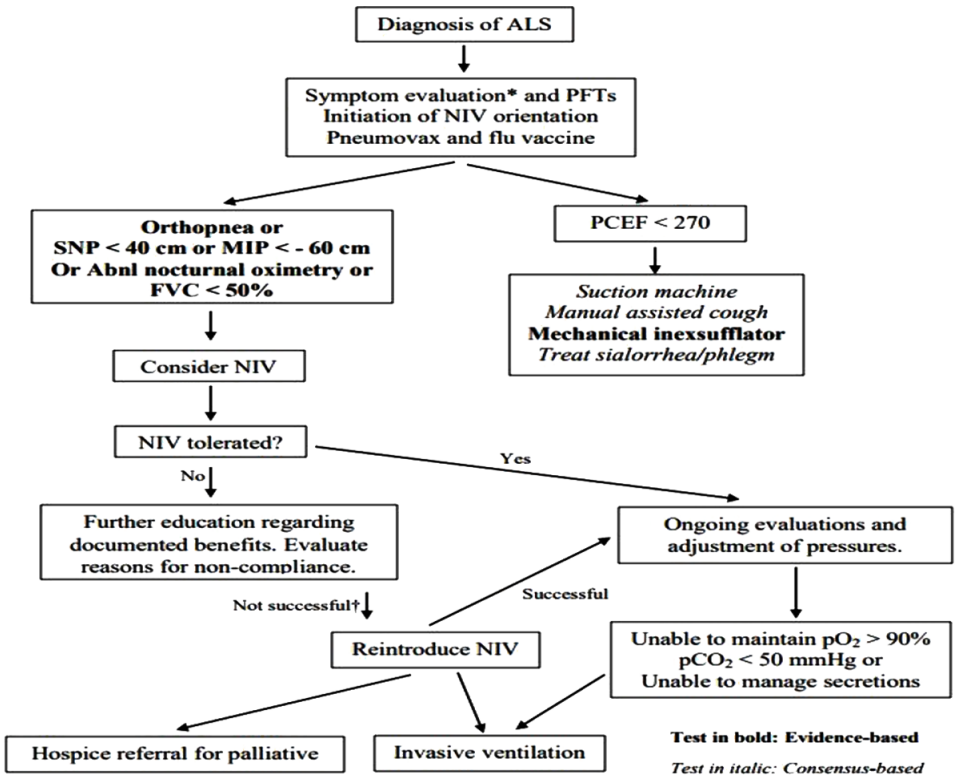
Results from nine studies indicate that enteral nutrition administered via PEG is probably effective in stabilizing body weight/body mass index (Desport et al, 2000; Desport et al, 2005). In patients with ALS with impaired oral food intake, enteral nutrition via PEG should be considered to stabilize body weight (Miller et al, 2009). There are no clear-cut indications for the timing of PEG insertion in ALS patients. However, Kasarskis and his colleagues demonstrated that, patients with dysphagia will possibly be exposed to reduced risk if PEG is placed when FVC is above 50% of predicted (Kasarskis et al, 1999). Risks of PEG placement include laryngeal spasm, localized infection, gastric hemorrhage, failure to place PEG due to technical difficulties, and death due to respiratory arrest (Mazzini et al, 1995).

Respiratory Support

The diagnosis and management of respiratory insufficiency is important because respiratory failure causes most deaths from ALS (Miller et al, 2009). The presenting symptoms of respiratory muscle weakness include dyspnea on exertion or talking, orthopneoa, disturbed sleep, excessive daytime somnolence, morning headaches, fatigue, anorexia, depression, poor concentration, vivid nightmares and nocturia (Leigh et al, 2003; Heffernan et al, 2006). Despite uncertainties in respiratory care of ALS patients, several controlled studies have provided evidence to guide its management (Figure 1).

Abbreviations: PFT: Pulmonary function tests; PCEF: Peak cough expiratory flow; NIV: Noninvasive ventilation; SNP: Sniff nasal pressure; MIP: Maximal inspiratory pressure; FVC: Forced vital capacity (supine or erect); Abnl.nocturnal oximetry: $pO_2 < 4\%$ from baseline.

Figure 1. Algorithm for the airway management of ALS (Adapted from AAN Practice Parameter Update, 2009)



*Symptoms suggestive of nocturnal hypoventilation: frequent arousals, morning headaches, excessive daytime sleepiness, vivid dreams. †If NIV is not tolerated or accepted in the setting of advancing respiratory compromise, consider invasive ventilation or referral to hospice.

FUTURE RESEARCH DIRECTIONS

It is almost impossible to translate animal studies on ALS to humans though such studies have been ongoing for about three decades. This stems from the fact that ALS has not been identified in animals and currently studies only try to subject animals to artificial gene expressions which however differs from human ALS phenotypically (Clerc et al, 2016). Again, some drugs which had been studied to be effective in managing ALS in animals such as celecoxib (Drachman et al, 2002; Cudkpwicz et al, 2004), creatine (Klivenyi et al, 1999; Groeneveld et al, 2003), gabapentin (Gurney et al, 1996; Miller et al, 2001) and acetylcysteine (Kuther & Struppler, 1987; Andreassen et al, 2000) showed no therapeutic benefit in human ALS. This can be attributed to intraspecies differences that exist between humans and animals (Oliveira & Pereira, 2009). This makes these animal models not entirely valid.

However, with advances in molecular biology, human diseases biomonitoring and computer science, there is hope of improved research, potentially more relevant and more effective. These may include *in silico*, disease pathway approach and human-based studies. These offer ethically superior know how which are more succinct, robust, and more astute into human biology and disease hence speeding up transition from the bench to the bedside (Clerc et al, 2016).

A common mutation associated with ALS is an unstable repeated DNA sequence within the *C9orf72* gene that could reach into the thousands (Xi et al, 2015). Xi and his colleagues have also reported that less than 30 repeats of the *C9orf72* gene have been established to be common in most individuals. With further research, there could be utilization of this information to come up with genetic test(s) that can identify if parents are likely to pass a mutation that may cause ALS to their progeny. By increasing this research to include other multi-generational families, as well as study unaffected parents, there is a hope of identifying a range of *C9orf72* repeats that can be used to predict a genetic predisposition to ALS in children (Xi et al, 2015).

CONCLUSION

This chapter has constructively detailed ALS based on available sound literature on the condition. However, future advances will seek to better comprehend the symptomatic management of ALS and also provide an improved insight into the etiology of the condition. This will offer valuable piece in the research objective of finding effective therapy that does not just slow the progression but would also stop and/or reverse this deleterious neurodegenerative process.

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Chapter 16
Spectrum of Neurodegeneration in Autism Spectrum Disorder

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ABSTRACT

Autism spectrum disorder (ASD) is neurodevelopmental disorder which is characterized by lack of social behaviors and impaired non-verbal interactions that start early in childhood. It can also lead to progressive neurodegeneration like schizophrenia disorder, Alzheimer's disease, Parkinson's disease, and dementia. Genetic studies of ASD have confirmed the mutations that interfere with neurodevelopment in mother's womb through childhood and these mutations are further involved in synaptogenesis and axon motility. Crucial role of amygdala is found to be deficit in ASD individuals whose association cognition with nucleus accumbens lead to impaired social behaviors and cognitive stimulus. Educational and behavioral treatments are considered the key steps used for its management along with pharmacological and interventional therapies. In this chapter, the author presents the etiology of ASD, proof of neurodegeneration in ASD, as well as the clinical feature and the management of ASD.

INTRODUCTION

ASD is a set of neurodevelopmental disorders characterized by a lack of social interaction, verbal and nonverbal communication which is noticed in the first 3 years of childhood. In some of cases, mental and health conditions are progressively deteriorates with the time if not diagnosed and treated at time. The distinctive social behaviors include an avoidance of eye contact, fluctuate emotional control and difficulties in understanding the emotions of other people (Mattila *et al.*, 2011). Environmental factors are also likely to interact with the genetic profile and cause aberrant changes in brain growth, neuronal development, and functional connectivity. Increase in prevalence of ASD has been found and higher rate is reported in males than females (Kim *et al.*, 2011; Elsabagh *et al.*, 2012; Fombone *et al.*, 2011). Various post-mortem evaluations of ASD individuals have been postulated that these individuals experienced a loss of neuron cells and pyramidal cells in their amygdala than control samples. These observations have supported that these microglia can be responsible for the dissolution of neurons that can also induce the

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production of toxic cytokines that can damage neurons and lead to neurodegeneration in ASD individuals (Kern *et al.,* 2013). In last decades, despite growing evidence for the involvement of endogenous biomarkers in the pathophysiology of ASD is reported and early detection of this disorder remains a big challenge that describes the main behavioral and cognitive features of ASD, as well as the symptoms that differentiate autism from other developmental disorders such as reduced brain connectivity, mirror neurons deficits, and inhibition-excitation imbalance in individuals with ASD. In ASD patients, the frontal and temporal lobes are the markedly affected brain areas. And the role of amygdala in cognition and ASD has been proved in numerous neuropathological and neuroimaging studies (London & Etzel, 2001; Kern & Jones, 2006). The amygdala is a major component of the limbic system and affective loop of the cortico-striato-thalamo-cortical circuit. The amygdala located the medial temporal lobe anterior to the hippocampal formation has been thought to have a strong association with social and aggressive behaviors ASD patients (London & Etzel, 2001; Kern & Jones, 2006). ASD is clinically diagnosed on the basis of the presence of its associated non-specific manifestation like individual abilities in intelligence and verbal domains. The onsets of nonspecific manifestation are noticed in infants or toddlers such as irritability, passivity, and difficulties with sleeping and eating, followed by delays in language and social involvement (Kolevzon *et al.,* 2007). Previously, some of reported data of few ASD patients have been studied for experiencing the improvements after deep brain stimulation as one of the interventional treatments. The key bone of neurobiology of ASD development is still a target for laying out its treatment and clinical management that required broadening its clinical horizons to understand ASD (Kolevzon *et al.,* 2007). Hence, ASD is noted as multifactorial disorder and still unpredictable for investigators for drawing its fate to postulate its correlation with neural loss and progressive neurodegeneration in ASD individuals. So, the information provided in this chapter can be helpful for the researchers to postulate the effective therapies and treatments for ASD individuals. As well as, to provide points know more about the role of various genetic, environmental and epigenetic factors that have deleterious effects in ASD individuals such as cognitive impairment and immune homeostasis.

BACKGROUND

ASD affect the brain with the time that leads to neurodegeneration in ASD individual if left untreated or neglected so, many clinicians and researchers are involved to understand the ASD for long decades. However, pinpointing ASD's root cause may be aided by postulated all previous findings and clinical studies into a neurodegeneration hypothesis. This hypothesis can suggests that ASD can be regressive if ASD children are diagnosed and treated at time, so that they can acquire certain skill abilities before any serious neurological impairments happens to them. This ASD regression is said to helpful in 15% to 65% of ASD cases and hence, whether ASD can be considered a neurodegenerative disorder has remained under clinical critics and debate (Kern *et al.,* 2013). Previously, the development of the brain in individuals with ASD is discussed to be a complex neurodevelopmental disorders which is followed by interaction of various genetic and environmental factors and their interactions. Genetic studies of ASD have identified mutations in genes that interfere with typical neurodevelopment in childhood that involved in synaptogenesis and axon motility. An altered ratio of short to long diameter axons and disorganization of cortical layers are also observed along with MRI studies assessing brain volume in ASD individuals. Hence, as a result of the observed altered pattern of axons and MRI studies are found to responsible for altering the socioemotional networks (Mattila *et al.*, 2011). Characteristics of normal

children in the sample which used for criteria of autism based on their caregivers reports were similar to those reported in the general population of individuals with ASDs. Even when taking into account the disproportionate percentage of males in the sample, the male-female ratio in children which used for autism was 3–4: 1 (Burd, Severud, Kerbeshian, & Klug, 1999; Fombonne, 1999, 2003; Steffenburg & Gillberg, 1986). In addition, although, developmentally delayed children who met criteria for ASD is tended to have more severe cognitive delays is considered key line path in past research findings that has suggested that ASD is often co-morbid with severe to profound cognitive impairments (Fombonne, 1999, 2003; Gillberg *et al*., 1990; Lord & Volkar, 2002; Sigman & Capps, 1997).

ETIOLOGY OF AUTISM SPECTRUM DISORDER

ASD is broadly considered to be a multi-factorial disorder resulting from genetic and non-genetic risk factors and its respective interaction along with various diverse environmental causative elements including pre-natal, peri-natal, and post-natal factors that contribute ASD. This diagnostic bias towards males might result from under-recognition of females with ASD (Kern & Jones, 2001; Kolevzon *et al.,* 2007; Baron *et al.,* 2011). Also, some clinicians have suggested the possibility that the female-specific protective effects against ASD might exist (Robinson *et al.,* 2013). Previously, various prenatal factors are found to related with ASD such as exposure to teratogens, thalidomide, certain viral infections (congenital rubella syndrome), maternal anticonvulsants (valproic acid) as well as low birth weight, abnormally short gestation length and birth asphyxia are considered the peri-natal factors (Davidson *et al.,* 2004; Gorlin *et al.,* 2016). The lesion of the amygdala results in fear-processing, modulation of memory with emotional content, and eye gaze when looking at human face which found to reported in ASD patients (Adolphs *et al.,* 2005; Spezio *et al.,* 2007). The amygdala receives highly processed somatosensory, visual, auditory, and all types of visceral inputs that sends efferent through two major pathways, the stria terminalis and the ventral amygdalofugal pathway. Several studies proposed the use of an animal model to confirm the evidence for the association between amygdala and ASD (Emery & Clayton, 2001; Sweeten *et al.,* 2002). Previously, monkeys with the Kluver-Bucy syndrome have been reported ASD like disorder that show absence of social chattering, lack of facial expression, absence of emotional reactions, repetitive abnormal movement patterns, and increased aggression (Soydyk & Shekhar, 2000). Recently, the development of functional neuroimaging also provided some evidence for the correlation between amygdala deficit and ASD. A study using Technetium-99m (Tc-99m) single-photon emission computed tomography (SPECT) is found that regional cerebral blood flow (rCBF) was decreased in the bilateral insula, superior temporal gyri, and left prefrontal cortices in individuals with ASD compared to age- and gender-matched controls with mental retardation (Quirk & Mueller, 2008; Stores-Bayon & Quirk, 2010; Ohnishi *et al.,* 2000). Medial prefrontal cortex (mpFC) involves in fear learning and extinction by reciprocal synaptic connections with the basolateral amygdala (Bishop *et al.,* 2007; Fuchs *et al.,* 2007). Disturbed communication within amygdala-mPFC circuitry caused deficits in memory processing this information provides support for a role of the mpFC in the development of ASD. Besides amygdala, nucleus accumbens (NAc) is also considered as the key structure which is related with the social reward response in ASD and NAc borders ventrally on the anterior limb of the internal capsule, and the lateral subventricular fundus of the NAc is permeated in rostral sections by internal capsule fiber bundles (Mashhoom *et al.,* 2010).

NEURODEGENERATION AND AUTISM SPECTRUM DISORDER

Impact of Oxidative Stress in Neurodegeneration

Over production of reactive oxygen species (ROS) due to oxidative stress is a central feature of neurodegenerative disorders which is confirmed with postmortem study done in brain tissues from ASD individuals diagnosed (Anderson, 2004). Free radicals and other ROS are harmful because the unpaired electron oxidatively reacts with other ions and molecules lead to progressive neural damage (Gutman, 2002). The oxidative degradation of the lipid membrane called lipid peroxidation that results in loss of membrane integrity and fluidity, which ultimately leads to neural cell death. ROS also react with proteins and nucleic acids which can lead to neural cell death via apoptosis or necrosis which further lead to neurodegenerative disorders (Kannan & Jain, 2000). The brain is highly vulnerable to oxidative stress when antioxidant capacity is halted due to any brain inflammatory diseases like Alzheimer's diseases, Parkinson's disease and dementia (Granot & Kohen, 2004). Several post-mortem studies have been performed in ASD individuals who revealed that affected areas of the brain associated with accelerated cell death under conditions of oxidative stress. It is also observed with this study that the density of lipofuscin, a matrix of oxidized lipid and cross-linked protein is increased in cortical brain areas that usually formed as a result of oxidative injury in the neural tissues (Evans *et al.,* 2008). From earlier findings, it is postulated that brain regions are observed with the highest levels of the oxidative stress marker, 3-nitrotyrosine (3-NT) in the orbitofrontal cortex, Wernicke's area, cerebellar vermis, cerebellar hemisphere, and pons in ASD individuals. This elevated oxidative stress markers in the brains of ASD individuals is found to associate with evaluating the level of oxidative stress metabolites of carboxyethyl pyrrole (CEP) and iso[4]levuglandin (iso[4]LG)E2-protein adducts in cortical brain tissues when compared to neurotypical samples (Sajdel-Sukouska, 2008). DNA oxidation and glutathione redox status have been also studied in postmortem brain samples from the cerebellum and frontal, temporal, parietal and occipital cortex from ASD individuals when compared with age-matched neurotypical controls. These observations were confirmed that DNA oxidation was significantly increased by two-fold in the frontal cortex, temporal cortex, and cerebellum in ASD individuals compared to healthy controls (Chauhan *et al.,* 2011). The levels of reduced glutathione were significantly reduced and inversely proportional to increased levels of oxidized glutathione in samples of the cerebellum and temporal cortex from ASD individuals as compared to the corresponding levels in the control brain samples. It was also confirmed that significant increase in the levels of lipid hydroperoxides (oxidative stress marker) in the cerebellum and temporal cortex in ASD individuals as compared to controls (Wyss-Coray & Muke, 2002).

Impact of Neuronal Loss in Neurodegeneration

Earlier clinical studies of ASD is characterized by neuronal cell loss which occurred due to significant reductions of neural-cerebellar Purkinje cells count (PCs) in ASD individuals when compared to neurotypical controls according to a postmortem study (Whitney *et al.,* 2008). Other ASD studies also supported the neuronal pathology found in the brain of ASD individuals that is suggestive tool of ASD associated neurodegenerative process when compares to neurotypical subjects. It has been also reported that degeneration in PCs and also microglial activation associated with gliosis. These finding are indi-

cated that these changes are acquired rather than neurodevelopmental because gliosis is proliferation of neuroglial tissue that leads to progressive neural damage (Casanova, 2007 & Vajda, 2002). From earlier reports, it has been postulated that neuronal numbers in fusiform gyrus were found to be significantly reduced in the amygdala of individuals diagnosed with ASD individuals than controls, especially, in neuron densities of neural layer III (Schumanon & Amaral, 2006).

Impact of Microglia Activation in Neurodegeneration

Microglial reactivity is found to reported in neurodegenerative diseases that induces inflammation in infected or damaged brain tissues which also important for maintaining homeostasis in non-infected regions (Vargas *et al.,* 2005). So, microglial cells act as key cellular mediators of the neuroinflammatory processes and are associated with the pathogenesis of many neurodegenerative disorders such as Alzheimer's diseases, Parkinson's diseases, stroke, spinal cord injury, encephalitis, and multiple sclerosis (Carson, 2007). Although the role of microglia in neurodegeneration is clearly understood yet but, many evidence indicates that microglia can become transiently activated to an amoeboid phenotype responsible for the phagocytosis of living neurons (Huuskonen *et al.,* 2005). It is also reported that during long-term or sustained neuroimmune activation, microglia produce cytokines that are toxic to neurons and this neurotoxicity plays a potential role in collateral neurodegeneration processed in many brain inflammatory diseases or disorders (Rock *et al.,* 2004). SH neurons (i.e., SH-SY5Y) are also found to have their over expressive pattern followed by uncoupling of protein-2 that exhibited an increase in neuron-microglia interactions which represented an early step in microglial phagocytosis of neurons. Although, neurodegeneration also found to associated with degeneration of presynaptic neurons. Hence, some clinical debate is still with this type of involvement of microglia in synaptic stripping and synapse degeneration (Perry & O'Connor, 2010). Some of documented evidences from post-mortem brain tissue have been postulated for activated microglia and astrocytes responses in ASD individuals (Vargas et al., 2005; Enstrom *et al.,* 2005). Previous findings are consistently supported with an active and ongoing postnatal process of neurodegeneration and neuroinflammation that leads to elevated level of proinflammatory chemokine, monocyte chemotactic protein-1 (MCP-1) in neural regions in individuals diagnosed with an ASD (Margan *et al.,* 2010). As well as immunocytochemically identified microglia and stereologically quantification has been proposed for studying the microglial densities in the fronto-insular and visual cortex from autopsies of the brain in ASD individuals in comparison to controls by using positron emission tomography (PET) and a radiotracer. These observations are determined that increased microglial activation in the cerebellum, midbrain, pons, fusiform gyri, and the anterior cingulate and orbitofrontal cortices in ASD individuals as compared to controls (Suzuki *et al.,* 2013).

Impact of Proinflammatory Cytokines in Neurodegeneration

Activated microglia are reported to induce the release of many potentially neurotoxic substances, such as reactive oxygen species, nitric oxide, and various proinflammatory cytokines that evidenced for implication of neuroinflammation and overproduction of proinflammatory cytokines which are potent contributor to pathophysiology of chronic neurodegenerative disorders (Vagas *et al.,* 2005; Chez *et al.,* 2007). It is also proved from previous clinical observation that proinflammatory cytokines (tumor

necrosis factor (TNF)-α, interleukin (IL)-6 and granulocyte-macrophage colonystimulating factor (GM-CSF), Th1 cytokine (interferon (IFN)-γ) and chemokine (IL-8) were significantly increased in the brains tissues of ASD compared with controls by using a protein array technique, it is also confirmed that that MCP-1, IL-6, IL-8 and IFN-γ were significantly increased in the cerebrospinal fluid (CSF) in individuals diagnosed with an ASD individuals when compared to healthy controls (Li X, 2009).

CLINICAL FEATURES OF AUTISM SPECTRUM DISORDER

ASD in children is also manifested with non-specific symptoms such as unusual sensory perception skills, motor clumsiness, disturbed emotional control and insomnia along with associated phenomena like mental retardation, emotional indifference, hyperactivity, aggression, self-injury and repetitive/ stereotyped behaviors such as body rocking or hand flapping. It is characterized by complex behavioral phenotype with eficits in both social and cognitive functions. Although the main findings of ASD emphasize the role of genetic and environmental factors in the development of autistic behavior. As well as, environmental factors are also likely to interact with the genetic profile and cause aberrant changes in brain growth, neuronal development, and functional connectivity. Despite growing evidence for the involvement of endogenous biomarkers in the pathophysiology of ASD, early detection of this disorder remains a big challenge. An attempt will be made to integrate all the available evidence which made the reduced brain connectivity, mirror neurons deficits, and inhibition-excitation imbalance in individuals with ASD (Fakhoury *et al.,* 2015). Increased recognition and awareness of autism in the last few decades have been driven by the significant growth in research evidence. Well controlled cohort studies following-up pregnant mothers are likely to clarify the effects of some pre- and perinatal risk factors implicated in autism. Significant strides have also contributed towards developing and validating screening and diagnostic instruments to reduce heterogeneity in clinical characterization in research studies (Elsabbagh *et al.,* 2012). However, developed countries have more improved and effective provisions for screening, diagnosis, and intervention are highly variable and many cases absent in community settings. Repetitive or stereotyped behaviors are often accompanied by cognitive impairment, seizures or epilepsy, gastrointestinal complaints, lack of sleep and other problems whose differential diagnosis reported for various associated disorders such as childhood schizophrenia, learning disability and deafness. Previously, longitudinal study of high-risk ASD infants have been initiated with 150 infant siblings, including 65 followed to age 24 months (Zwaigenbaum *et al.,* 2005). Preliminary results of the proposed study are indicated that by 12 months of age, siblings who are later diagnosed with autism may be distinguished from other siblings which are low-risk controls on the basis of:

- Including atypicalities in eye contact, visual tracking, disengagement of visual attention, orienting to name, imitation, social smiling, reactivity, social interest and affect, and sensory-oriented behaviors (Zwaigenbaum *et al.,* 2005);
- Prolonged latency to disengage visual attention (Zwaigenbaum *et al.,* 2005);
- Delayed expressive (Zwaigenbaum *et al.,* 2005);
- Receptive language (Zwaigenbaum *et al.,* 2005);
- Poor visual orienting (Zwaigenbaum *et al.,* 2005).

DIAGNOSIS OF AUTISM SPECTRUM DISORDER

ASD is diagnosed on the basis of the presence of its associated core symptoms especially non-specific manifestation of individual abilities in intelligence and verbal domains (Elsabbagh *et al.,* 2012). The onsets of nonspecific symptoms are recognized in infants or toddlers include irritability, passivity, and difficulties with sleeping and eating, followed by delays in language and social engagement. However, many researchers have reported that about 50% of infants showed behavioral abnormalities or atypical behaviors including extremes of temperament, impaired visual contact, fluctuated emotional control, lack of response to parental voices or interaction, imitation, social responses and motor control (Zwaigenbaum *et al.,* 2005; Sab *et al.,* 2003). The frontal and temporal lobes are the markedly affected brain areas in ASD patients especially the deficit of amygdala in cognition and ASD that have been observed under numerous neuropathological and neuroimaging clinical studies. These reports are confirmed for abrupt social and aggressive behavior (Sab *et al.,* 2003; Alexander *et al.,* 1986). Prefrontal lobe has been considered as playing an important role in higher-level control and a key structure lined with autism and its deficit demonstrate higher-order cognitive, language, social, and emotion dysfunction, which is deficient in ASD patients (Stuss & Knight, 2013; Mashhoon *et al.,* 2010). One of the more ubiquitous behavioral findings in ASD population has been found prevalence of social skills difficulties (Niklasson, Rasmussen, Oskarsdottir, & Gillberg, 2001, 2002; Swillen *et al*., 1999; Woodin *et al*., 2001; Shprintzen, 2000). Several earlier studies and report evidence of social skills deficits including withdrawn and shy behaviors, difficulties initiating interactions, and anecdotal evidence of a limited range of facial expressions (Gerdes *et al*., 1999; Niklasson *et al*., 2002; Swillen *et al*., 1999). Despite the evidence that a large percentage of individuals with the 22q11.2 deletion experience psychiatric, social and communication difficulties which used for diagnosis of an autism spectrum disorder (ASD) with greater frequency than the general population.

ASD are atypical developmental delays characterized by impairments in communication, social skills, and restricted or stereotyped patterns of behaviors and interests with diagnosis of Asperger's syndrome in ASD individuals. This diagnosis is reserved for those with impaired social behavior, including inability to read nonverbal cues, and stereotyped and restricted patterns of interest, but without concomitant delayed language and cognitive ability (Yergin-Allsop *et al.,* 2003).

Children diagnosed with an ASD experience marked social impairment characterized by a lack of relatedness and lack of emotional connections with other surrounding people. For example, they exhibit inappropriate or constricted ranges of facial affect when compared to normal children without ASDs (Yirmiya *et al.*, 1992). Similar behaviors have been reported in some studies of individuals with the 22q11.2 deletion (e.g., Roubertie *et al*., 2001), but other findings are mixed in terms of the prevalence of ASD symptoms and disorders in this population. Some researchers have reported that the occurrence of ASDs in children with 22q11.2 deletion is relatively uncommon (e.g., Kozma, 1998). Using the Autism Diagnostic Interview to confirm a diagnosis of autism based on strict criteria, one research group reported that none of the 103 autistic children in their sample had a chromosome 22 deletion (Ogilvie, Moore, Daker, Palferman, & Docherty, 2000). Although the Ogilvie *et al*. (2000) was proposed a clinical observations where samples was drawn entirely from multiplex families, which limits the generalizability of their findings, they concluded that behavioral and psychiatric symptoms observed in the 22q11.2 deletion population were likely inconsistent with autism when strict criteria for diagnosis is used for ASD genetic studies (Ogilvie *et al*. (2000).

Besides amygdala and nucleus accumbens (NAc) is also considered as the key point structure which is found to deficit in ASD patients to have impaired social reward and pleasure response in ASD (Knuston *et al.,* 2001; Stingler *et al.,* 2011).

Limitation of this diagnostic tool is the use of the ADI-R to detect ASD within this sample of children with an established genetic diagnosis. The ADI-R has been revised to discriminate ASD from other genetic disorders (e.g., Fragile X). However, that the estimated prevalence of ASD in this sample of children with 22q11.2 deletion may have been somewhat inflated due to a measurement artifact. ADI-R may not be able to reliably discriminate behaviors that characterize children with ASD from behaviors of children with 22q11.2 deletion. This potential weakness in the ADI-R which mostly applies to other measures such as the Vineland "Adaptive Behavior Scales", highlights the importance of using multiple methods to carefully and thoroughly assess ASD, particularly in children who have genetic diagnoses. Certain characteristics of the sample may also limit the plot of these findings. There is a possibility of ascertainment bias, in that all children described in the present study had experienced manifestations of the 22q11.2 deletion that were apparent enough to challenge the genetic testing. This characteristic suggests that they may have been more seriously affected than other children who have this kind of deletion but have not experienced the structural anomalies such as congenital heart defects or the other health problems such as hypocalcemia associated with the deletion. Further research focusing on linkages between specific genes and ASDs is greatly needed, as phenotype research on family characteristics and personality types remains imprecise and relies upon clinical interviews that require further testing and standardization in ASD individuals (e.g., M-PAS, FHI; Bolton *et al*., 1994; Folstein *et al*., 1999; Piven, Palmer *et al.,* 1997; Szatmari *et la.,* 1995; Szatmari *et al*., 2000).

It is also possible that parents of children who were more seriously affected by the 22q11.2 deletion were more motivated to respond to the invitation to participate than parents of children with fewer difficulties (Folstein *et al*., 1999). As a result, the findings may represent an overestimate of the prevalence of ASD in the population of children with 22q11.2 deletion. Moreover, participating families had the time and resources to allow their children to travel to The Children's Hospital of Philadelphia, in some cases from considerable distances, to participate in the larger study and they were further able to take the time to participate in the current study over the telephone which may represent a slightly more economically privileged group. Given these sample characteristics, findings should be interpreted with caution, as this sample may not be fully representative of all individuals with the 22q11.2 chromosomal deletion (Bolton *et al*., 1994; Szatmari *et al*., 2000).

TREATMENT OF AUTISM SPECTRUM DISORDER

In order to assess behaviors and symptoms that are characteristic of ASDs, caregivers completed a measure that screens for these behaviors. Caregivers of children ages four years and older (n = 78) completed the Social Communication Questionnaire, Lifetime Version (SCQ, previously known as the Autism Screening Questionnaire. So, correct line of treatment can be given to ASD individuals (Berument *et al.,* 1999).

Many treatments (Txs) have been proposed for ASD with the most effective being combined Tx involving specialized and supportive educational programming, communication training (e.g., speech/language therapy), social skills support, and behavioral intervention (Lord & McGee, 2001: Mayer *et al*., 2007). Occupational and physical therapy also may promote progress by addressing comorbid difficulties of motor coordination and sensory deficits (Levy & Hyman, 2008). Behavior modification

(e.g., applied behavior analysis [ABA]) has the most empirical support for a single Tx, with documented improvements in language, social, play, and academic skills, and reduction in severe behavioral problems (Schreibman *et al.*, 2000). However, behavioral Txs are time and staff intensive, requiring up to 30–40 hours of Tx per week for several years by trained staff working directly with the child and typically focusing on one or a few behaviors at a time. Risperidone and aripiprazole are the only FDA-approved medications for ASD and they are approved only for the Tx of irritability in 5–16 year olds with ASD. Still no fixed medications are currently established to treat ASD core symptoms. "Off-label" medications are often prescribed for various cognitive behaviors such as inattention, impulsivity/hyperactivity, sleep problems, repetitive/perseverative behaviors, anxiety, mood, agitation, aggression, and disruptive and self-injurious behaviors but may have significant side effects (Finding *et al.,* 2005). Previous survey on ASD individuals has estimated the utilization of psychotropic medication for youth with ASD as high as 47% (Witwer & Lecavalier, 2005), but there is ongoing debate about the role of such agents (Bryson et al., 2003). Response rates to medication for comorbid diagnoses in ASD children may be lower than for children without ASD e.g., the response rate of methylphenidate for typically developing children with attention deficit hyperactivity disorder (ADHD) is 70% (Spancer *et al.,* 1996). Complementary and alternative medicines are also commonly reported, but their effectiveness remains unproven (Newschaffer et al., 2007). Therefore, given the limitations of available Txs for ASD and the severe and chronic nature of ASD, there is a large public health need for additional interventions.

Because these interventions can include both ingestible via oral administration and noningestible when externally administered Txs is referred to them collectively as complementary and alternative Txs (CATs). They are complementary when these practices are used together with conventional medicine and alternative when used in place of conventional medicine. However, newly designated complimentary Tx, incremental effects when added to conventional Tx should be empirically demonstrated (Hanson *et al.,* 2007; Harrigton *et al.,* 2006).

ASD medical management criterion includes typical antipsychotics, atypical antipsychotics, antidepressants, selective serotonin reuptake inhibitors, α2-adrenergic agonists, β-adrenergic antagonist, mood stabilizers and anticonvulsants (Farmer *et al.,* 2013). Antidepressants are most commonly prescribed agents followed by other stimulants and antipsychotics for ASD patients. The high prevalence of comorbidities is found to reflect in the rates of psychotropic medication used in some of ASD patients. So, antipsychotics are found more effective in treating the repetitive behaviors in children with ASD (Kerbeshain *et al.,* 2001). Music therapy is also reported for ASD children involving playing and/or listening to music that has been used to Tx ASD because of its potential for assisting communication, joint attention, expression, engagement, and relationships with the environment (Wigram & Gold, 2006). Most research on music therapy is still in progress for ASD case studies with only two randomized single-blind, repeated measures, within-subject comparison designs (Buday, 1995; Kim *et al.,* 2008). These studies had a total of 20, 3-to-9 year-olds with ASD, with varied Tx presentations, given 1–20X/week for 1–12 weeks for 30 minutes. Significant results and potential clinical outcomes include improvement in imitating signs and words, longer and more eye contact and turn-taking, joint attention, nonverbal communication, longer and more joy, emotional synchronicity, initiating engagement and compliant behavior. Research on music therapy for ASD lacks evidence-based assessment of ASD, large samples, randomized controlled trials (RCTs), standardized protocols, double-blind, sham, use of standard Tx outcome measures, follow-up, monitoring of adverse-effects, or concomitant Txs. However, it appears safe, seems sensible, easy and cheap and is therefore acceptable. There is limited scientific evidence of efficacy for some CATs, but research on CATs for ASD is imperative because key safety and efficacy questions remain

for the majority (Kerbeshain *et al.,* 2001). Berman and Straus (McPheeters *et al.,* 2011) observed that many CAT studies assume that Txs are well defined, including optimal dose/duration/intensity, that the sample has been correctly diagnosed and selected, and that the Tx is consistent from one practitioner to another. They note that CATs should meet the same fundamental requirements as for conventional Txs, using the same tools and techniques as those for conventional research to isolate the specific effects from the nonspecific effects of Tx as much as possible. However, to be a truly designated complimentary Tx, incremental effects when added to conventional Tx should be empirically demonstrated. Likewise, to be truly designated an alternative Tx, similar effects when compared to conventional Tx should be demonstrated. Few CATs for any psychiatric condition (and none for ASD) fulfill these requirements, so the majorities are not valid CATs. Such controls include rigorous protocols, RCTs with, where possible, placebo/sham control conditions with double-blind designs, and careful diagnosis. Such kind of controlled and well programmed research activities are vital because, even though people often assume CATs, particularly natural ones are safe as well as their use without supportive evidence is risky because they may have dangerous, sometimes life-threatening and irreversible side-effects which fail to reduce symptoms or improve functioning in ASD patients with severely impairing disorders accompanied with delay use of other more established Txs, waste of time, waste of energy and waste of money. These days, there are also alternative medication which are chosen by some of physicians includes opiate antagonist, immunotherapy, hormonal agents, megavitamins and other dietary supplements to treat ASD patients (McPheeters *et al.,* 2011).

FUTURE RESEARCH DIRECTIONS

Findings from the present study may directly impact current practices and medical care for ASD children with a 22q11.2 deletion. In this study, hospital stays and previous diagnoses might have delayed the detection of ASDs (Folstein *et al*., 1999; Piven, Palmer *et al.,* 1997; Szatmari *et al.,* 1995). Parents may not be mentally prepared to recognize behaviors that did not confirm the primary diagnosis or may have ignored these behaviors as the result of the trauma of their child's hospitalization. These factors suggest that certain situations, such as prematurity or regular hospital stays, require careful attention and consideration of missed diagnoses. Future studies should investigate methods to prevent biased interpretations of symptoms in the context of the 22q11.2 deletion. In addition, it might be fruitful to provide all children with a 22q11.2 deletion with more stringent developmental assessments that specifically rule out or confirm ASDs.

Given the host of difficulties faced by many children with a 22q11.2 deletion, such as chronic medical conditions, learning disabilities, and other psychiatric issues, some may question the incremental value to families of formally diagnosing an ASD. However, the existence of empirically supported treatments and interventions for individuals with autism means that children who are diagnosed can have access to early intervention and ongoing special services that can improve social, behavioral, and language functioning (Goldstein, 2002; Horner *et al.*, 2002; McConnell, 2002). Complementary and alternative medical (CAM) therapies are commonly recommended by physician for ASD children who have ADHD. The use of these therapies is well documented but, evidence of its safety and efficacy of these treatments in children is limited. This article describes the current evidence-based CAM therapies for ADHD and autism that focusing on nutritional interventions; natural health products, including essential fatty acids, vitamins, minerals along with other health supplements (Geraghty *et al.,* 2011; Huffman,

2011; Rossignol *et al.,* 2009; Schechtman, 2007; Weber & Newmark, 2007). Diagnosis that combat with understanding to parents and informs their attributions about their children's behaviors. In addition, this type of ASD diagnostic measure prepares parents for areas of difficulty that develop in the later years of autism, including depression among higher functioning individuals (Ghaziuddin *et al*., 2002; Volkmar *et al*., 1999) and also have the need of residential living and preparation for sheltered occupations (Frith, 1991). An accurate diagnosis of ASD may expedite acquisition of services and be particularly empowering for families of children with a 22q11.2 deletion which alarmed the medical and educational professionals about this little known fact of ASD but relatively common genetic disorder, about which we still have so much to learn.

CONCLUSION

So, this chapter is helpful to sort the outline of neurobiology of ASD and its associated disorders and non-specific manifestations which is considered a neurodevelopment disorder. The causes of ASD are not still known and various conducted researches suggest that both genes and environment play important roles to develop this neurodevelopment disorder. Although many children with ASDs are currently treated with medical interventions, strikingly little evidence exists to support benefit for most treatments. Risperidone and aripiprazole have shown benefit for challenging and repetitive behaviors, but associated adverse effects limit their use to patients with severe impairment or risk of injury. Its respective early diagnosis and medical management is important to improve the mental and physical health of ASD affected individuals. Otherwise, with the time, neurodegeneration happens followed by dementia and schizophrenia in some of ASD patients with the increased age. There is currently no one standard medical treatment used for ASD in affected population. Although, proposed treatments are including behavior and communication therapies, skills training, and use of opiate antagonist, immunotherapy, hormonal agents, megavitamins, other dietary supplements or medicines that proposed to increase affected patient's ability to grow and learn new skills to achieve better results to control its associated symptoms.

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Chapter 17
Creutzfeldt–Jakob Disease: A Prion-Related Neurodegenerative Disorder

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ABSTRACT

Creutzfeldt-Jakob disease (CJD) is a rare disease associated with neurodegeneration mostly characterized by damage to the neurons. CJD is caused by aggregation of misfolded proteins known as prions; thus, CJD is said to be a prion-related illness. CJD and other prion-related illnesses such as Kuru and Gerstmann-Sträussler-Scheinker disease (GSS) have been reported to have complex mechanisms due to their association with the brain and the nervous system in general. A lot of questions have been raised about the mechanism, diagnosis, and pathogenesis of this disease. The complexity of prion proteins themselves have contributed to more questions about the complications of CJD, whether misfolding of the prions are responsible for neurodegeneration or the misfolding are mere symptoms of the disease. This chapter attempts to explore some details about CJD and answers most related questions about the disease's mechanism. The author finally attempts to explore recent development in pathogenesis, diagnosis, and treatment of CJD.

INTRODUCTION

Human NDs have been one of the most deadly disorders with complex mechanisms and complicated treatment processes (Montie & Durcan, 2013).Particularly, thehumanprion diseases are one of the most rare human neurodegenerative diseases widely studied. These are associated with misfolding of proteins which accumulated and cause destruction of cells of the system (Friedman-Levi *et al.*, 2011). These proteins otherwise called prions, are misfolded leading to their aggregation into opaque amyloid structures. The pathogenesis of these diseases are mostly related to accumulation of the amyloid aggregates which in most cases, is associated with neural damage (Holman *et al.,* 2010). Prion diseases are therefore a group of progressive but fatal neurodegenerative disorders affecting both humans and animals, they are otherwise referred to as transmissible spongiform encephalopathies (TSEs) (Jackson &

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Krost, 2014). Some of these prion diseases including CJD, Alzheimer's disease (AD), and Huntington's disease (HD) are having rare occurrence with complicated pathogenesis (Kovacs & Budka, 2008). CJD is a prion related illness characterized by aggregation of misfolded proteins or prions. It belongs to a family of human diseases associated to and or characterized by neurodegenerative conditions and they include; Gerstmann-Sträussler-Scheinker syndrome (GSS), fatal familial insomnia etc. These diseases are thought to be having similar characteristics with animals spongiform encephalopathies such as ''cow madness" also known as bovine spongiform encephalopathies (BSEs) (Lang, Heckmann, & Neundörfer, 1998). These could have both sporadic or spontaneous occurrence or could be genetical depending on occurring cases. As such as in BSEs, prions could also be transmitted resulting in the spreading of the disease (States *et al.,* 2005). Most researches in this area are focusing towards establishing a link between variant phenotypes of CJD and with the molecular features studied in wide ranges of CJD conditions.

This chapter attempts to explore details on CJD including the basic description of disease, its pathogenesis, classification, diagnosis, and epidemiology. The author objectively attempts to explain different perspectives of the current researches on Creutzfeldt-Jakob and a future sight as well recommendation on the treatment of the disease.

BACKGROUND

Neurons being the major cells of the nervous system could be damaged progressively by one cause or another leading to neurodegeneration and consequently diseases, such diseases are known as NDs (Aguzzi & Zhu, 2012). NDs are diseases associated with damage in structure and functions of the neurons, one of the important cells of the nervous system (Aguzzi & Zhu, 2012). In neurobiology, neurons form the complex network of communication around the central nervous system. Damage to neurons due to a number of factors has been reported to be lethal and associated with a number of diseases and disorders (Murray & Davis, 2003).

CJD was discovered by the German neurologist, Hans Gerhard Creutzfeldt and Alfons Maria Jakob in 1921 (Cordery *et al.,* 2003). Creutzfeldt was the first to describe the disease characterized with neurodegeneration and Jakob proposed the disease to be associated with prions (Holman *et al.,* 2010). However some of descriptions of the disease made by Jakob and Creutzfeldt did not match the current description of the disease (Creutzfeldt, 2002). This including being transmissible as well as currently being observed to be part of a class of both human and animal diseases called TSEs.

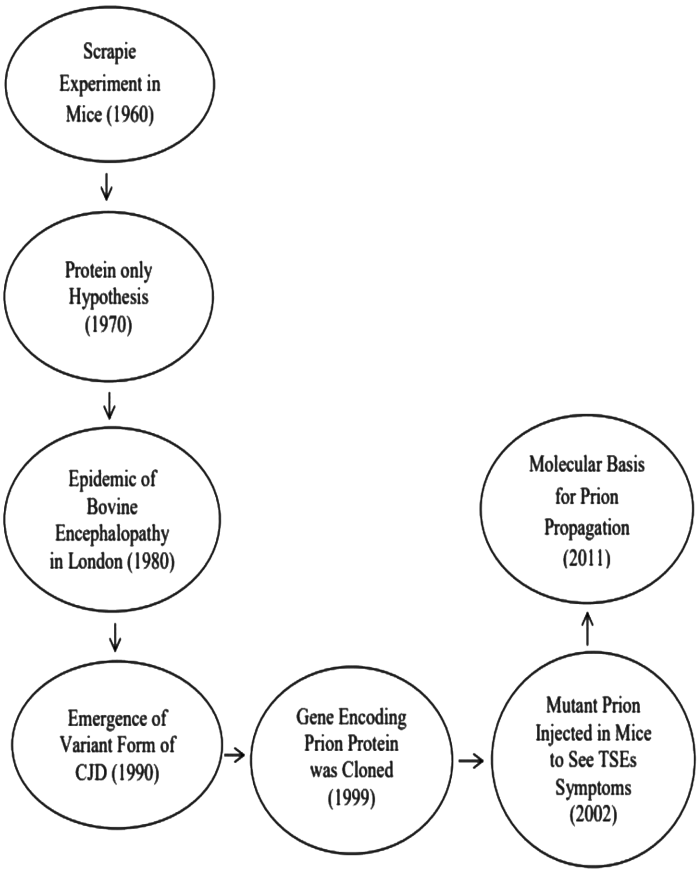
CJD as a TSE is associated with and mostly caused by diseased or misfolded prions (Aguzzi & Zhu, 2012). Prions are proteins that often misfold into amyloid structures and can possibly infect other proteins resulting into spreading or transmission (Jackson & Krost, 2014). In other words, prion proteins affect other neighboring proteins converting them into misfolded prion proteins and initiate the pathogenesis of TSEs including CJD (Lang, Heckmann, & Neundörfer). Spongiform refers to the characteristic appearance of infected brains, which become filled with holes until they resemble sponges under a microscope (Aguzzi & Zhu, 2012) . Transmission of the prion proteins in CJD was not initially established (Belay, 2004). The idea that prion proteins can be transmitted in CJD was established in 1986 after the London epidermic (Garske & Ghani, 2010). The incidence of the epidermic has stimulated interest in study of CJD with major aspects on the molecular mechanisms of its pathogenesis (Wilesmith *et al.,* 1988). Studies on prion proteins in fungi has already established the transmissible property of normal prions in the cell (Anderson *et al.,* 1996). Similar prion studies on vCJD was carried on human patients sample which

confirmed the spreading ability of misfolded prions in CJD (Griffith, 1967). Protein only hypothesis was established and served as a model for supporting transmissibility of prion proteins (Soto, 2011). Consequently, studies were on to provide experimental basis for the hypothesis. Particularly, transgenic animals expressing mutant prion protein that develop clinical and pathological signs of TSE, were produced (Soto, 2004). Figure1 shows a brief timeline of the major occurrences and findings related to TSEs.

MISFOLDED PROTEINS' AGGREGATION AND THEIR ROLES IN PROTEINOPATHIES

Misfolded proteins existing together with unfolded proteins in the cell are re-folded by molecular chaperones (Kim, *et al.,* 2013). Proteins that refused to fold properly are immediately degraded however in pathologic cases, this protein resist degradation and accumulate (Halasi *et al.,* 2017). The ability to resist degradation has been attributed to folding into specific abnormal forms which are the infectious prion forms (Currais *et al.,* 2017). During biosynthesis cells continuously form stream of misfolded proteins and are refolded, degraded, or sequestered into specified cellular compartments such as aggresomes (Hartl, Bracher, & Hayer-Hartl, 2011). Many of such proteins have been seen to be misfolded and consequently

Figure 1. Timeline of experimental events during the discovery of prions



aggregates to form insoluble structures in the cell (Stefani, 2004). These faulty or abnormally aggregates of proteins have been seen in many neurodegenerative diseases. Table 1 shows a brief summary of the misfolded proteins in some NDs. Molecular chaperones are proteins that bind assist in protein folding and remaining infolded form. They bind nascent polypeptides as they emerge from ribosomes and participate in every step in the handling of misfolded proteins. These proteins play crucial roles by monitoring the quality of the folded chains and like highlighted earliar, refold misfolded proteins *(*Kim *et al.,* 2013). Chaperones also target the misfolded proteins that couldn't be refolded/repaird for degradation.

PRION MISFOLDING AND CREUTZFELDT-JAKOB DISEASE

Prions are thought to be found all over the body with yet to be known function (Friedman-Levi *et al.,* 2011). In TSEs, when a prion enters a healthy organism, it induces an healthy protein to misfold into anonymous abnormal form through a chain of unknown processes (Aguzzi & Zhu, 2012). Certain proteins in cells of both lower and higher organisms such as bacteria and humans, promote or assist folding of proteins into various forms and conformations, these are known as chaperons. Thus as a prion promote misfolding of a normal protein into its own prion form, it results into spread of the prion protein which consequently form amyloid aggregate forms or plagues (Fania *et al.,* 2017). The amyloid form refers to an aggregate of misfolded or prion proteins with characteristic opaque sheets (Jackson & Krost, 2014).

Prion aggregates or amyloids are characteristically stable and show resistant to denaturation processes caused by temperature and chemical changes and as such stay for prolonged periods in the infected cell consequently resulting into its death (Kovacs & Budka, 2008). One question that is yet to be answered is, "misfolding of the prions causes the damage to the cell or other external damages to the cell causes the initiation of the misfolding resulting into the prion aggregation'' (Kovacs & Budka, 2008). However some scientists believed mutations in some genes initiated prion development in HD, a prion related disease (Mercado *et al.,* 2015). However in most TSE, infection of a prion resulted into transmission and spreading of neighboring prions resulting into their misfolding and aggregation into amyloid prion forms (Jackson & Krost, 2014).

Table 1. Some proteins Misfolded and the consequencing proteinopathies

Proteinopathy	Aggregating Protein(s)
Spongiform Encephalopathies	Prion protein
Parkinson's Disease	α-Synuclein
Cerebral β-amyloid angiopathy	Amyloid β peptide
Frontotemporal lobar degeneration	TAR DNA-binding protein 43 (TDP-43)
Alzheimer's disease	Tau protein
Huntington's disease	Huntingtin protein
Amyotrophic lateral sclerosis	Superoxide dismutase 1
Multiple tauopathies	Tau protein (microtubule associated)
Alexander's disease	Glial fibrillary acidic protein
Enfuvirtide amyloidosis	Enfuvirtide protein

The ability of misfolded prions (mostly from bovine encephalopathies) to infect neighboring normal prions was initially a not accepted (Murray & Davis, 2003). With the ability to infect prion to cause disease upon incubation, it resembles the commonly accepted processes of pathogenesis in microbes including bacteria, viruses and fungi (Nuvolone *et al.,* 2017). Critics of infectious prion pathogenesis argued that bacteria and viruses, major causative agents of diseases are mostly living organisms with delicate and distinct structures (Whalley, 2017). These organisms either secret toxins that temper normal cellular processes and or insert their genomes into the host cell thereby destroying the hosting cells and continue to spread and transmit to other cells by similar mechanism (Jackson & Krost, 2014). According to these critics, a protein would not be able to be transmitted in a similar fashion. However researches in various prion-related illnesses including CJD described the mechanism of prion transmission especially in TSEs *(*States *et al.,* 2005). Normal prion proteins being found all over the cell can be infected by an infectious prion mostly coming from contaminated food (e.g meat from cattle suffering from BSEs, also known as cow madness). These infectious agents infect the normal prion by facilitating the folding its into a similar abnormal form hence becoming a potential infectious prion. The infected prion infects another and the process continues all over the neighboring prions consequently aggregating into amyloid forms (Nuvolone *et al.,* 2017). However it is not exactly known how it facilitates the misfolding process, some hypothesized that by acting in a similar way as molecular chaperons (Whalley, 2017). In Figure 2, the underlying mechanism of prion misfolding is mentioned.

In CJD, aggregation of misfolded prions has been thought as the cause of neurodegeneration due to increased destruction of neuronal cells (Lang et al., 1998). However the actual mechanism by which these aggregates cause cell damage has not been clearly established and appears to be variable within each of the disease (Montie & Durcan, 2013). Some scholars hypothesized that misfolded disease proteins appear to act primarily by toxic gain-of-function and/or dominant-negative effects, although loss-of-function effects have also been observed (Whalley, 2017).

Although most misfolding events might be associated with toxicity leading to disease but not all events are responsible for toxicity (Valastyan, 2014). In the fungal organism, *Saccharomyces cerevisiae*, the presence and availability of prions are regulated and most of these prions utilized for various adaptive purposes (Chernova, Wilkinson, & Chernoff, 2014). Prion proteins in CJD are infectious and are associated with progressive neural damage hence dementia and other symptoms and conditions of neurodegeneration (Kovacs & Budka, 2008).

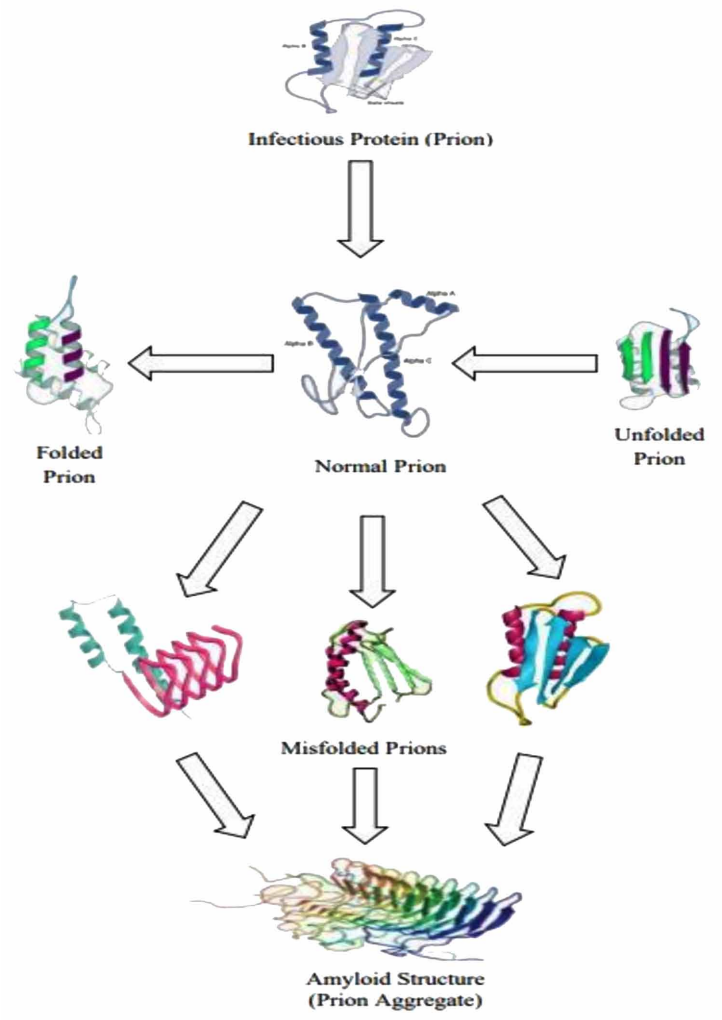
CLASSES OF CREUTZFELDT-JAKOB DISEASE

Different studies have suggested variety of classification of CJD. Some of the classifications were made based on the neuropathology of the disease (Hill *et al.,* 2003). However, based on the occurrence and cause of CJD, the disease can be classified into two main groups.

Sporadic Creutzfeldt-Jakob Disease

Sporadic CJD (sCJD) refers to the rarest yet the most common form of the disease. Its major cause has been established to be genetically associated (Brandt, 2003). sCJD is reported to possess variability in its clinical and neuropathological phenotype (Mead *et al.,* 2013). However, It remains to be seen whether the variability might be related to variations in the causative TSE agent strains, or to the influence of

Figure 2. The mechanism of prion misfolding



the methionine/valine polymorphism at codon 129 of the *PRNP* gene. The polymorphism on the PRNP gene encoding either methionine or valine remain the major susceptibility factor of sCJD with mutant methionine prototype dominating in most cases than valine (Rubenstein, Petersen, & Wisniewski, 2016). The germline mutation in the *PRNP* gene can be inherited in an autosomal dominant fashion leading to harboring a homozygous allele (Mead *et al.,* 2001). Key phenomenon in the molecular mechanism of sCJD is the conversion of PrP^{C} (normal prion) to the pathological PrP^{Sc} (diseased Prion) which is the pathological form associated with the disease. However the conversion is caused initially by mutation as earlier described (Bilheude *et al.,* 2008).

sCJD constitute about 85% of all recognized prion diseases in humans (Safar *et al.,* 2005). It has been reported that 1 person in every million of people suffers from sCJD every year (Chen & Dong, 2016). It usally affects people between the ages of 40-60 and mostly takes upto 6-8 weeks while taking upto

a year in some minority (Mastrianni, 2010). Similarly Brown et al. (1984) reported that about 10% of cases of sCJD have prolonged clinical course with the duration of the disease taking upto 2 years. Major symptoms associated but peculiar to sCJD are less pronounced and are mostly seen in other forms of the disease, however, a significant percentage of sCJD has been associated with cerebellar ataxia (Cooper *et al.,* 2006). Other symptoms including fatigue, weight loss, immediate loss of coordination, and Hallucination. Later stage symptoms include depression and sensory disturbances are common in sCJD that consequently progress to profound dementia (Geschwind *et al.,* 2013).

Variant Creutzfeldt-Jakob Disease

Variant CJD is the most widely known form of CJD as it can be transmitted between individuals via blood transfusion and can be acquired through ingestion of food contaminated with the agent of BSE (Maheshwari *et al.,* 2015). BSE is a TSEs in cattle and bovine family (Creutzfeldt, 2002). Consumption of a meat of cattle infected with BSE results into infection and transmission of infectious into the body of the healthy consuming individual resulting into infection of normal prions in the individual (Friedman-Levi *et al.,* 2011) The mechanism of conversion or transmission of a normal prion to an infectious one has been argued (Jackson & Collinge, 2001). However certain researchers have described key mechanisms involved. A Normal prion ($PrP^{C)}$ is converted to an infected or diseased prion (PrP^{Sc}) during a post-translation modification process involving structural modifications of the protein and resulting in a higher β-sheet content (Riesner, 2003). PrP^{C} is completely degraded after controlled digestion with proteinase K (PK) in the presence of detergents. PrP^{Sc} is N-terminally truncated under such conditions, resulting in a PK resistant core, termed PrP^{RES} (States *et al.,* 2005) . Most symptoms associated with the vCJD are similar to vCJD. However, in vCJD cognitive disorders appeared at much earliar stages than sCJD with severe behavioural disturbances (Mastrianni, 2010).

EPIDEMIOLOGY OF CREUTZFELDT-JAKOB DISEASE

Before the identification of vCJD in 1996, only three forms of CJD were thought to be existing and represent the most common prion related illness in humans. The three forms include:

- Familial CJD, comprising of about 5-15% of CJD cases. It has been found to be with one or more mutations on the *PRNP* gene (Babi *et al.,* 2016, WHO, 2010).
- Iatrogenic CJD, representing about 5% of CJD cases and mostly occurs as result of contamination from used surgical equipment (WHO, 2010).
- Sporadic CJD, most common form of CJD consisting of about 85% of CJD cases of CJD. It is also associated with mutation of the *PRNP* gene and was reported to occur throughout the world at the rate of about one per million people (Bonda *et al.,* 2016, WHO, 2010).

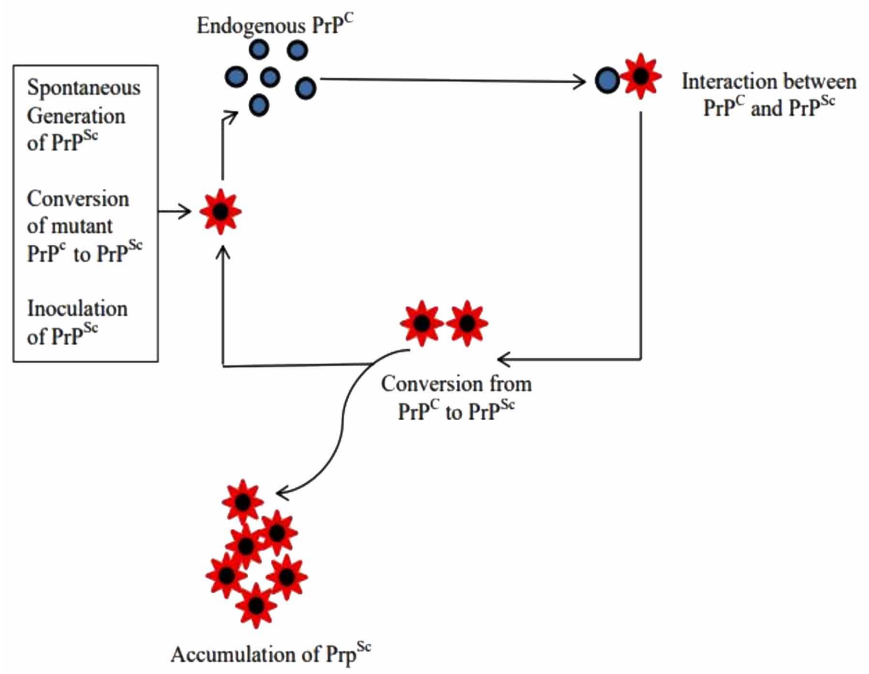
CJD occurs world and among every population with an average of 1.5-2.5 cases in every million per years (Brandel *et al.,* 2015). According to the centers for disease control and prevention (2017), the average case occurrence of CJD is 285.19 from 1979-2015 with the cases increasing with time progress.

PATHOGENESIS OF CREUTZFELDT-JAKOB DISEASE

Destruction of neurons due to an accumulation of these proteins consequently resulted in neurodegeneration (Whalley, 2017). A major characteristic of CJD and by extension most TSEs is formation of sponge-like appearance in the brain (Acevedo-Morantes & Wille, 2014). The conversion of the normal prion protein PrP^{C} to PrP^{Sc} initiates the pathogenesis of the disease (Riesner, 2003). Normal PrP^{C} is a membraned surfaced protein of whose clear function has been unknown. Structurally, it has a predominantly α-helical structure that is highly conserved between species (Trevitt & Singh, 2003). The pathogenic prion form, PrP^{Sc} is formed by posttranslational modification of the normal PrP^{C} form without the alteration of the primary structure of the normal protein. PrP^{Sc} is characterized by highly β-plated structures and being protease resistant (Kovacs & Budka, 2008). In vCJD, prion infection is caused eating meat or any contaminated food from cattle with ''cow madness'' also known as bovine spongiform ESEs (Billette de Villemeur *et al.,* 1996). The infected prion facilitates the misfolding of the normal prion PrP^{C} into the pathogenic prion PrP^{Sc} (Figure 3). Most biochemical evidences have shown that both BSE and vCJD were caused by invariably similar prion strain (Riesner, 2003). Distinct prion related diseases or illnesses can be differentiated by their biological properties including incubation periods and patterns of neuropathology (Trevitt & Singh, 2003).

Major symptoms of associated generally with CJD include loss of memory, coordination, sight and dementia. At early stage symptoms include memory failure and behavioral changes. As the disease progress, individual suffer from involuntary movements, loss of sight and even coma (World Health Organization [WHO], 2010).

Figure 3. The pathogenesis of Creutzfeldt-Jakob disease



DIAGNOSIS OF CREUTZFELDT-JAKOB DISEASE

Clinical symptoms associated with CJD are more are less similar in most neurological impairment (Van Everbroeck *et al.,* 2004). Neurological signs characterizing CJD include;lack of coordination, difficulty in walking and involuntary movements. These signs progress with each developmental stage of the illness as it progresses and, by the time of death, patients become completely immobile and mute (Poser *et al.,* 2000). In diagnosis of CJD, disorders with similarl features with CJD can be ruled out using several tests, one of which is biopsy test. Brain biopsy is the most accurate test in CJD diagnosis. It involves a procedure where a small piece of brain tissue is removed for study (Heinemann *et al.*, 2008). However, any brain surgery carries risk of damage to the brain and a tissue might be removed from a non-infected area thus will likely show an inaccurate representation of the disease (Creutzfeldt, 2002). In such case, the biopsy cannot be a reliable test to confirm or rule out the diagnosis. Similarly, autopsies on the whole brain can be used in given cases of CJD diagnosis. Autopsy is the study carried out on dead bodies to analyse different systems of the body (Heinemann *et al.,* 2008). It also is useful for research. Other tests commonly used for CJD diagnosis include:

- A brain magnetic resonance imaging (MRI) which uses magnetic and radio waves to capture a detailed image of the whole or portion of the brain in other to have a detailed picture and observe defects in the brain peculiar to CJD (Morgan *et al*., 2009) present
- A brain computed tomography (CT) scan, which provides much more details on the structural components of the brain tissues and can be used to observe patient's symptoms related to stroke or brain tumor (Rubenstein *et al*., 2016).
- A blood and fluid test, where different techniques can be used on blood of patients' sample to rule out other forms of dementia that may be treated (Zerr *et al.,* 1998). Cerebrospinal fluid tests such as 14-3-3 protein test, are particularly carried out to see if proteins such as the 14-3-3 protein that is associated with dementia or CJD are present (Zanusso *et al.,* 2016).

TREATMENT OF CREUTZFELDT-JAKOB DISEASE

In general, there is no treatment available to cure CJD. Treatment of prion diseases remains supportive; no specific therapy has been shown to stop the progression of these diseases (Belcastro *et al.,* 2010). Treatments are mostly done to alleviate the symptoms and to make the patient as comfortable as possible (Pocchiari & Ladogana, 2015). However for patients with CJD at initial stages, therapeutic measures can be take via use of many some drugs such as amantadine and acyclovir that target misfolding of a normal prion (Appleby & Lyketsos, 2011). Similarly, some pentosan polysulfate were used to target protease resistance of the diseased or misfolded prions and thus increasing their susceptibility to protease attack (Zuber, Ludewigs, & Weiss, 2007). Another target initial accumulation of the misfolded prions into an amyloid structure and promotes its clearance (Gauczynski *et al.*, 2006). Although some of the drugs have been successfully used for those purposes, their use has not been consistent in subsequent CJD patients (Vetrugno *et al.,* 2015). Researchers are now targeting protein regions on the misfolded proteins and designing specific antibodies to target them for destruction (Panegyres & Armari, 2013).

Due to the circumstances associated with treatment of CJD, the World Health Organization and other supporting agencies set up measures to alert the public about CJD (WHO, 2008). Some measures are taken to protect public health include:

- As researches established links between vCJD and BSE, governments through Health departments enlist CJD as a major health concern for the public. Example government of the United Kingdom made CJD a notifiable disease in 1988 (Ponte, 2006).
- The UK government similarly placed a ban on individuals that have lived in countries with high risk of BSE as a means to prevent a possible spread of infections to patients (Food and Drug Administration, 2002).

World Health Organization's Recommendations

The World Health Organization in its effort to provide measures that could decrease spread of BSEs and TSEs including CJD, made the following recommendations:

- WHO recommended that countries should ban use of ruminant tissues in food supplement preparation of domestic animals particularly members of the bovine family. All tissues potentially containing BSE agent, nor part or product of any animal which has shown signs of a TSE should be prevented from entering the (human or animal) food chain. (Centers for Disease Control and Prevention, 1996).
- WHO also recommended ban on pharmaceutical industries on the use of materials and product from the bovine family in which TSEs naturally occur. Id such materials are to be necessary be used, they should be important from countries with 0% reported cases of BSEs (WHO, 2003).
- The guidelines on tissue infectivity distribution in TSEs in 2006 provide information and assist national regulatory authorities in conducting risk assessments of vCJD. The tables on tissue infected were later updated in 2010 with the aim of providing current knowledge of tissue infectivity providing information on the possible transmissions in TSEs (WHO, 2010).

FUTURE RESEARCH DIRECTIONS

Previously researchers have been towards understanding mainly the pathogenesis and spread of the disease as being transmissible (Kovacs & Budka, 2008). Current and future researches focus on elucidation of the process of prion proteins associated with CJD (Aguzzi & Zhu, 2012). Targeting abnormal prions is crucial in treatment of CJD (Pocchiari & Ladogana, 2015). Recent development of techniques in immunotherapy and proteomics are used to understand structural organization of prion proteins and how they aggregate to amyloid plaques (Biasini *et al.,* 2012). Other researches focus on stimulating physiological processes to eliminate prion aggregates (Karapetyan *et al.,* 2013). For example astemizole is an antihistamine drug which has been found to stimulate autophagy through its action of being an antagonist of H1 receptor, leading to generation of reactive oxygen species and activation of autophagy (Jakhar *et al.,* 2017). Prion-based screening assays have been used in model organisms such as yeast to

identify infectious prions and allowed identification of drugs active against mammalian prions (Voisset *et al.,* 2009). Similarly researches are also focusing on ways to develop agents that will block transmission of infectious prions as ways to provide cure to CJD. Future researches should stress the following:

- With the progress made in immunotherapy, directing immune cells towards recognizing specifically abnormal prions and destroying them should be a focal research area to be exploited.
- Similarly designing specific agents that target molecular chaperones that aid abnormal folding of prions can similarly be exploited.
- Different types of chaperones are associated with re-folding of abnormal prions back into normal prions. Researches should focus on these chaperones as a potential target in therapy.
- Although biopsy has been used for period in treatment of CJD, advanced technique in radiotherapy can be used to target and eliminate aggregates of misfolded proteins. Researches can be focus in neuroimaging to study the structures of these aggregates. This will ensure success of the radiotherapy.

CONCLUSION

CJD is a major concern as most researchers believed neurodegeneration progressively becomes irreversible and the disease could not be cured. The chapter described the pathogenesis of different types of CJD and their distribution. It also revealed how a number of drugs have been unsuccessfully used in treatment of CJD. As the use of most therapeutic agents has proven to be consistently unsuccessful, there is a need to change focus towards the studies to find a possible cure to the disease. Studies are now focused more towards the molecular mechanisms underlying the development and spread of the different types of the disease. With advanced techniques currently in used, it is believed that a final cure for any type of CJD will be developed.

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Chapter 18
Childhood Neurodegenerative Disorders

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ABSTRACT

Neurodegenerative disorders (NDs) are a group of disorders with the deterioration of attained skills often with no solutions, usually ending with death or crippling disabilities. This chapter contains a classification for childhood NDs as well as an algorithmic approach for easy management of these disorders. Genetic defects and pathophysiology of disorders like Canavan, Krabbe, subacute sclerosing panencephalitis (SSPE), etc. are written in detail. Suggestions regarding management of some of these conditions are described as a lifecycle approach, from birth to death, to enable those who are taking care of such kids. Allogeneic hematopoietic stem cell transplantation (HSCT), gene therapy, combination therapy, and other experimental therapies have enlarged the scope of diagnosis and treatment options for these disorders. The author aims to brush up the existing and latest possibilities in NDs, including those at the experimental stage, for an easy understanding and for further research, especially as treatment options.

INTRODUCTION

Childhood NDs are neglected group of central nervous system (CNS) disorders by clinicians, as much of these disorders have no answers and hence any investigations to find out cause of a developmental problem due to NDs are mainly of academic interest. Fresh interest among clinicians in this is kindled by recent advances in molecular diagnosis and neurosciences, in addition to newer modalities on treatment. Childhood NDs are mainly genetic mutations resulting in either enzyme deficiencies or formation of abnormal products in nervous system (Marder, K et al,1998). Most of the disorders, where definitive mutations and abnormal products have been identified in CNS, have significant variations in their clinical presentations. The knowledge about the cause of this individual variations is however limited. Individuals who carry the same mutation in the same disease-causing gene may display a range of different clinical symptoms (Kwon, 2016). This chapter gives a bird's eye view of the common NDs in children and tries

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to bridge the gap between research and possible application of the knowledge in real life. It shall be the authors endeavor to put in approaches where ever such new knowledge can be inserted to find new ways of analyzing these disorders clinically. In this process author tries to bring in an algorithmic model utilizing the existing and new knowledge to find easy clinical approaches that also serves as a clinical classification. Where ever possible the author puts in life cycle approach, i.e., birth to death, to solve the difficulties these children undergo. Recent advances and possible areas of new researches are also added in this chapter, along with each disorder. The main objective of this chapter is to consolidate the existing knowledge from diverse sources to help in easy understanding to facilitate clinical management and bring out to fine tune the ideas and possibilities from the new options emerging out of researches.

BACKGROUND

NDs are a group of disorders often associated with constellations of findings suggesting loss of acquired skills, loss of memory; impairment of intellect; personality and behavioral changes, in addition to definite neurological signs like vision and hearing loss, changes in tone, seizures etc. However quite many NDs are due to identifiable causes like genetic, biochemical defects, chronic viral infections. With the advent of better imaging techniques and biochemical and molecular markers, a specific diagnosis is possible in many case; but thorough history and clinical examination still give chances to suggest a possible diagnosis (Kwon, 2016).

Most of the NDs of childhood are neurometabolic disorders. Often multisystem involvement with CNS signs and regression of attained milestones points to a neurometabolic disorder affecting the CNS. The age of onset, progression of the disease process and primary finding helps one to determine whether we are dealing with white matter or grey matter disorders (GM) (Kwon, 2016). Increasing spasticity and Upper Motor Neuron signs is a pointer towards white matter (WM) disease while seizures, visual impairment, loss of memory and executive functions are pointers to grey matter injury. This over simplification cannot explain the reason behind behavioral changes occurring in WM lesions. In fact, WM lesion often results in neurobehavioral disconnection syndromes due to disruption in nerve bundle connecting 2 cortical areas (Schwachman et al, 2008).

With the differentiation between presentation of GM and WM disorders decreasing and newer magnetic resonance imaging (MRI) evidences blurring these distinctions, a newer method of classification based on abnormal molecules or mutations is warranted. Even when options are limited, work up for a diagnosis is still needed for the promotion of preventive care in subsequent pregnancies. Advances in enzyme therapies can be of use only if diagnosed at an early age. This scenario necessitates the consolidation of emerging knowledge at different domains, including animal research, and linking it with existing ones.

CLASSIFICATION OF CHILDHOOD NEURODEGENERATIVE DISORDERS

The classification offered in some textbooks based on site involved is too simplistic and often confusing as mixed presentations are seen (Shu et al, 2017).

Clinical Classification

Another way of classification suggested is the clinically useful algorithmic way based on age of presentation and clinical features:

NDs With Regression Below 2 Years

A simple approach is to look out for hepatomegaly and presence of extra neural manifestations (Kwon, 2016) (Figure 1 and 2).

Regression in Children Between 2-5 Years

Progressive neurological deterioration between 2 and 5 years may be classified as follows given in Figure 3. These may be addressed by having a clear look at history and clinical examination and grouping accordingly.

Regression in Children Between 5-18 Years

History and clinical examination gives clear clues to classify the disorders in this age group. They may be subdivided into predominantly white matter, grey matter, extrapyramidal or ataxic group of disorders. Disorders like SSPE usually make their appearance in this age group (Figure 4).

Figure 1. Regression starting at < 2 years
Abbreviations: MPS: Mucopolysaccharidosis; GSD: Glycogen storage disease.

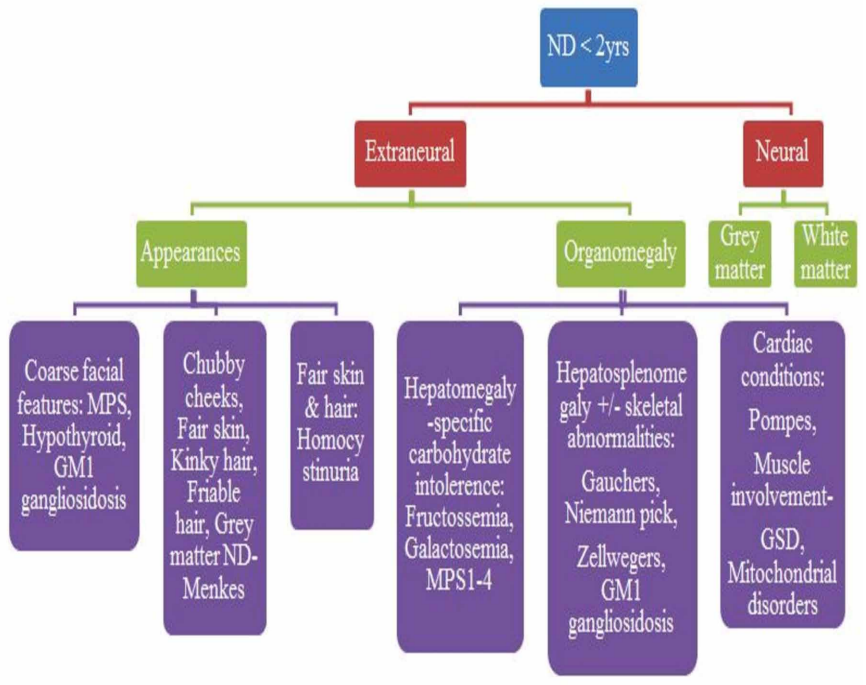


Figure 2. Regression starting at < 2 years with mainly neuronal involvement
Abbreviations: NCL: Neuronal ceroid lipofuscinosis; MLD: Metachromatic leukodystrophy.

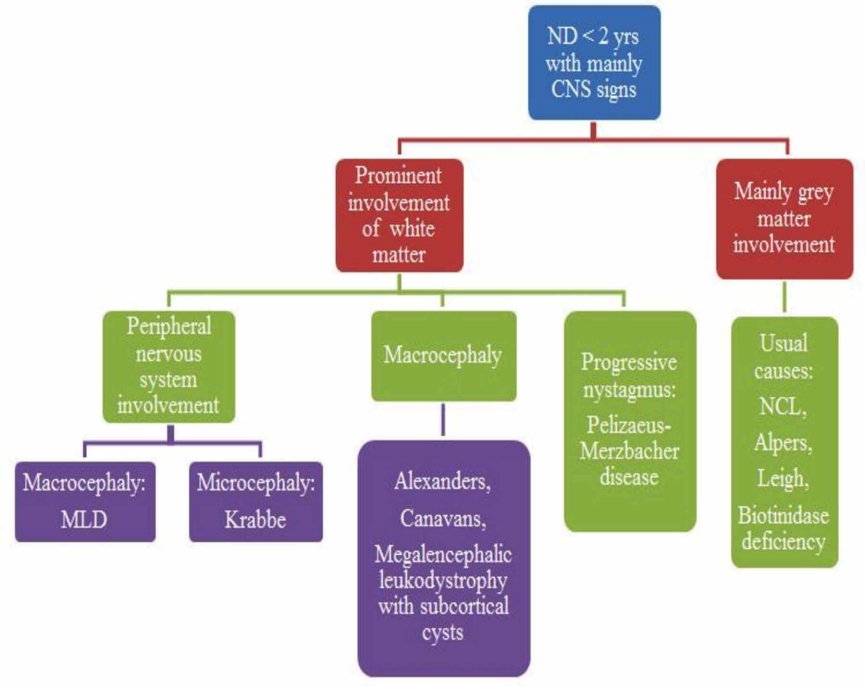


Figure 3. Regression starting between 2-5 years old
Abbreviations: MPS: Mucopolysaccharidosis; PKAN: Pantothenate kinase associated neurodegeneration; NBIA: Neurodegeneration with brain iron accumulation; ALD: Adrenoleukodystrophy; MLD: Metachromatic leukodystrophy; NCL: Neuronal ceroid lipofuscinosis; MERRF: Mitochondrial ragged red fibers.

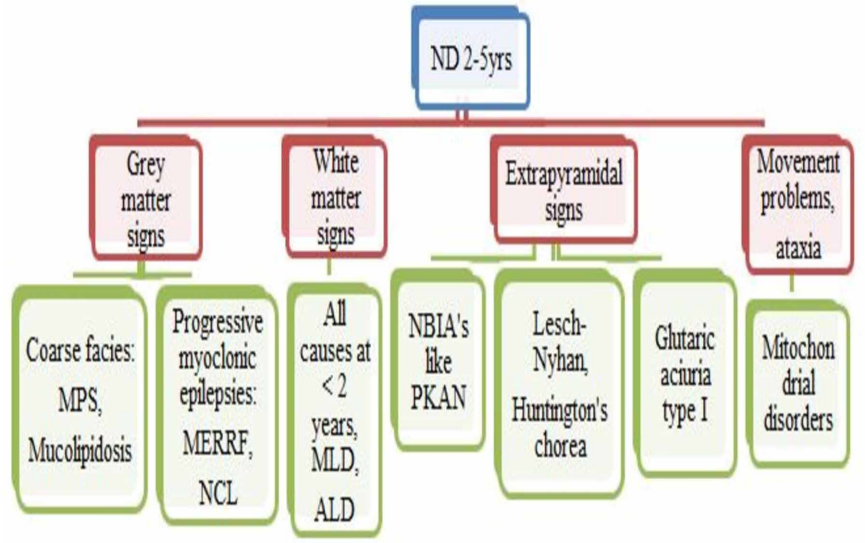
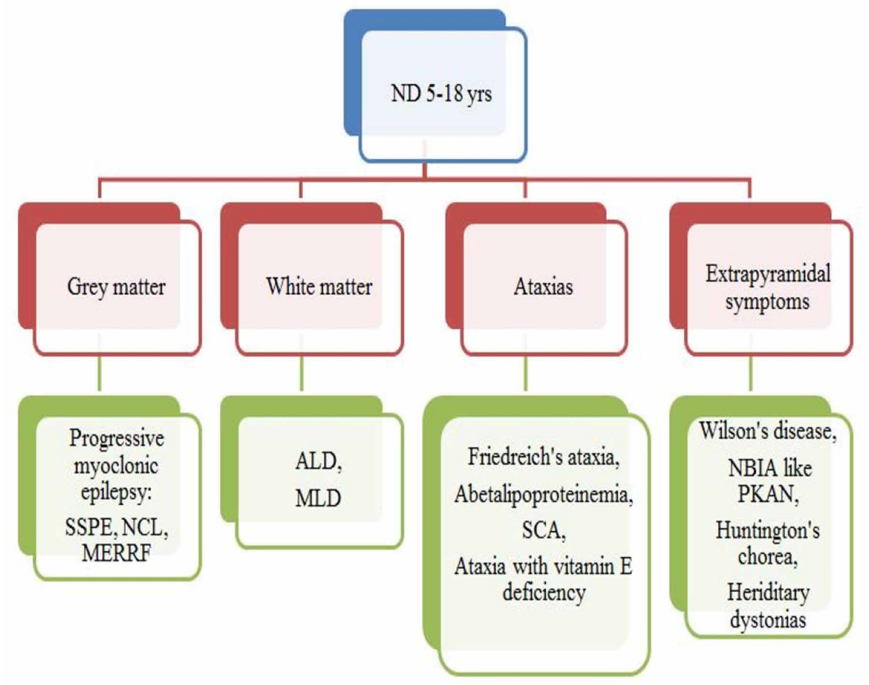


Figure 4. Neuroregression starting between 5-18 years
Abbreviations: PKAN: Pantothenate kinase associated neurodegeneration; NBIA: Neurodegeneration with brain iron accumulation; SCA: Spinocerebellar ataxia; ALD: Adrenoleukodystrophy; MLD: Metachromatic leukodystrophy; SSPE: Subacute sclerosing pan encephalitis; NCL: Neuronal ceroid lipofuscinosis; MERRF: Mitochondrial ragged red fibers.



NEURODEGENERATIVE DISORDERS OF CHILDHOOD

Canavan's Disease

This autosomal recessive (AR) disorder was first described by Myrtelle Canavan (1879-1953), an American neuropathologist, in her 1931 seminal paper (Canavan, 1931). Though Canavan's disease (CD) or cerebral spongy degeneration is seen pan ethnically (Zeng et al, 2002), it is most often noted in Ashkenazi Jews. The incidence of the disease is 1: 6,400 if both parents are carriers and 1: 13,500 if only one parent is carrier with no sexual predilection. Non-Jew's are mostly Europeans, Turks, African-Americans, Middle East people and Japanese. In these non-Jew population, the incidence is 1:1,00,000 (Makalon et al, 2015).

High quantities of N-acetyl-L-aspartic acid (NAA) produced and stored by the neurons are pushed into the extracellular fluid on its depolarization. NAA is further degraded into acetate and aspartate by asparto-acylase (ASPA) present in oligodendrocytes. Mutations in the *ASPA* gene in17p13.2 reduce the function of ASPA (Baslow et al, 2015). Since *ASPA* gene expresses in oligodendrocytes in the brain, this mutation results in elevated levels of NAA in the brain and cerebrospinal fluid (CSF). Over 40 mutations have been identified, main ones are listed in Table 1.

Spongiform changes occur in cerebrum, cerebellum and brain stem with loss of demarcation between cortical white and grey matter and multiple vacuoles throughout the white matter (WM). There is ac-

Table 1. Mutations in Canavan's disease

Mutation	Population	Percentage	Reference
E285A; Y231X	Jews	98	Makalon et al, 2015
P.Ala.305Glu	Non-Jews	57	Feigenbaum et al,2004; Marlon,2015
A305E missense mutation	Western European	48	
32deltaT	African American		Kaul et al, 1996
876delta AGAA	England		
D114E, R168 C	Turkey		
116T	Netherlands		
G27	Germany		
C152Y	Ireland		
G123E	Canada		

cumulation of extracellular fluid between myelin lamellae of oligodendrocytes and astrocytes (Gambetti et al,1969). There is subcortical spongy WM degeneration with swelling and abnormal astrocyte mitochondria (Matalon et al,1988). NAA produced by neurons in high concentration increases near axons and may cause myelin injury by osmotic (Leone et al, 2012) and metabolic effects. This results in intact cell bodies of nerve cells but degeneration of myelin sheath.

Clinically, they are normal till 3-6 months when symptoms like floppiness (hypotonia), developmental delay, macrocephaly (91%) develop with mental changes like apathy, irritability or lethargy. Some, especially congenital form, have dysphagia, with delay in GM mile stones and progressive psychomotor regression. In addition, they may have seizures, sleep disorders, feeding difficulties, nasal regurgitation and reflux with vomiting and optic atrophy causing reduced visual responsiveness (Rodriguez, 2013). Eventually spasticity and dystonia develop and end up in decerebrate rigidity with admixture of different seizure types.

Alexander's Disease

The first recognized patient with Alexander's disease (AD) was a 16-month-old child with megalencephaly, hydrocephalus and developmental regression by Alexander (Alexander,1949). In a survey conducted in Japan, an incidence of 1:2.7 million was noted (Yoshida et al, 2011). Conventionally AD was classified based on age of onset into Infantile (0-2years), juvenile (3-11years) and adult (>12 years). Currently it is classified as 2 forms-those which begin before 4 years- (type1) and those that can present at any age but mainly after 4 years (type 2) (Prust et al, 2011). 42% of AD is infantile form with Glial fibrillary acidic protein (GFAP) mutation, 22% are juvenile forms and the adult form accounts for 33% (Srivastava & Naidu, 2002).

AD is an autosomal dominant leukodystrophy resulting from a mutation in the gene for glial fibrillary acidic protein (GFAP) in chromosome17 q 21.31. 95% of the patients have mutations for *GFAP* gene (Brenner et al, 2009). Mutations are mostly de-novo without any gender bias and occur in type I; but in late onset AD, often autosomal dominant inheritance is seen with penetrance of nearly100%. All the mutations are located in the rod domain of *GFAP* and the clinical severity correlated well with the

affected amino acids (Rodriguez et al, 2001). *GFAP* gene expresses mainly on astrocytes and hence AD is an astrocytopathy. Pathologically, abundant astrocytic accumulations of eosinophilic cytoplasmic inclusions, recognized by neuropathologists as Rosenthal fibers (after the 19th century German pathologist who first described them in the context of an old astrocyte scar; Rosenthal, 1898) accumulate in cerebral cortex, in the white WM of the brain, brainstem and the spinal cord (Wippold et al, 2006). Abnormal GFAP appear mainly under the meninges (pia mater), sub-ependymal in ventricles, and in the perivascular regions. It is the overexpression of *GFAP* mutant gene that causes formation of these inclusion bodies in astrocytes (Li et al, 2002). A higher level of mutant proteins requires higher expression of *GFAP*; hence Rosenthal fibers are predominantly seen in sub-pial and white matter CNS regions, which are areas of high GFAP content, when compared with gray matter areas. AD astrocytes have excessive amounts of the small heat shock protein, αB-crystallin indicating role of stress (Tang et al, 2010). Accumulation of abnormal GFAP oligomers appears to cause of dysfunctional proteasomes resulting in an inability to break up substrates facilitating Rosenthal body formation. Another feature noticed in AD astrocyte is the progressively decreasing levels of GLT-1, the major glutamate transporter in astrocytes, exposing the cells to damage due to excitotoxic cell death (Tian et al, 2010). This explains the seizures seen in type I AD, where the major inhibitor viz, Glutamate action is less making grey matter neurons more excitable. However, this role is not seen in white matter where glutaminergic transmission has lesser role. Here the over expression of *GFPA* in axons and myelin and astrocytes of white matter causes clinical signs due to white matter diseases in late onset AD (Tian et al, 2010).

Clinically, infantile form (type 1) is typically spastic with developmental delay, seizures, megalencephaly and intellectual disability. Common problems in juvenile and adult forms (type 2) of AD include seizures, bulbar/pseudobulbar signs (speech abnormalities, swallowing difficulties -50%), ataxia (75%) and about 33% spasticity, delay or regression of development, macrocephaly, autonomic dysfunction, sleep apnea and psychomotor decline (Springer et al, 2000). Rare forms may present in the neonatal period with developmental delay, hydrocephalus, and seizures (Springer et al, 2000). Sometimes significant accumulation of altered GFAP sub-ependymally results in obstructive hydrocephalus (Prust et al, 2011).

Krabbe Disease

Krabbe disease (KD) or globoid cell leukodystrophy, named after Knud Haraldsen Krabbe, a Danish neurologist (1885-1961), is a lysosomal storage disorder. This affects both the CNS and peripheral nervous system. The approximate incidence of AD is 1 in 1,00,000–2,50,000 individuals worldwide (Haneef & Doss, 2016). KD is an AR disorder due to mutations in chromosome 14q24.3-q32.1 resulting in deficiency of β-galactocerebrosidase (GALC) leading to accumulation of galactocerebroside (galactosylcreamide) and psychosine (galactosyl sphingosine) in oligodendroglial cells. Though elevation of galactosyl ceramide is not detrimental in KD; the byproduct of galactosyl-ceramide metabolism, psychosine, gets accumulated resulting in extensive damage to oligodendroglia leading to demyelination (Kohlschütter, 2013). The architecture of regions in cell membrane called lipid rafts, which contain high concentration of sphingolipids and cholesterol, gets disrupted by psychosine resulting in damage to oligodendrocytes and schwann cells (White, 2009). More than 145 GALC mutations have been known to cause KD; but it is difficult to predict the age of onset based on mutation analysis alone (Wenger et al, 2011). These mutations result in abnormal enzyme folding in endoplasmic epithelium resulting in loss of functions of enzyme in lysosomes (Samantha et al, 2016).

Depending on age of onset of clinical manifestation, they may be classified as 4 subtypes- type-1(infantile onset), type 2 (late infantile onset), type 3 (juvenile onset), type 4 (adult onset) (Suzuki, 2009). Born normal they develop symptoms as early as 6 months like unexplained cry, irritability, vomiting, feeding difficulty and hyperpyrexia prompting many to change the feeds or treat as colic. Early seizures and hypersensitivity to stimuli including sound develops (mimicking Taysach's disease). Soon rigidity, opisthotonus spasms and ataxia sets in. Optic atrophy leading to blindness, sensorineural deafness, absent Deep Tendon Reflexes along with decerebrate rigidity appears later. Late onset (type 2to 4) presents as optic atrophy and cortical blindness with both spasticity and ataxia resulting in slowly progressive gait disturbances; hence confused with Adrenoleuko**d**ystrophy. They may present as spastic paraparesis or with impaired control of voluntary movements, vision loss and poly neuropathy. Childhood onset and adolescent onset KD is more likely to have optic atrophy (54, 33% respectively) and cerebellar ataxia (57 and 50%) (Rabab et al, 2013)

Metachromatic Leukodystrophy

Metachromatic leukodystrophy (MLD) is due to arylsulphatase A deficiency (ARSA) in the lysosomes, which is inherited as an AR trait. Incidence is 1 in 40,000-160,000 (Wang et al, 2011). *ARSA* gene is in chromosome 22q13-13qtr. Cerebroside sulfate accumulates in the neurons- both CNS and peripheral nervous system (PNS), due to partial or complete deficiency of ARSA enzyme leading to demyelination. The name MLD is given because of the peculiar appearance of the cells with an accumulation of galactosyl-3-sulfate ceramide, when stained with crystal violet produces granules known as metachromatic staining, since they stain differently from their surrounding cellular material as golden brown (Gomez-Ospina, N.,2017).

Based on when it presents, MLD is classified as late infantile, juvenile and adult. 50 to 60% of all individuals with MLD are infantile form presenting at 2nd year of life, usually beginning as gait disturbances between 1-2 years of age with hypotonia, weak deep tendon reflexes, clumsy gait and frequent falls (Fluharty, 2014). Intellectual deterioration, dysarthria, diminished visual fixations and nystagmus with optic atrophy, initial hypotonia with rigidity and finally decorticates posturing sets in. Feeding difficulties due to pseudobulbar palsy, peripheral neuropathy and death happens by 6 years due to aspiration pneumonia or bronchopneumonia. Both the lower and upper motor neuron involvement are seen in patients with MLD; hence absence or exaggeration of DTR should not deter one from making the diagnosis.20-30% are juvenile forms of MLD presenting between 4-10 years as behavioral issues or deterioration in scholastic performance, gait incoordination, urinary incontinence, hypertonia, ataxia, dysarthria and dystonia/tremors with difficult to control generalized tonic-clonic seizures (GTCS).

Adrenoleukodystrophy

This rapidly progressive X-linked ND affecting the white matter of children, also known as Schilder's disease, was first recognized in 1923. This disease affecting CNS, adrenals and testicles affects almost all races with an incidence of 1:20000 (Kwon, 2011). Being XLR disorder it affects boys before 10 years of age and girls are carriers. Mean age of appearance is around 7 years at which a previously normally developing male child develops signs of white matter involvement.

X-linked adrenoleukodystrophy (ALD) results in impaired peroxisomal β-oxidation of very long-chain fatty acids (VLCFA), which is reduced to about 30% of control levels due to a mutation of *ABCD1* gene located in X chromosome-Xq28. Mutation causes absence or deranged function of ALD protein (a peroxisomal transmembrane protein transporting VLC acyl-co-esters from cytosol to peroxisomes. These VLCF acyl-CoA esters are incorporated into different lipid fractions and act as substrate for further elongation to even longer fatty acids (Ofman et al, 2010). Very long-chain fatty acids (VLCFA) inside cells results in oxidative stress and oxidative damage to proteins, microglial activation and apoptosis (Fourcade et l, 2008). This may lead to destabilization of the myelin sheath and impairment of function of astrocytes and microglia which helps in myelin integrity. Not all males with X-ALD develop cerebral ALD, pointing to the fact that other factors like genetic, epigenetic and/or environmental may modify this process. *ABCD1* mutation, resulting in less/no production of ALDP1 protein. Though plasma levels of VLCFA are elevated, no correlation between neurological phenotypes, blood levels of VLCFA or biochemical defects and type of mutation exists. The severity of disease correlates with the level of perivascular infiltration and inflammation. In about 80% of children with ALD, there will be demyelination of splenium of corpus callosum. Lesions may also be seen involving pyramidal tracts including inside pons and internal capsule (van der Knaap et al, 2005).

The presentation may vary significantly even with in the family with one male having the childhood form and his brother manifesting as adult form. The 7 phenotypes identified are the childhood cerebral form, adrenomyeloneuropathy (AMN), adult cerebral, adolescent, adrenal insufficiency without neurologic disease, asymptomatic, and heterozygotes. The childhood form mainly manifests as behavioral issues like inattention, hyperactivity, emotional labiality and school difficulties in a child who was normal till at least 3-4 years. Gum and mucosal hyperpigmentation often precedes hyperpigmentation of skin. Its progression into seizures, visual symptoms, auditory processing difficulties (auditory discrimination) and motor in-coordination proceeds rapidly and in 2 years' time they become vegetative. The difficulty with auditory discrimination results in difficulty in using telephones and low scores in verbal part of intelligence quotient tests. Adolescent form of ALD manifests around 10 years with slow disease progression and may have status epilepticus.

Lafora Disease

This fatal progressive myoclonic epileptic disorder was first described by Lafora and Glueck (1911). Prevalence of Lafora disease (LD) is 1-9/10,00,000 with AR inheritance manifesting towards adolescence. *EPM2A* mutations in 6q24.2, which codes for Laforin- a dual-specificity phosphatase or *NHLRC1* gene in 6p22.3 coding for an E3 ubiquitin ligase called Malin, together results in production of glycogen (Spuch et al, 2012). This glycogen accumulates inside the cytoplasm producing "lafora bodies" which is damaging to the neurons. For the functional activation of Malin in endoplasmic reticulum of neurons, Laforin is required. Gentry found that Malin binds and interacts with the laforin protein in HEK293T cells in vivo (Gentry et al, 2005). This results in Laforin getting polyubiquitinated in a Malin-dependent manner leading to Laforin degradation. Laforin polyubiquitination and degradation gets abolished due to mutations in the *NHLRC1* gene. This led them to conclude that malin regulates laforin protein concentrations and that mutation in the *NHLRC1* gene results in reduced E3 ligase activity of malin leading to Lafora disease (Gentry et al, 2005). Disease progression is slower in *NHLRC1* mutations and hence

they live longer. Lafora bodies (LBs) develop in the cytoplasm of cells from brain, kidney, skin, liver, and cardiac and skeletal muscle. LBs are composed of α 1,4-glycosidic linkages between glucose residues with α 1,6 branches, but with lesser number of branches (Worby et al, 2008). Polyglucosans, due to unknown reasons, accumulate in dendrites, initiating severe progressive myoclonus epilepsy after a threshold amount of accumulation is reached (Turnbull et al, 2011).

They are normal during their early childhood with few having minor learning problems. The earliest manifestation in children are- a decrease in scholastic performance with headaches and seizures (Minassian et al, 2001). Seizures in LD may be symmetric or generalized myoclonus or GTCS, occipital seizures resulting in visual hallucinations; progressive neurodegeneration results in deteriorated cognition and/or behavior, dysarthria and ataxia (Monaghan & Delanty, 2010). Over time they become intractable and recurrent may present as Status epilepticus. Though dysarthria and ataxia occur early, spasticity appears late. Initially children may have visual hallucinations, depressed mood and cognitive deficits. Later on, increasing hallucination, dementia and agitation along with frontal executive dysfunction and cognitive impairment will interfere with performance ability.

Mucolipidosis

A child looking similar to mucopolysaccharidosis (MPS), but with developmental delay and dysostosis multiplex is usually a mucolipidosis (ML). The name ML was given after their phenotypical resemblance to both mucopolysaccharidosis and sphingolipidosis. Though originally classified as type1 to 4, currently type 1(sialidosis) is a glycoproteinosis and type 4 is under gangliosidosis.

ML III is a rare AR disorder, estimated to occur in about 1 in 100,000 to 400,000 individuals worldwide. Type 2 or I cell disease and type 3 or pseudo hurler polydystrophy are due to the deficiency of N-acetyl glucosamine -1- phosphotransferase in varying grades resulting in appearance similar to Hurlers syndrome. Type 2 is due to a defective phosphotransferase, whereas type 3 is due to partial deficiency (Kudo et al, 2006). Hence clinical features are not recognizable in type III till about 3-5 years, whereas type II may be appreciated early.

Phosphotransferases present in Golgi apparatus transfer phosphates to mannose on specific proteins so that these proteins are marked to be transported to lysosomes. If this doesn't happen then those proteins will be transported out of the cell, similar to the pathway taken by all proteins as they move through Golgi apparatus. Inside lysosomes these proteins actually function as enzymes for breaking down oligosaccharides, lipids, and glycosaminoglycans, failing which the substrates accumulate resulting in inclusion bodies inside lysosomes– hence called inclusion cell diseases (I cell disease)/ MPS-II. Mutations in *GNPTAB* gene (12q23.3) coding for α and β subunits of the N-acetylglucosamine phosphotransferase complex leads to a decreased synthesis of mannose-6-phosphate, which targets the enzymes to the lysosomes of connective tissue cells. This results in decreased functioning of lysosomes rather than the true storage of undigested products. This is the true pathogenesis of ML II (Cathey et al, 2010).

ML II usually presents at birth with hypotonia, intra uterine growth retardation and gradually increasing skeletal deformities like ulnar deviation of hands, broadened and campomelic fingers, kyphosis, dislocation of hip, and deformation of long bones. Range of movement of shoulder joints is limited from birth itself. Some severe children may have neonatal transient hyperparathyroidism. In the neonatal period they have flat facial profile with shallow orbits resulting in proptosis, depressed nasal bridge, prominent mouth and gingival hypertrophy. There is progressive coarsening of facial features with thickening of skin, noticeably around the earlobes. They have delay in early motor as well as in cognitive domains.

Postnatal growth usually ceases at 2nd year of life and contractures in all joints prevent many from walking (Leroy et al, 2012). Most have mitral and aortic valve thickening and regurgitation. Progressive narrowing of airways results in hoarse voice and noisy breathing. Mucosal thickening and stiffening of connective tissues together with cardiac involvement, results in cardiorespiratory failure.

Neuronal Ceroid Lipofuscinosis

Neuronal ceroid lipofuscinosis (NCLs) or Batten disease are a genetically and phenotypically heterogenous group of lysosomal storage disorders associated with progressive visual loss, motor deterioration, dementia, seizures and early mortality. NCLs are the most common hereditary progressive neurodegenerative disease with a prevalence of approximately 1.5 to 9/ million population. The incidence varies from1.3 to 7/ 100,000 live births in different countries (Mole et al, 2011). Based on age of onset, they are subdivided into- congenital, infantile (age of onset-6-24 month), late infantile (onset-2-8 years), juvenile (4-10 years). There are at least 9 genetically different types. Accumulation of autofluorescent storage material-ceroid and lipofuscin happen in NCL and hence the name. Most are AR except adult onset-caused by mutations in CLN4/DNAJC5 which is AD. The *NCL* genes codes for proteins in the secretary and or endosomal or lysosomal pathways. The main lysosomal proteins are encoded by *CLN1*, *CLN2*, *CLN5*, *CLN10*, *CLN13* and transmembrane proteins are encoded by *CLN3, CLN6*, *CLN7, MFSD8/, CLN12/ ATP13A2*. The transmembrane proteins CLN6 and CLN8 directed to the endoplasmic reticulum (ER); and progranulin, the product of *CLN11*/*GRN*, are localized in compartments in the secretory pathway (Ryan et al, 2009).

CLN1 disease presents between 6-24 months with delayed development, myoclonic jerks, and/or seizures, speech problems, loose interest in playing and in toys, but remain interested in their surroundings. Some may have stereotypic hand movements of autistics with moderate motor dysfunction. By 4 years many have retinal blindness. CLN2 disease appears between 2-4 years usually starting with epilepsy. GTCS, clonic, partial and myoclonic seizures are seen. After seizure onset there is regression of cognitive and motor milestones and blindness ensues by 6 years. CLN2 mutations may also produce atypical Juvenile type (Wisniewski, 2017). CLN-3 (Juvenile NCL) has an onset at 5 years as rapidly progressing vision loss as the first clinical sign; it may be the only sign for two to five years. Soon they go into permanent vision loss within 2-5 years on its onset with initial macular changes soon progressing to pan-retinal degeneration with pigmentary changes in the retinal periphery, vascular attenuation and optic nerve pallor. Behavioral problems, extrapyramidal signs, and sleep disturbance occur in second decade. Speech disturbances and slow cognitive decline occur around the time of onset of seizures (Backman, 2005).

Subacute Sclerosing Pan encephalitis

SSPE is a chronic, demyelinating disease affecting brain of children and young adults, caused by a chronic infection with defective measles virus. It is also known as Dawson's encephalitis after Dawson who first described it and suggested a viral etiology (Dawson, 1934). Green field coined the word SSPE. Boutillee et al. (1965) demonstrated in 1965 the presence of measles virus in the brain tissue using electron microscope.

After the introduction of measles vaccination, though the incidence of SSPE in developed countries is negligible, in countries like India despite higher coverage of measles vaccination, it is still the most common cause of ND (Abajirao et al, 2013). Following an infection with Measles, after a latent period

of 6-8 years, progressive neurological deterioration develops. In immunocompetent children it causes SSPE; where as in immunocompromised it causes measles inclusion body encephalitis. Unlike in adult forms, the presentation in childhood is different with personality change and ophthalmic manifestations as common presenting features. Occurrence of SSPE was noticed among vaccinated children. This may be due to previous subclinical infection prior to measles vaccination or poor maintenance of cold chain. Since, in none of the cases vaccine strain has been isolated, SSPE in vaccinated may not be due to vaccine associated SSPE. Wide spread immunization had reduced the incidence of SSPE in developed countries. A recent study in Germany found that the risk of developing SSPE for children infected with measles below 5 years of age as 1 : 1700 to 1 : 3300. This risk is in the same order of magnitude as the risk of a fatal acute measles infection (Schönberger et al, 2013). The risk following measles infection under 1 year of age was 18/100 000 compared with 1.1/100 000 after 5 years of age in the UK (Campbell et al, 2007).

Measles demyelinates oligodendrocytes and at later stages of disease develop atrophy of grey and white matter due to infiltration of brain parenchyma with B cells and perivascular cuffing by CD4+ T cells. 2 types of inclusion bodies are seen in nucleus and cytoplasm- Cowdry-A saw in neurons and oligodendroglia and indicate fatal disease. Cowdry-B is small inclusions seen in brain stem. These inclusion bodies contain viral antigens (Gadoth, 2011; Scully, 1969).

Clinical Stages of SSPE

The progression of SSPE and stages was first proposed by Dr. J.T. Jabbour, a neurologist and hence known as Jabbour classification given in Table 2 (Jabbour,1969).

DIAGNOSIS OF CHILDHOOD NEURODEGENERATIVE DISORDERS

Canavan's Disease

Gas chromatography-mass spectrometry, detects elevated levels of NAA in the urine which is diagnostic (Shoji Tsuji, 2007). CSF shows elevated levels of NAA (Granata, 2012). APSA deficiency can be identi-

Table 2. Jabbour classification of subacute sclerosing panencephalitis (Jabbour,1969)

Stages	Jabbour Classification
Stage1	IA. Behavioral, mental, and personality changes IB. Myoclonic spasms; focal and non-periodic
Stage 2	IIA. Additional mental deterioration; Myoclonus becomes periodic and generalized, Myoclonus may cause "drop" (falling) attacks when attempting to walk IIB. Apraxia, agnosia, language difficulties, motor dysfunction; ataxia, spasticity, inability to walk unaided, EEG; periodic synchronous discharges coincident with myoclonic spasms
Stage 3	IIIA. Patient speaks less, vision deterioration, seizures may occur, myoclonic spasms every 3-5s IIIB. Patient is bedridden and has swallowing difficulties, choreiform movements, ballismus (both are involuntary movements), EEG background delta
Stage 4	Myoclonus stops; akinetic mutism (coma/persistent vegetative state) EEG low voltage without periodic slow wave complexes

Ophthalmology findings- most have optic atrophy, chorioretinitis and macular pigmentation; in 20% early in the course, papilledema is seen.

fied from white blood cells and cultured skin fibroblasts. Preventive measures can be taken by prenatal diagnosis at 16 to18 weeks by measuring amniotic fluid NAA levels using amniocentesis (Matalon et al, 2011).

MRI confirms the megalencephalic appearance and shows white matter affected as diffuse, bilateral, and involving the sub cortical U-fibers" (Kantor, 2014). In T1weighted image- low signal in white matter; T2 weighted image- high signal in white matter mainly in cerebrum, Globus pallidus and thalamus; no enhancement of affected regions is seen on either computerized tomography (CT) or MRI (Singer, 2010). MR spectroscopy shows markedly elevated NAA and NAA: creatine ratio (Karim Zadeh et al, 2014).

Visual evoked potentials may be low showing cortical blindness; impairment in BAER may be due to problems in cochlear development (Kantor et al, 2014).

Alexander's Disease

MRI shows frontal leukodystrophy more common in the younger patients and occipital lesions, with occasional atrophy of the medulla oblongata and cervical spinal cord, in type-II patients. A multicentric study identified that four of the following five MR imaging criteria is required for diagnosis: extensive cerebral white matter changes with frontal predominance, a periventricular rim with high signal on T1-weighted images and low signal on T2-weighted images, abnormalities of basal ganglia and thalami(elevated signal intensity and swelling, atrophy, elevated or decreased signal intensity on T2-weighted images), brain stem abnormalities particularly involving the medulla and midbrain (T2 hyper intensities in caudate nucleus > globus pallidus > thalamus > brain stem), and contrast enhancement (gadolinium) of particular gray and white matter structures of 1/>(ventricular lining, periventricular rim, frontal white matter, optic chiasm, fornix, basal ganglia, thalamus, dentate nucleus, brain stem) (vanderKnapp et al, 2001). In type 2 cases there may not be any MRI abnormalities. Sometimes atypical MRI abnormalities may be seen like predominant or isolated involvement of posterior fossa structures, multifocal tumor-like brain stem lesions and brain stem atrophy, slight and garland-like feature along the ventricular wall, more likely in juvenile /adult onset AD (Knaap et al, 2006).

Sequence analysis shows 98% of proband with GFAP mutation in 17q 21, failing which exome sequencing studies have to be performed.

Krabbe Disease

In KD, the abnormal Visual Evoked Potential (VEP) response (decrease gradually with no response in later stages of disease- absent P100 wave) but normal ERG is characteristic. (Al-Essa et al, 2000). BAER shows only waves1 & 2. Marked delay in nerve conduction velocity (NCV) due to segmental demyelination obtained by nerve conduction studies (NCS) appears to correlate with clinical severity. NCS shows prolongation of distal latencies, low amplitude and absent evoked responses of prolonged F wave latencies. These findings may be the first signs in KD even before any symptoms develop even in newborns (Siddiqi, 2006). NCS along with brain MRI may be the most sensitive tool in the evaluating the severity and classification of globoid cell leukodystrophy.

CT shows hyper dense areas symmetrically involving the thalami, cerebellum, caudate nuclei, posterior limbs of the internal capsule, and brainstem (Loes et al, 1999). Changes may also extend into the centrum semiovale/corona radiata. There may be marked reduction in white matter in cerebellum and centrum semiovale. MRI on T2 imaging shows hyper intensity involving periventricular white matter centrum

semiovale and deep gray matter; resulting in marked reduction of white-matter with relative sparing of subcortical U-fiber until late in the course of the disease. T1C with Gadolinium enhancement shows no contrast enhancements. MR spectroscopy shows abnormal choline elevation in centrum semiovale.

In infantile form, after testing the enzyme levels of the proband, a targeted analysis for a 30kb deletion is tested. If 2 of the pathogenic variants are not there, then sequence analysis followed by deletion/duplication analysis should be performed. For late onset forms, targeted analysis for c.857G>A -2variant- should be first performed; if this is negative then search for 2 pathogenic variants for 30kb deletions should be followed. If this is also negative then sequence analysis followed by deletion/duplication analysis should be performed (Wenger et al, 2000).

Metachromatic Leukodystrophy

An ARSA-A enzyme level blood test with a confirming urinary sulfatide test using toluidine blue is the best biochemical test for MLD. The urine sediments have metachromatic galactosphingosulfatides which accumulates in the renal epithelial cells and finally gets excreted through urine. A 24-hour urine samples collection gives ten- to 100-fold higher values than controls and appears as red after staining using thin layer chromatography/mass spectroscopy. The conforming urinary sulfatide is important to distinguish between MLD and pseudo-MLD blood results. In Baun type assay where aryl sulfatase is incompletely blocked, the ARSA enzyme levels should be < 10% of normal controls. When ARSA enzyme activity in WBC is 5-20% of normal controls, are seen in otherwise healthy individuals, then the term "pseudo-deficiency is used. CSF proteins are also elevated (Fluharty, 2014).

NCS shows demyelination; all evoked potentials (VEP, BAER, SSEP) are abnormal.

Electromyographgraphy (EMG) is abnormal with demyelinating sensorimotor neuropathy pattern.

CT/MRI shows diffuse atrophy of WM of cerebrum, cerebellum with arcuate fibers sparing and "subcortical U" rim in WM and periventricular involvement. Axial T2WI MR shows the typical butterfly-shaped pattern of white matter involvement in MLD (Groeschel et al, 2011).

Targeted analysis for pathogenic variants - p.Arg84Gln, p.Ser96Phe, c.459+1G>A, p.Ile179Ser, p.Ala212Val, c.1204+1G>A, p.Pro426Leu, and c.1401_1411del- identifies up to 50% in late infantile and juvenile MLD and 73-90% of adult MLD. (Lugowska et al, 2005).

Prenatal diagnosis is possible by doing ARS-A assay levels in cells of either chorionic villi cells or amniotic fluid.

Adrenoleukodystrophy

Impaired cortisol challenge test by injecting ACTH250mcgI/V (low rise of cortisol) is seen, especially Addison only form. Elevated ACTH is seen in 85% of children with childhood form (Kown, 2016). In males with neurological symptoms raised VLCFA levels gives the diagnosis. In females who are carriers, mutation analysis needs to be done. MRI shows symmetric periventricular white matter involvement in parietal and occipital lobes in most cases. The perivascular lymphocytic infiltration, on T2-weighed and FLAIR sequences in the parieto-occipital region and the splenium, results in increased signal intensity in 50% of ALD resulting in a garland of contrast material adjacent to the posterior hypodense lesion (vander Knap & Valk, 2005). Newborn screening done with dried blood spots obtained in special paper is assessed for C26:0 lysophosphatidylcholine (26:0-lyso-PC).

Lafora Disease

Though initial EEG's may be normal, at later stages, focal abnormalities in occipital area or generalized irregular spike-wave discharges with occipital predominance against a slow background are seen. The most characteristic seizures include myoclonic and occipital lobe seizures with visual hallucinations, scotomata, and photo convulsions.

Visual Evoked potential (VEP) - initial stage- high voltage potentials. Prolonged P110- absent in some and in some it may be normal. BAER, SSEP- shows high voltage somatosensory evoked potentials (14-170μV) in initial stages. Patients with LD have varied cortical relay times. In response to afferent stimuli, a delayed and prolonged facilitation, evidenced as sustained hyperexcitability of the sensorimotor cortex, happens. The findings are suggestive of an impaired inhibitory mechanism in LD. Later in disease, these giant waves become normal with some prolongation of central and brain stem latencies. NCS and MRI are normal throughout (Jansen, A.C,2015)

Diagnosis is made by axillary skin biopsy in which pathognomic finding of Lafora bodies (polyglucosans) are seen in myoepithelial cells surrounding axillary apocrine (odoriferous) glands. In other areas outside the axilla, Lafora bodies (PAS positive) are found in the cells composing the ducts of the eccrine (perspiration) glands (Jansen, 2010).

Mucolipidosis

X-rays- shows progressive osteopenia and dysostosis multiplex (diaphyseal widening and shortening of tubular bones; long pubic and ischial bones and anterior-inferior hook configuration of 1st and/or 2nd lumbar vertebra). Plasma enzyme assays-A 5-20 times high levels of lysosomal hydrolase and hydrolases in other body fluids are seen (normal 0-200 pg/mL) (Leroy et al, 2012). Confirmation may be made by molecular mutation screening of the *GNPTAB* gene by single-gene testing, use of a multi-gene panel, or more comprehensive genomic testing.

MRI brain- shows typically, corpus callosal abnormalities like-corpus callosal hypoplasia, absent rostrum and a dysplastic or absent splenium; white matter on T1 weighted images shows signal abnormalities and thalamus and basal ganglia shows increased ferritin deposition. Cerebellar atrophy is seen in older. EEG- shows epileptiform discharges.

Neuronal Ceroid Lipofuscinosis

The ERG is not recordable by four years in CLN-1. In CLN-2, ERG is usually abnormal at presentation and becomes undetectable soon thereafter. Visual evoked potentials (VEPs) are enhanced for a long period and diminish in the final stage of the disease. In CLN-3, ERG shows loss of photoreceptor function early on (Weleber, 1998).

From 18 months onwards, EEG changes may be seen in CLN-1. In CLN-2 it shows spikes in the occipital region on photic stimulation at 1-2 Hz. In CLN-3, EEG shows nonspecific disorganization and spike-and-slow-wave complexes.

MRI findings in CLN1 are variable cerebral atrophy; signal change in the thalami and basal ganglia; and thin, hyperintense, periventricular high-signal rims of white matter (Riikonen et al, 2000). MRI in CLN-2 shows progressive cerebellar and cerebral atrophy with normal basal ganglia and thalami. CT and MRI in CLN-3 reveal cerebral, and to a lesser degree, cerebellar atrophy after 15 years of age.

Since the finding of 13 different mutations in genes, NCL is classified based on genes as seen in Table 3 (Williams & Mole, 2012).

Subacute Sclerosing Panencephalitis

The diagnosis of SSPE is made by Dyken's criteria. The diagnosis of SSPE can be established, if the patient fulfills any three of the following five criteria (Dyken, 1985):

1. Typical clinical presentation with progressive intellectual deterioration with signs of myoclonus;
2. Characteristic electroencephalographic (EEG) pattern;
3. Elevated cerebrospinal fluid (CSF) globulin levels, presence of oligoclonal IgG bands;
4. Elevated CSF measles antibody titers; and
5. Brain biopsy suggestive of measles-perivascular inflammatory cuffing, cortical and subcortical white matter astro-microgliosis, neurophagia and Cowdry type A, eosinophilic intaranuclear inclusion bodies.

Most characteristic EEG abnormality is bilaterally symmetrical, periodic (4-10seconds), stereotyped, high voltage delta wave discharges which appear along with the myoclonic jerks-type 1 waves. In early stages, bursts of high voltage delta waves are interspersed with a normal background at constant interval. The periodic pattern emerges with disease progression first during sleep, much before myoclonic jerk come. Later the characteristic periodic discharge pattern can be seen also during wakefulness, happening along with myoclonus (Garg, 2002).

CT/MRI shows cerebral edema and atrophy in all stages of the disease and the signal intensity changes in stages II-III. In stage II-Parieto-occipital white matter was affected, while diffuse frontoparietal changes were more common in stage II-III. There is no correlation between the imaging features and focal EEG changes or the abnormal neurological findings.

Table 3. Genetic mutations and presentation of neuronal ceroid lipofuscinosis

Gene Involved	Wide Spread Common Mutation	Phenotype - Clinical Features
CLN10/CTSD	Not known	Congenital - severe seizure, rigidity, blindness,
PPT1/CLN1	p.Arg122Trp; p.Arg151X- over 67 mutations reported	Infantile - early seizures, psycho- motor regression, vision loss. PPT1 has juvenile like presentation
CLN2/TPP1 CLN-5-8	c.509-1G>C; p.Arg208X; 116 mutations are identified- CLN-2 resulting in abnormalities in tripeptidyl peptidase, ; others result in abnormalities in membrane proteins	Late infantile - presentation as myoclonic seizures in 2-4 years; microcephaly, dementia, ataxia, loss of visual acuity. Black bony spicule like in Retinitis pigmentosa, optic atrophy, brown pigment in macula.
CLN3	1 kb intragenic deletion	Juvenile- most common form; first 5 years normal, then visual loss. Retinal pigmentary changes-RP; the rapid decline in psychomotor, motor incoordination, seizures. Later parkinsonism develops; die in twenties.
CLN12/ATP13A2		Juvenile
CLN14/KCTD7		Infantile

TREATMENT OF CHILDHOOD NEURODEGENERATIVE DISORDERS

Canavan's Disease

Management is limited currently to supportive measures and management of complications. Physical therapy aiming at maintaining postures and early intervention for communication skills are advised. Insertion of feeding tube for swallowing difficulties and G-tube if at risk of aspiration improves nutrition and hydration. Often multiple anticonvulsants for seizure control and oral supplementation with acetate is advised (Leone et al,1999). Survival beyond adolescence depends on medical and supportive care given; those with congenital forms will die in first weeks of life. Juvenile forms have often very protracted course (Kantor, 2014).

Alexander's Disease

Neurosurgical intervention should be considered on an individual basis, if need arises. For type-2, management of sleep apnea and autonomic symptoms alleviates encephalopathy and increase the quality of life. Life span of AD children is based on the type of disorder; the median age of survival of type -I is 14 years and of type -II is 24 years (Prust et al, 2011).

Krabbe Disease

HSCT is currently the standard of care for KD patients; however, it serves only to delay disease progression and is not an effective cure (Sakai, 2009). It is effective only when performed early during the disease course. If performed early in pre-symptomatic child, umbilical cord blood (UCB) transplantation can preserve the cognition and prolong life; however most experience a decline in language, motor functions and adaptive behavior. There are evidences that combination therapies that target multiple pathogenic mechanisms/pathways (CNS-directed gene therapy, substrate reduction therapy, and BMT to target GALC deficiency) have been more synergic. Hence, they were more effective at reducing histological signs of disease, delaying onset, prolongs life span, and improve the behavioral/cognitive functions in rodent models of KD. Supportive care to control irritability and spasticity may be given for KD in later stages of disease (Table 4).

Metachromatic Leukodystrophy

Enzyme -replacement therapy, bone marrow/UCB transplant, *ex vivo* transplantation of genetically modified hemopoietic stem cells, all have been tried with minimal benefits during clinical trials. Gene therapy with adeno associated viruses AAVrh10 serotype for clinical development as a treatment for MLD has been proposed recently as a possible ideal treatment (Rosenberg, 2016). The 5-year survival for metachromatic leukodystrophy is reported to be-late infantile: 52%, juvenile: 100% and adult: 95%. The late infantile subtype was the worst survivor than any other subtypes (Asif Mahmood, et al, 2010).

Table 4. Management of Krabbe disease complications

Complications	Management
Vomiting/ reflux	Upright position during and after feeding; > 1 year-use Lanzoprazole; Nissen's fundoplication for reflux
Constipation	Sufficient fluids; PEG, lactulose
Dysphagia	Modify thickness of food. If not feeding orally, swallowing ability can be improved by providing juices many times in a day. The gastrostomy tube for terminally ill to be inserted for feeding while the child is still able to swallow rather than waiting until the child is undernourished and dehydrated. Caloric intake provided-to be based on the child's length than age or weight (7-9 calories/cm/day, adjusted to the child's activity level).
Spasticity; contractures	Wedges, cushions and pillows for seating; gentle stretching, use of orthotics, splints and adaptive devices for standing etc. Botox injections
Neuropathic pain	Gabapentin
Seizures	Diazepam for breakthrough seizures. Monotherapy for seizures
Urogenic bladder in later stages	Crede manavoure for complete emptying.
Respiratory infection	Chest physiotherapy, postural drainage, frequent suctioning; annual influenza vaccine

Adrenoleukodystrophy

Early start of intervention gives a better prognosis. Measure the adrenal insufficiency, document adrenocortical hypofunction and measure plasma VLCFA levels in all children and also in all male patients with Addison's disease as in > 25% of boys with Addison's disease, ALD causes adrenal crisis. Corticosteroid replacement is started for adrenal insufficiency as it is lifesaving, though it does not alter the course of disease. Coordination between the treating physician and school authorities helps in recognizing appearance of subtle behavioral issue and attentional issues early in course of disease to give proper counseling. Melatonin may be used for sleep cycle problems.

An initial and 6 monthly MRI should be done, especially in neurologically asymptomatic male children and adolescents. Usually MRI abnormalities precede the neuropsychological manifestation. Positive MRI should be followed by repeating every 3 months to see the progression of disease. Performance (nonverbal) IQ scores are shown to correlate well with MRI findings and hence can be used as a monitoring tool. Both MRI and performance IQ can be used as a predictive tool for assessing the need for early bone marrow transplantation in those who have not developed neuro/psychological manifestations (Suzuki, et. al, 2000).

Lorenzo oil therapy (4:1 mixture of glyceryl trioleate and glyceryl tri crucate) with dietary therapy has been used in asymptomatic boys with normal MRI and is < 8-year-old. Upon deterioration, they are considered for hemopoietic stem cell therapy. It has been found to reduce the childhood form of ALD by a factor 2 or more. However, in those who are already having neurological manifestation, Lorenzo's oil therapy is of no use. Bone marrow transplantation is indicated in boys with rapidly progressive neurological inflammatory demyelination seen by MRI. BMT cells are found to produce ALDP, the protein which is deficient in ALD oligodendroglial cells. However, BMT is not effective in those who have established brain damage and in fact may increase the progression in such cases. Hence careful selection of case is important as BMT itself has 10-20% mortality. Also 50% of those ALD who are not treated will not develop inflammatory demyelination and hence transplantation is not needed (Orchard, J., P,2010).

Gene modification of stem cells by inserting normal copy of ALD gene via a virus, after ablating the residual bone marrow of the child was found to be favorable. Infusion of their own genetically corrected stem cells with normal gene showed 15% of their cells produced ALDP with a 38% reduction of VLCFA in plasma with arrest of demyelination as measured by MRI and clinical findings (Cartier et al, 2009).

Another investigational study (Star beam study) to determine the safety and tolerability of Lenti-D (autologous hematopoietic cells that were genetically corrected with a lentiviral vector) while determining if the one-time treatment can stop the progression of cerebral ALD is under way. Interim results of the study are encouraging.

Lafora Disease

Valproate, levetiracetam, topiramate, and benzodiazepines are used with modest efficacy on seizure frequency. Phenytoin, carbamazepine, oxcarbazepine, vigabatrin, tiagabine, gabapentin and lamotrigine may be avoided as they aggravate the myoclonus and even precipitate GTCS. There are recent reports suggesting that a new drug, Perampanel, given as monotherapy produces dramatic reduction in seizure frequency with a striking improvement in cognition, behavior, and cerebellar function (Dirani et al, 2014).

Perampanel's anticonvulsant effect is because of its selective noncompetitive antagonistic action on AMPA type glutamate receptors. A recent study suggested that loss of GABAergic cortical neurons and the resulting imbalance in GABAergic: Glutamatergic neurons might be pathophysiologically related to Lafora's disease (Ortolano et al, 2014). This probably explains the mechanism by which Perampanel, by blocking the AMPA receptors, partially normalizes the imbalances in the inhibitory: excitatory neurotransmitters in cortex and cerebellum and thereby reducing seizures and restoring the manifestations to near normalcy. Vagus nerve stimulation may also help as an adjuvant in seizure control.

Mucolipidosis

Treatment options are limited, minimal exercises to avoid joint and tendon strain, like aqua therapy, cognitive stimulation through interactive programs; gingivectomy - for oral health; myringotomy tube placement-recurrent ear infections.

Neuronal Creroid Lipofuscinosis

Symptomatic treatment for the management of seizure, gastroesophageal reflux, sleep issues, drooling, behavioral issues has to be given. Lamotrigene has been found to be useful in this case as monotherapy with 100% control vs. valproic acid (60%) control (Aberg et al, 2000). For feeding issues when it becomes riskier, G-tube may be inserted. Trihexphenidyl may be used for drooling and dystonia.

Subacute Sclerosing Panencephalitis

Mostly they die in 2-3 years from presentation. A relative better result was achieved with either daily oral Isoprinosine or in combination with weekly intrathecal INF-α. (Garg, 2002). Isoprinosine (Inosiplex), improves immunity by its action on natural killer cell function; by increasing the number of CD4+ cells and by increasing the production of interleukin-1 and interleukin-2. Currently, the most effective treatment is the combined treatment of oral inosiplex for life and intraventricular interferon-α. Spontaneous

remission may occur during any stage of the disease only to relapse later. Age of onset < 12 years, disappearance of periodic complexes, normalization of the background of follow up EEGs, and a progressive increase in measles antibody titers in cerebrospinal fluid are associated with favorable outcome in SSPE.

FUTURE RESEARCH DIRECTIONS

In the management of NDs like CD, new treatment options are emerging like the introduction of a vector expressing *ASPA* gene by injection into 6 brain parenchymal sites resulting in reduction in seizures, slowed the progression with reduction in brain NAA, no severe long-term adverse effects, with slowing of atrophy of brain, significant improvement in motor functions and reduction in seizure frequency (Leone et al, 2012). Further studies are required to confirm these beneficial effects. Further studies using drugs which reduce the NAA levels in brain or increases the acetate levels in humans, after adequate trials, may give an idea about managing CD better. However, in a recent study *ASPA* gene replacement therapy targeted against oligodendrocytes resulted in reversing of preexisting neural pathology and lasting neurological benefits in rats (von Jonquieres et al, 2017). Similarly, Mohri et al. (2006) using twitcher mouse model, similar to KD, found that hematopoietic prostaglandin D synthase inhibitors may have a role as anti-neuroinflammatory therapy. This is based on the finding that activated microglia and astrocytes expresses H-PGDS and DP1 receptors respectively, in the brain of the mice and PGD2 is a key neuroinflammatory molecule involved in demyelination in twitcher mice.

Pharmacological chaperone therapy (PCT) where chaperons bind directly to a partially folded biosynthetic intermediate, stabilize the protein and allow completion of the folding process to yield a functional protein, is emerging as useful idea in many NDs. This may be used for selectively correcting defective protein folding and trafficking and for enhancing enzyme activity by small molecules in Krabbes disease. Potential therapeutic benefits of chaperons in Krabbes disease noted in preclinical studies is worth taking to next level of research (Graziano et al, 2016). Mutations leading to misfolding, giving rise to lack of secretion, processing and ER co-localization, may be good targets for pharmacological chaperone therapies. Those that retain significant capacity for correct trafficking and processing will require future enzyme replacement approaches. But the extend of misfolding caused by specific mutations will alter the effectiveness of pharmacological chaperones. Specifically, the misfolding caused by some mutations may be too severe to respond to these approaches and hence will require enzyme replacement strategies (Spratley et al, 2016).

In many diseases like ALD, the effect of several factors like epigenetics and environmental modifiers are still not known fully. There is a need to identify such factors /modifiers of human gene expression so that they can be used constructively and may also be used to predict the clinical outcome.

CONCLUSION

The genetic basis of NDs, deranged gene products and its effects on children, gives an option to classification of these disorders in the future. The newer advances at cellular level/molecular levels especially as treatment options are at experimental level in many disorders. Soon those options may become operationalized like, interventions aimed at substrate replacement/substitute (enzyme replacement therapy)

or may be an alternate one in which abnormal molecule is prevented from forming like in chaperon therapy. In many cases, prompt recognition and early treatment favor a better therapeutic response. Next generation sequencing technologies have helped to fill gaps in diagnosis. Finding the biomarkers of many of these disorders has made it possible to think in terms of finding solutions for treatment for many of these disorders. Future researches focusing on the biomarkers may be the right direction for finding solutions for treatment.

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Section 3

Therapeutic Interventions for Neurodegenerative Disorders

Chapter 19
Neurosurgical Treatments of Neurodegenerative Disorders

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ABSTRACT

Functional neurosurgery consists of procedures that either promotes judicious destruction or chronic stimulation of the nervous system in order to treat disordered behavior or aberrant function, as it is expected in neurodegenerative disorders ([NDs], e.g., movement disorders [Parkinson's disease, Tourette's syndrome, essential tremor, ballism, and dystonia]). Over the past 20 years, approximately 100,000 deep brain stimulation implant procedures have been performed worldwide. Neurosurgery is also a well-established therapeutic option for people with epilepsy whose seizures are not controlled by anti-epilepsy drugs. The most common pathological finding in patients with drug-resistant mesial temporal lobe epilepsy is hippocampal sclerosis. The aim of this chapter is to present the main NDs that can be treated through surgical procedures, and to describe the surgeries with a focus on the pathophysiology of diseases.

INTRODUCTION

Researchers have directed their efforts towards finding effective treatments for neurodegenerative diseases. The concept that neurological diseases are not treatable has been dissipated with the advances of the last decades. There is a great success with clinical therapeutics, genetic findings and immunology.

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This chapter will show movement disorders and epilepsies that had their limiters and disabling results on patients altered by surgical procedures. Examples of diseases that can be treated by functional neurosurgery comprise movement disorders (Parkinson's disease [PD], Tourette's syndrome [TS], essential tremor [ET] and dystonia), spasticity, chronic pain, epilepsy and psychiatric disturbances (obsessive-compulsive disorders [OCD] and depression).

Over the past 20 years, approximately 100,000 deep brain stimulation implant procedures have been performed worldwide (Strauss et al., 2014). The efficacy of these functional procedures in the treatment of Parkinson's disease was verified up to 10 years after surgery (Moro et al., 2010-b). For patients who are compromised by such seizures, referral to an epilepsy surgery center should be strongly considered (Engel et al., 2003). Surgery is a well-established therapeutic option for people with epilepsy whose seizures are not controlled by anti-epilepsy drugs.

The aims of this chapter are to present the main NDs that can be treated through surgical procedures and to describe the surgeries with a focus on the pathophysiology of diseases.

BACKGROUND

The first image about neurosurgery is of a specialty that utilizes surgical techniques aimed at correcting structural / anatomical problems of the nervous system such as aneurysms, brain and spine tumors, fractures and herniated disks. For several years, this type of surgery was the only treatment option available for PD and movement disorders. These procedures were ablative in nature and consisted of surgeries performed on both the peripheral nervous system, including rhizotomies and sympathectomies (Teixeira and Fonoff, 2004), and in the brain, such as corticectomies, trans-ventricular accesses to the basal ganglia nuclei and even section of the cerebral peduncle, procedures that were performed under direct vision and not by a stereotactic approach (Speelman and Bosch, 1998), as the first stereotactic procedures for the treatment of movement disorders would only be performed by Spiegel and Wycis in 1947 (Speelman and Bosch, 1998).

These new perspectives, the "Functional Neurosurgery", are completely different. Functional neurosurgery consist of procedures that either promote judicious, localized destruction of a target area within the central nervous system, or chronic stimulation of specific structures in order to treat disordered behavior or aberrant function of the nervous system, as it is expected in NDs (Teixeira and Fonoff, 2004).

NEURODEGENERATIVE DISEASES WITH POSSIBLE SURGICAL TREATMENT

Movement Disorders

Parkinson's Disease

PD is a ND, characterized by movement disorders and non-motors symptoms (Salat et al., 2016), associated mainly with the death of dopaminergic neurons located in the substantia nigra, leading to progressive depletion of dopaminergic nigrostriatal and mesocorticolimbic neurons (Callesen et al., 2013), but also there is abnormal deposition of α-synuclein in the remaining cells and gliosis in specific areas of the nervous system (Lees et al., 2009; Salat et al., 2016). However, such changes are not restricted to

these brain regions and can be found in other nuclei of the brainstem, in the cerebral cortex and even in peripheral neurons, such as those in the myenteric plexus. Non-dopaminergic pathways are also involved, including the serotoninergic and cholinergic neurons located in the spinal cord and peripheral nervous system, correlating mainly with the non-motor symptoms of the disease (Poewe, 2008).

Since its original description, the clinical diagnosis of PD has centered on a defined motor syndrome. The prerequisite for applying the MDS-PD criteria is the diagnosis of parkinsonism, which is based on three cardinal motor manifestations. Parkinsonism itself is defined as bradykinesia, in combination with either rest tremor, rigidity, or both (Postuma et al., 2015). However, over the years the non-motor manifestations became better characterized and can now be identified in most, if not all, patients (Seppi et al., 2011). The non-motor manifestations of PD comprise autonomic, neuropsychiatric dysfunctions, changes in the sleep-wakefulness cycle and in pain perception (Poewe, 2008; Goldman et al., 2015).

Dopamine replacement therapy, currently the most efficacious treatment for PD, so much so that it's considered the gold standard, mainly comprises the use of the dopamine precursor levodopa, either isolated or in combination with dopamine agonists, monoamine oxidase B inhibitors, and catechol-O-methyltransferase inhibitors. Long-term use of levodopa may result in several complications, including motor fluctuations and levodopa-induced dyskinesia, which cause serious distress to patients. Moreover, symptoms that appear at the later stages of PD are often not responsive to dopaminergic treatments. (Du and Chen, 2017).

Dystonia

In 1984 an *ad hoc* committee of Scientific Advisory Board of the Dystonia Medical Research Foundation developed the modern concept of dystonia (Teive et al., 2001-b; Albanese et al., 2013). Although the 1984 definition was seminal, over the following decades several shortcomings have been recognized. Therefore, in view of these limitations of the 1984 definition, an international Consensus Committee proposed in 2013 the following revised definition: Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation (Albanese et al., 2013).

If defining dystonia is difficult and controversial, classifying the various forms of dystonias is a much more complex task, primarily because the term dystonia can mean not only a disease, but also a symptom that can be part of many disorders with a wide range of causes. In an attempt to clarify the term dystonia, three "surnames" for dystonia were proposed: "symptom", "movement" and "disorder". A patient may complain of dystonia if, for example, he has a twisted neck. Therefore, the patient has a dystonia symptom (dystonia^{Sx}) and on examination the signs of dystonia may be confirmed. This patient then has a dystonia movement (dystonia^{Mov}). Finally, dystonia as a disorder (dystonia^{Dx}) requires a clinicopathologic understanding of the underlying etiology of the disease: genetic, late-onset, post-traumatic, etc (Frucht, 2013; Camargo et al., 2015). These new concepts led to the replacement of the 1998 dystonia classification (Albanese et al., 2013) with the one proposed in 2013. In the 2013 classification, dystonias are subdivided according to clinical features and etiology.

Dystonia remains a challenging field in both diagnostic and therapeutic aspects. Further understanding of its pathophysiology may shed light on more specific therapies. Three main approaches are employed in the treatment of dystonia: pharmacological therapies, botulinum toxin injection (BoNT) and surgical

interventions (Termsarasab et al., 2016). Treatment of dystonic symptoms with botulinum toxins is now a major area of medical practice. Botulinum toxins are established as the first line of treatment for cervical dystonia, blepharospasm, and laryngeal dystonia and are considered a major treatment modality for limb dystonias, including task-specific dystonias (Jabbari, 2016). Four major categories of medications are most commonly used: anticholinergics (particularly trihexyphenidyl), baclofen, benzodiazepines (particularly clonazepam), and dopamine-related medications. Symptomatic medical therapy can improve quality of life and should not be overlooked (Termsarasab et al., 2016).

Tourette's Syndrome and Tics

There is no specific diagnostic test for TS and diagnosis is made solely on clinical grounds. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) it is defined by:

1. Multiple motor tics and one or more vocal tics.
2. Tics occur several times a day, almost every day or intermittently for one year or more.
3. Onset of tics must occur before the patient is 18 years-old.
4. The disorder is not due to the use of drugs nor to another disease (APA, 2013).

It is a quite complex neurobehavioral disorder in which patients may present with coexistent obsessive-compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), and other behavioral comorbidities (Teive et al., 2001-a). It has been much maligned amid laypeople as one of its most striking features, the occurrence of coprophenomena (coprolalia and/or copropraxia), has been described even in the first historical accounts, regardless of its low prevalence (around 14 – 19%), but carries great social impact. (Germiniani et al. 2012).

A meta-analysis of antipsychotics for the treatment of TS found no difference in efficacy among risperidone, haloperidol, pimozide, and ziprasidone (Weisman et al., 2013). Side effects such as sedation, weight gain, and hyperprolactinemia have limited their tolerability (Thenganatt and Jankovic, 2016). A systematic review of aripiprazole for TS found a similar efficacy of aripiprazole and haloperidol (Yoo et al., 2013). Tetrabenazine has been shown to be effective in open-label trials for the treatment of TS. Alpha agonists such as clonidine have been found to be useful in the treatment of mild tics and may have a particular benefit in patients with co-existing ADHD and impulse control disorder. Botulinum toxin may be helpful in the treatment of focal motor tics (Thenganatt and Jankovic, 2016).

Ballism

Jakob (1923) was the first to demonstrate the relationship between hemiballism and injury to the contralateral subthalamic nucleus, coining the term Luy's body syndrome (Shannon, 1998). Ballism is a rare hyperkinetic movement disorder characterized by an abnormal, choreic, large-amplitude, violent, pitching involuntary movement using the proximal appendicular and associated axial musculature (Vidakovid et al., 1994; Shannon, 1998). A distinction must be made between ballism and other hyperkinetic movement disorders, mainly chorea (Coral et al., 2000).

Treatment is based on neuroleptics, mainly haloperidol, and in selected patients chlorpromazine and pimozide. Other drugs such as tetrabenazine, reserpine and clonazepam can be used. Clinical treatment

is supported by few open-label studies with small samples (Dewey and Jankovic, 1989; Vidakovid et al., 1994).

Essential Tremor

Essential tremor (ET) is among the most common movement disorders, and the most prevalent tremor disorder (Louis, 2014). Tremor itself is not a featureless, nondescript action tremor; rather, it is characterized by a specific pattern of features:

1. Kinetic tremor is usually greater in amplitude than postural tremor.
2. Tremor involves movement at specific joints in specific directions.
3. Intention tremor of the arms is seen on finger-nose-finger maneuver in approximately 50% of cases.
4. Rest tremor occurs in as many as 20% of cases as a late feature.
5. Arm tremor precedes cranial tremor, for which there is a female preponderance.
6. The prevalence of neck tremor is greater than that of jaw tremor, which is greater than that of tongue/cheek/forehead tremor.
7. There is a tendency for tremor severity to increase over time. (Louis, 2014)

Although the pathophysiology of ET is only partially understood; the notion that ET may be neurodegenerative is one that has been proposed recently (Louis, 2014). An emerging topic is related to how substantial is the role played by the cerebellum in the pathophysiology of underlying movement control pathways in ET. Cerebellar-like symptoms, with abnormalities in tandem gait and balance, have been repeatedly described in ET patients. Intention (i.e., "cerebellar") tremor of the arms occurs in approximately one-half of ET patients, and there are a variety of other motor abnormalities that point to what is likely to be a more pervasive underlying abnormality of cerebellar function in ET. As for the thalamus, it is considered to be a cerebellar outflow region and a final common nodal point for diatheses-affected pathways that emerge from more proximal points within the cerebellar system in ET (Louis, 2014).

Drugs thought to improve tremor include beta-adrenergic antagonists, primidone, topiramate, ethanol, and benzodiazepines (Troiano et al, 2004). Less consistent efficacy is reported with many other medications, usually anti-epileptic drugs (AEDs) (Ondo et al., 2016).

Epilepsy

Epilepsy is a common condition. According to the World Health Organization, epilepsy accounts for 1% of the global burden of disease, more than breast cancer in women and almost as much as lung cancer in men (Murray et al., 2012). It is estimated that as many as sixty-five million people around the world have epilepsy (Sirven and Shafer, 2014).

The International League Against Epilepsy (ILAE) in 2014 recommended broadening the definition of epilepsy to include several different etiology groups, as well as epileptic encephalopathies. Therefore, epilepsy is a disease of the brain defined by any of the following conditions: 1) at least two unprovoked (or reflex) seizures occurring more than 24 hours apart from each other; 2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the expected general recurrence risk after two unprovoked seizures (at least 60%), occurring over the next 10 years (Fisher et al., 2014).

In April 2017 the ILAE presented a revised operational classification of seizure types. Changes include the following:

1. "Partial" becomes "focal".
2. Awareness is used as a classifier of focal seizures.
3. The terms dyscognitive, simple partial, complex partial, psychic, and secondarily generalized are eliminated.
4. New focal seizure types include automatisms, behavioral arrest, hyperkinetic seizures, autonomic, cognitive, and emotional seizures.
5. Atonic, clonic, epileptic spasms, myoclonic, and tonic seizures can be of either focal or generalized onset.
6. Focal to bilateral tonic–clonic seizure replaces the term secondarily generalized seizure.
7. New generalized seizure types are absence with eyelid myoclonia, myoclonic absence, myoclonic–atonic, myoclonic–tonic–clonic seizures.
8. Seizures of unknown onset may have features that can still be classified. The new classification does not represent a fundamental change, but allows greater flexibility and transparency in naming seizure types (Fisher et al., 2017).

Mesial Temporal Sclerosis

Studies have shown that in some patients, the development of epilepsy does not stop at the time of diagnosis and that recurring seizures may contribute to the progression of the disorder, so that to that effect, progressive reduction of hippocampal volumes documented over time on brain MRI, correlates with lower neuron cell counts (Bronen et al., 1991; van Paesschen et al., 1997; Devinski et al., 2013).

Temporal lobe epilepsy (TLE) is the most common form of focal (partial) or location-related epilepsy - it accounts for approximately 60% of all people living with epilepsy (Holmes et al., 2017). There are two types of TLE, one which involves the medial or internal structures of the temporal lobe; while the second, called neocortical temporal lobe epilepsy, involves the outer portion of the temporal lobe. The most common version of these two types is mesial temporal lobe epilepsy (MTLE) (Holmes et al., 2017).

Many patients with MTLE develop pharmacoresistance to antiepileptic drugs, and the most common pathological finding in patients with drug-resistant MTLE is hippocampal sclerosis (HS). HS is a unique pathologic condition characterized by specific neuropathologic features (Berg et al., 2010).

An ILAE task force reviewed previous classification schemes and proposed a system based on semi-quantitative hippocampal cell loss patterns that can be applied to any histopathology laboratory and classified three types in anatomically well-preserved hippocampal specimens (Blümcke et al., 2013).

PATIENT SELECTION FOR SURGERY

Surgery for Patients With Movement Disorders

Parkinson's Disease

Traditionally, surgery has been reserved for patients with advanced PD, when medications no longer deliver the desired effect or induce extremely debilitating side effects. A multi-center study evaluated the effect

of surgery in patients less than 60 years of age, Hoehn and Yahr score below 3 and with shorter duration of motor fluctuations (Schüpbach et al., 2013). The primary outcome measure considered was quality of life of the patients and the results suggest that surgery should be considered in this specific population, with very favorable results, although there are still insufficient data to consider that surgical procedures may have some neuroprotective effects or even slow the rate of disease progression (Benabid, 2007).

Surgery should not be offered for patients with short disease time, thus avoiding surgery neither in patients who may eventually develop atypical parkinsonism and not have idiopathic PD, nor for patients with very advanced age and disease, as in these populations surgery will probably have no long-term improvement in quality of life, but can also add unnecessary risks to the patient. More specific criteria such as disease length, minimum or maximum age, and clinical staging of the disease based on appropriate rating scales are still controversial.

A set of very specific criteria adequately selects the possible candidate for surgery for Parkinson's disease, thus providing a better therapeutic result, while also decreasing the incidence of possible complications.

1. Certainty about the diagnosis of idiopathic PD - despite modern and innovative technologies, both in the field of radiology with high-resolution magnetic resonance imaging (Lotfipour et al., 2012), ultrasonography (Bor-Seng-Shu et al., 2010), PET-scan (Stoessl, 2014) and available biomarkers (Sharma et al., 2013), the diagnosis of PD is still based on clinical criteria and observation of the patient's evolution as the disease progresses.
2. Unquestionable response to levodopa therapy, at least in the early years and early stage of the disease. Another important thing to consider is the asymmetric onset with progressive evolution of the symptoms, which is suggestive of idiopathic PD. (Brooks DJ).
3. Improvement in motor scores (sub-item 3) of the Unified Parkinson Disease Rating Scale (UPDRS) (Goetz et al., 2008) of at least 30% with the levodopa challenge test comparing the "on" and "off" phases. An exception to this criterion, are patients who present totally incapacitating tremor, which, by itself, already justifies the indication of the procedure (Munhoz et al., 2014).
4. A score equal to or less than 4 on Hoehn and Yahr Scale (Hoehn and Yahr, 1967).
5. Identification of motor symptoms that are responsive to levodopa and by consequence, will improve with surgical treatment (Munhoz et al., 2014).
6. Absence of a structural lesion in preoperative neuroimaging exams that may make it impossible to structurally identifies or physiologically locates the therapeutic target. Patients who have undergone previous ablative or neuromodulatory neurosurgical procedures can be reoperated, provided they are correctly evaluated (Ellis et al., 2008)
7. In cases of previous psychiatric history, the patient should be evaluated by a qualified professional, who will determine if the patient is able to understand and mainly collaborate with the surgical procedure (Voon et al., 2006).
8. In cases where there is suspicion of, or caregivers report symptoms of cognitive impairment, the patient should undergo a careful preoperative neuropsychological evaluation (Voon et al., 2006)..

Hyperkinetic Movement Disorders

Idiopathic dystonia – both generalized and segmental – is the best indication for deep brain stimulation (DBS), while DBS in for either focal or secondary dystonia is not sufficiently supported by clinical

evidence (Moro et al., 2013). Surgery is indicated when medical therapy is no longer able to provide sufficient improvement of disability and quality of life. Younger patients with idiopathic dystonia and shorter duration of disease seem to benefit the most from DBS. The mechanisms by which DBS leads to symptomatic improvement in dystonia are far from being clear and well understood at present, which might at least partially explain the variability and unpredictability of clinical success of DBS (Mehdorn, 2016).

Essential tremor is the most common movement disorder. The severity of tremor is measured objectively using scales such as the Fahn–Tolosa–Marin Tremor Rating Scale or the Essential Tremor Rating Scale. Having the patient draw spirals or write his/her name is a rapid way of assessing tremor during the awake period of surgery, or on follow-up during routine DBS programming in the office (Larson, 2014).

The suitability of DBS in TS patients depends on many factors, yet there is much variability regarding specific inclusion and exclusion criteria across studies. Typically, core criteria focus on accurate diagnosis, high tic severity (typically a Yale Global Tic Severity Scale [YGTSS] score >35/50) and resistance to at least three different pharmacological agents (Temel and Visser-Vandewalle, 2004). Although psychiatric co-morbidity is a common component of TS, motor and vocal tics should be the main source of disability prompting surgical evaluation. Exclusion criteria typically include major poorly-controlled psychiatric disorders, pregnancy, current substance abuse or dependence, severe cognitive impairment and structural brain abnormalities on MRI (Akbarian-Tefaghi et al., 2016; Temel and Visser-Vandewalle, 2004).

Choice of the Therapeutic Target

Idiopathic Parkinson's Disease

With increased knowledge of PD it is clear that there is no more room for just one single surgical target to treat all symptoms of this multi-faceted disease. (Okun and Foote 2010). The adequate choice of the surgical target must be made individually, depending on the idiosyncrasies of each case. The targets that present the highest degree of evidence and efficacy in the treatment of PD are the GPi and the STN. Stimulating the STN would lead to a higher rate of improvement in the cardinal symptoms of the disease, reducing the dose of dopaminergic equivalents in the immediate postoperative period. Nevertheless, if this withdrawal is made somewhat abruptly, severe bouts of depression may occur, even leading to higher risk of suicide (Voon et al., 2008). There was also an increase in battery life of the neurostimulator in cases of STN, considering that the parameters used were much lower, than those of the GPi. The great advantage of targeting the GPi was restricted to those patients who had extremely pronounced dyskinesia, or previous cognitive deficits, as the use of the STN in these latter cases could lead to a marked worsening of some cognitive functions, more specifically those related to verbal fluency (Follett et al., 2010).

A recent meta-analysis showed that both targets present practically similar results when comparing pre and postoperative motor scores of the sub-item III of the UPDRS scale, corroborating the findings of other groups (Anderson et al., 2005; Nakamura et al., 2007; Weaver et al., 2012), both in bilateral and unilateral procedures. The concept that the GPi is safer from a cognitive point of view has been contested in a recent study comparing STN stimulation with GPi in patients with advanced PD (Odekerken et al., 2013), although the results presented were challenged because of low statistical power to avoid a type II error (Montgomery, 2013), showing how controversial this subject still is. The vast majority of centers that perform DBS surgery use the STN as a target, but this choice is based primarily on open clinical trials, personal conviction, as well as personal experience (Laitinen et al., 1992).

While surgical procedures performed on the STN and the GPi have shown consistent and effective results in the treatment of the cardinal symptoms of PD, their effect on axial symptoms, such as gait and balance, is at best irregular, if not disappointing (St George et al., 2010). The identification of numerous connections between the peduncle-pontine nucleus (PPN) and structures as distant as the cerebral cortex and the spinal cord, associated with the recognition of its extremely important role in gait control, rose the interest for this new target as the ideal one for treatment of axial disorders. Despite the lack of controlled and blinded trials, series with good results on a greater or lesser scale are found in the literature (Moro et al., 2010-a; Thevathasan et al., 2010). Additionally, the isolated stimulation of the PPN is arguably a limiting factor in the improvement of these patients, and some authors proposed that the combined and concomitant stimulation of both the PPN and the STN (Stefani et al., 2009; Khan et al., 2010) hoping that the synergistic and adjuvant effects between the two targets could concurrently improve both appendicular and axial symptoms of the disease. Despite these results, the isolated stimulation of the PPN is still considered experimental in many centers, due to the lack of well-designed trials demonstrating its real efficacy. The main side effects of PPN stimulation are dysesthesias, which usually occur by spreading of the electrical current, with undesired stimulation of structures such as the medial lemniscus and the spinothalamic tract.

The *nucleus ventralis intermedius* (VIM) of the thalamus was for many years the target of choice in the surgical treatment of PD, especially in those patients with incapacitating tremor. Considering that improvement of other cardinal symptoms of the disease, with the exception of rigidity, is poor in those patients who had undergone VIM procedures, the VIM currently plays an extremely limited role in the neurosurgical arsenal, restricting itself only to those patients with unilateral PD of extremely slow evolution and with otherwise intractable tremor. In patients with tremor as the main manifestation, but accompanied by other debilitating symptoms, such as marked bradykinesia and rigidity, the STN is the best target (Hariz et al., 2008).

An area that encompasses the region of the *zona incerta* (Zi) and the pre-lemniscal radiation (Raprl) known as the posterior subthalamic area (PSA) has been used more frequently in the treatment of refractory tremor (Sandvik et al., 2012). The Raprl in patients with PD was used in an attempt to alleviate the tremor and rigidity of patients with advanced disease, with improvement maintained even after 2 years (Velasco et al., 2001). In the same trial, the authors commented that Raprl can be approached by both the neuromodulatory and ablative methods, but that this would have the disadvantage of causing worsening of the patient's bradykinesia. Six years after this publication, where they initially emphasized only improved tremor and rigidity, the same group reported improvement in all cardinal symptoms of the disease (Carrillo-Ruiz et al., 2008). As there was no significant change in stimulation parameters or electrode design, this phenomenon is apparently related to the positioning of the most proximal poles in a more dorsal or dorsal-medial location in relation to the STN, which would include the more caudal portion of Zi.

Other targets like the motor cortex (Arle et al., 2008), the centromedian / parafascicular / habenullae complex of the thalamus (Benabid, 2009; Stefani et al., 2009) and the posterior aspect of the spinal cord (Thevathasan et al., 2010) were anecdotally tried, with a small number of cases and inconsistent results. One clinical trial showed a significant improvement in gait scores and postural stability in 15 patients with PD who underwent epidural spinal cord stimulation (Agari and Date, 2012). However, the main indication was chronic pain in the lumbar region with irradiation to the lower limbs.

Hyperkinetic Movement Disorders

Despite the fact that the GPi had been considered the optimal target for DBS in dystonic patients, the optimal target needs to be considered individually in every single patient depending on the most predominant symptom, and sometimes more than one surgical target may be required to optimize post-surgical results. STN DBS might be an alternative to GPi DBS, and VIM DBS in severe refractory dystonic tremor has also been suggested (Mehdorn, 2016).

Historically, the most commonly used target for DBS in ET is the VIM. Several studies report significant improvement with both unilateral and bilateral VIM stimulation, with long-term follow-up showing reduction in tremor severity rates ranging from 40% to 80% with corresponding improvement in quality of life (Huss et al., 2015). Other targets have emerged as an alternative to the VIM for patients with ET. Currently, the most widely studied area is the one inferior to the thalamus, and posterior and superior to the STN. Several other targets have been stimulated by different centers in this region, including the Zi and the prelemniscal radiations, although it is difficult to determine exactly where the mechanism of action is taking place, as is the case with most DBS targets. A broader anatomic term that incorporates both of these targets is the posterior subthalamic area (PSA). This is a particularly interesting region, not only because it appears to provide tremor reduction rates comparable to those of the VIM, but it may also have a lower adverse effect profile, better efficacy with proximal and intention tremor, and may avoid the development of "tolerance" seen with VIM stimulation over time (Larson, 2014).

In general terms, appendicular tremor responds better than voice tremor or midline tremor, the latter of which usually requires bilateral surgery (Obwegeser et al., 2000). We usually indicate unilateral surgery, aimed at improving the tremor on the more symptomatic side, or on the dominant side, depending on the patient's preference. Bilateral surgery is performed as a staged procedure in highly selected cases of severe bilateral, head or voice tremor. Although DBS is a non-ablative surgery, bilateral surgery, especially if simultaneous, has a specific risk of causing speech disorders and/or ataxia. Bothering induced "paresthesia" is also a relatively common side effect, due to spreading of the current in a posterior direction to the ventro caudalis (VC) nucleus of the thalamus. Many of these side effects can be bypassed with adjustments in generator programming.

Tractography (DTI) has been established as a powerful tool for understanding the functioning of the central nervous system, as it is virtually the only non-invasive method of visualizing structural connectivity in the brain (Calabrese, 2016). With the development of longer electrodes, with a greater number of contacts and the incorporation of tractography, it became possible to identify the entire projection of the dentate-rubro thalamic tract all the way up to VIM. The adequate placement of a longer electrode in a trajectory, which includes in its cranial portion the VIM and its more caudal portion the posterior subthalamic area, allowing the use of two distinct areas with neurophysiological characteristics (the posterior subthalamic area is composed in its majority by axonal fibers, whereas the VIM is made up mostly by neuron cell bodies). (Coenen et al., 2014; Tasker and Kiss, 1995). In cases of refractory tremor, the use of concomitant neuromodulation of these two distinct anatomical and neurophysiological targets has been proven to be effective in the control of the drug-resistant tremor, and they can be stimulated either isolated or in combination. Also, as the stimulation of white fibers usually requires lower voltages, the feasibility of saving the battery of the generators is highly likely to be seen over time (Fenoy and Schiess, 2017).

Currently, nine targets have been used for TS, including the thalamic-centromedian-parafascicular complex (CMPf), the cross point of the centromedian nucleus-substantia periventricularis-nucleus ventro-oralis nucleus (CM-Spv-Voi), the target of the nucleus ventro-oralis and posterior-ventro oralis anterior-

Voi complex (Vop-Voa-Voi), the GPi (anteromedial and posteroventral regions), the nucleus accumbens (NA), the anterior limb of the internal capsule (ALIC), the STN and the globus pallidus externus (GPe). The rationale behind each of these target choices has varied depending on whether tics are considered a movement disorder in which case sensorimotor areas such as the posteroventral pallidum have been stimulated, or if they are considered to be the result of either a compulsion or a failure of inhibition, wherein associative/limbic areas have been targeted. The thalamus and GPi have been the most widely stimulated with a combination of targets used in some studies (Akbarian-Tefaghi et al., 2016).

Surgery for Patients with Epilepsy

Drug resistant epilepsy may be defined as failure of adequate trials of two appropriately chosen anti-epileptic drugs (AED) schedules, used in appropriate therapeutic dosages in order to achieve sustained seizure freedom, and well tolerated (with no disabling side-effects), whether as monotherapies or in combination (Kwan et al., 2010).

For patients who are compromised by such seizures, referral to an epilepsy surgery center should be strongly considered (Engel et al., 2003). Surgery is a well-established therapeutic option for people with epilepsy whose seizures are not controlled by anti-epilepsy drugs.

NEUROSURGERY

Movement Disorders

Laitinen et al. (1992) published a series of 38 patients with advanced PD submitted to stereotactic posteroventral pallidotomy with excellent results in improving all cardinal symptoms of the disease, but mainly in the control of dyskinesias caused by chronic levodopa therapy. The results of this paper, combined with the development of more accurate stereotactic systems, the improvement of neuronal activity recording systems and intraoperative stimulation, new modalities of neuroradiology and, mainly, a better understanding of the pathophysiology of the base nuclei through of experimental studies on primates (Alexander et al., 1990; DeLong, 1990), led to a resurgence of stereotactic surgery for PD.

Further studies demonstrated the efficacy of ablative procedures either at the GPi (Lang et al., 1997; Vitek et al., 1997), or at the STN (Alvarez et al., 2001; Patel et al., 2003). These ablative procedures proved to be safe and efficient, and the excellent results presented by the Grenoble group in 1993 with chronic electrical stimulation of the STN (Pollak et al., 1993), led to establish this procedure as the gold standard for the surgical treatment of PD, despite preliminary good results with GPi stimulation (Anderson et al., 2005). The efficacy of these procedures in the treatment of PD was verified up to 10 years after surgery (Moro et al., 2010-b).

Deep Brain Stimulation

Technical Aspects of the Surgical Procedure

Two stereotactic techniques are available for performing the surgical procedure: “frame” or “frameless” (Machado et al., 2006). The first is the more classical technique, while the second one is more recent

and has shown promising results in the field of stereotactic procedures, especially regarding the patient's comfort during the procedure itself. Although some authors still infer that the use of the stereotactic frame seems to offer a greater accuracy in localizing and determining the target (Bjartmarz and Rehncrona, 1990), the development of the frameless technique and the training of the professionals who execute it, with their respective learning curves, may reduce or even nullify this difference in the future (Fukaya et al., 2010; Kelman et al., 2010; Tai et al., 2010).

The stereotactic frame is placed immediately before the surgery and following the frame placement, the patient is referred for preoperative imaging, which may consist of computed tomography (CT), MRI, ventriculography or a combination of these. The authors perform the acquisition of stereotactic images with a CT device, with volumetric acquisition and 1.25 mm thick slices, due to lower image distortion than MRI (Sumanaweera et al., 1995). The stereotactic study is then fused with the preoperative MRI, using designated softwares. MRI images are also obtained volumetrically, in the axial planes, with contrast-enhanced T1-weighted, T2-weighted and Inversion Recovery (IR) sequences acquisitions (Figures 1 and 2). The last two are used for delimitation by direct visualization of the targets and adjacent structures, which is a key aspect of the procedure, providing meaningful information that improves accuracy, while avoiding stimulation induced side effects (Machado et al., 2006). Contrast-enhanced T1 acquisition allows visualization of vessels from both the surface and depth of the brain, which helps in determining the safest path through the brain to the therapeutic target, reducing the risk of intraoperative bleeding and avoiding eloquent brain areas (Starr, 2002).

Targets

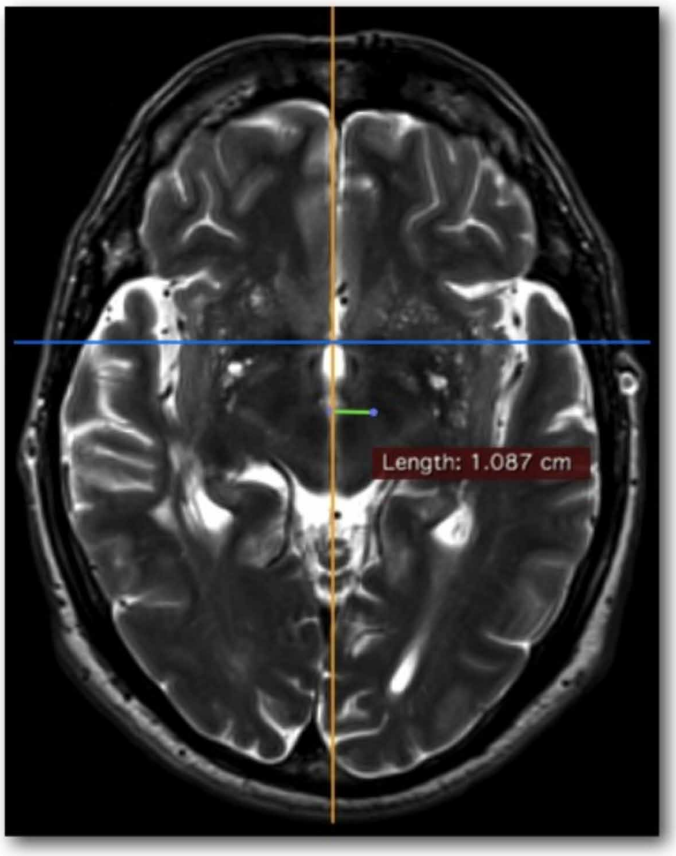
The most frequently used targets in the surgical treatment of Parkinson's disease are the subthalamic nucleus (STN), the globus pallidus internus (GPi), and the ventro-intermediate nucleus of the thalamus (VIM), with the best clinical results being obtained when the electrode or lesion are located in the sensory-motor portion of the corresponding target. In the case of the STN, the target must be located in its dorsolateral region (Herzog et al., 2004), whereas in the GPi, in its most lateral postero-ventral aspect (Rezai et al., 2008).

Direct Method of Target Determination

This method is based on direct visualization of the nucleus and its adjacent structures in order to precisely locate the ideal target. The boarders of the STN and adjacent white matter are well delimited in T2-weighted acquisitions (Figure 1). The red nucleus, also easily identifiable in this sequence, is posteromedially located to the STN, and its anterior border can be used as the anterior limit of the anteroposterior coordinate of this target (Machado et al., 2006).

The GPi and optic tract can be visualized in IR acquisitions - the optic tract is easily recognized, particularly in coronal sections in the intersection plane of the mamillary bodies, its dorsal border being adopted as the lateral and inferior limits of the GPi (Figure 2) (Starr, 2002). This coordinate serves, in fact, to facilitate intraoperative stimulation (visual response) and is not necessarily the ultimate target. Often the ablative therapeutic lesion or implant is located discretely in a more lateral position, to avoid the internal capsule, or superiorly depending on intraoperative stimulation findings.

Figure 1. Direct method of target determination - STN.
T2-weighted brain MRI, axial plane, with STN visualization at 10.87 mm from the midline.

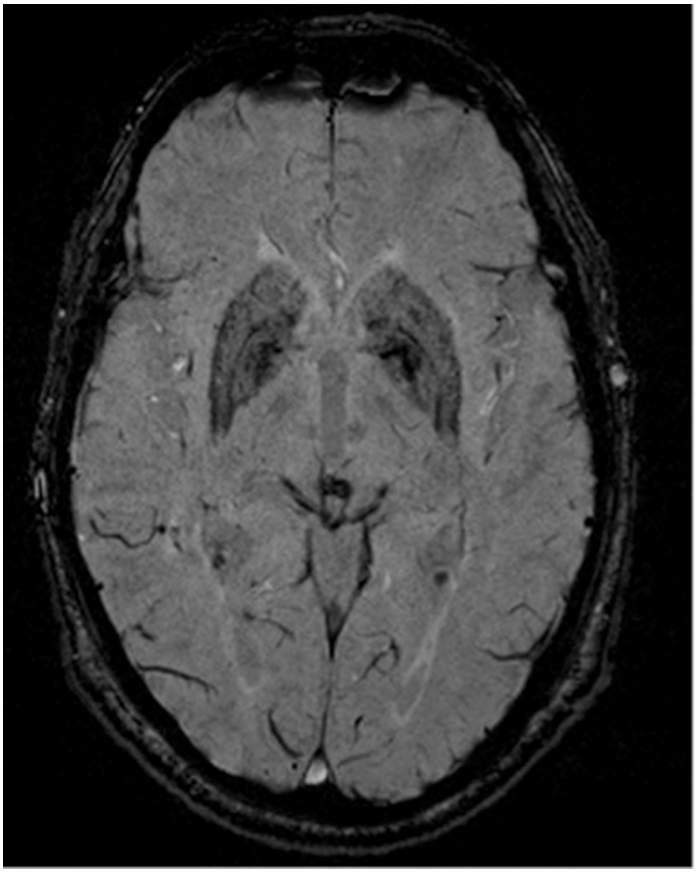


With the image restrictions still found with conventional MRI machines used for clinical purposes, either with 1.5 or 3 T fields, the VIM is still not precisely delimited, and its identification is performed only by using an indirect method, particularly as visualization of the internal capsule in MRI scans may help in determining the lateral coordinate of the VIM. This limitation may be overcome using unique and specific sequences with the 1.5 T MRI (Vassal et al., 2012) or with future widespread availability of new 7T-MRI (Lenglet et al., 2012).

Indirect Method of Target Determination

This method uses predetermined coordinates, calculated by obtaining the distances between the targets to the mid-commissural point (MCP). The main limitation of the method is the considerable variation between the different stereotactic atlases, developed through a reduced number of brain samples (Rezai et al., 2008). The delimitation of the ideal coordinates is often elaborated from the average of the coordinates with the best clinical response, based on the experience of different centers.

Figure 2. Direct method of target determination – Gpi.
IR sequence brain MRI, axial plane, with detailed visualization of both the GPi and the pallido-capsular transition.



Deep Brain Stimulation Systems Implantation

Before the insertion of the microelectrodes, the patient is examined by the neurologist to determine the baseline values of the UPDRS, rating the cardinal symptoms, namely rigidity, bradykinesia and tremor. The microelectrode is then introduced at 10 mm above the target and recording starts, with progression performed every 1 mm, for further microstimulation. The objective is to obtain a trajectory with adequate nuclear extension (STN, GPi or VIM), with adequate recording of sensory-motor driving (cellular activation with passive limb movement) and determination of the borders of the surgical target by the identification of adjacent structures.

Following microregistration and microstimulation, the electrode is positioned at the ventral edge of the ideal target location, defined by the combination of the anatomical target and the refinement of the microrecording. The procedure is monitored by fluoroscopy in order to confirm the positioning and to avoid movement or migration of the electrode during this whole phase. (Machado et al., 2006)

During stimulation of STN, it is possible to observe a reduction in rigidity, bradykinesia and tremor, in addition to defining the thresholds of adverse effects such as contractions of the limbs and/or face (stimulation of the cortico-spinal tract, situated anteriorly), paresthesias (postero-medialy) and conju-

gated deviation of the eyes (due to unwanted stimulation of the third nerve nucleus, situated inferiorly). For practical purposes, improvement of rigidity of the contralateral wrist (the Pollak-Limousin sign) with the lowest possible current without side effects, is the final goal of the macro-stimulation (Benabid et al., 2000). In some instances, contralateral dyskinesias, especially in the foot, can be observed, and they usually correlate with good surgical outcome. In procedures performed in the GPI, the goal is to improve contralateral rigidity and bradykinesia. However, in this case the latency between the start of stimulation train and the evidence of intraoperative clinical improvement is much higher than that observed with stimulation of the STN. In a considerable number of patients improvement of symptoms is often not observed intraoperatively and the role of intraoperative macrostimulation consists essentially in characterizing side effects resulting from stimulation of adjacent areas, such as stimulation of the cortico-spinal tract (postero-medially) and the optic tract (located below) (Kumar et al., 1998). When the surgical target is the VIM, intraoperative stimulation aims at obtaining total tremor control with the lowest possible voltage, while also avoiding side effects, notably paraesthesia (which denotes a very posterior position of the tip of the lead, close to the ventro-caudal nucleus of the thalamus or of the posterior lemniscus), dysarthria and compromise of contralateral movement (demonstrating a lateral position, very close to the internal capsule) (Kiss et al., 2003). As a safety parameter, a threshold of 4 volts for inducing transient side effects is considered adequate for the implantation of the electrode in the STN, whereas for the Gpi, which normally requires higher stimulation values for a better clinical result, a threshold of 1 to 2 volts above the values with clinical improvement is considered satisfactory.

Neuroablative Procedures: Pallidotomy and Thalamotomy

Thalamotomy (Fox et al.,1991; Linhares and Tasker, 2000) and pallidotomy (Iacono et al., 1995; Lang et al., 1997) are well established procedures with consistent results, but the potential for adjustability and reversibility of the neuromodulatory procedure led to a progressive replacement of these procedures by electrical stimulation of deep brain structures. In spite of these advantages, the neuromodulatory procedure is by no means free of limitations. Implanted devices are expensive, create greater interdependence between the patient and the medical center and need to be replaced at fixed intervals, even after the development of rechargeable pulse generators. The main disadvantages of the ablative method are the potential of causing an injury that is unduly localized and also the limitation in performing bilateral procedures. Nonetheless, ablative procedures may still play a role as a therapeutic surgical option in PD, especially in cases where the patient has difficulty attending routine evaluations, as is normally required in patients who have been implanted with neuromodulation devices or in patients with a recurrent history of infections (Pérez-Suarez et al., 2017).

The use of MRI-guided high intensity ultrasound devices has been the subject of recent research for the treatment of some neurological diseases. It consists in performing encephalic therapeutic lesions with real-time intraoperative monitoring by MRI-guided thermometry, causing temporary subclinical lesions, which allow us to evaluate both potential therapeutic and collateral effects prior to performing the definitive lesion, therefore increasing the safety profile of a procedure that is eminently ablative. Although most of the patients with movement disorders treated by this new technology were patients with essential tremor (Elias et al., 2013; Lipsman et al., 2013), it shows great potential for use in other movement disorders and even in psychiatric disorders, mostly due to its safety profile.

Radiosurgical ablative procedures, such as those using devices as the Gamma Knife®, still do not have a well-defined safety profile for their therapeutic use in procedures in either the GPi or the STN (Bronstein et al., 2013). In some particular situations, the procedure may be performed in patients who require an unilateral thalamic procedure and who are at high risk of developing postoperative complication with the implant of an electrical stimulation device.

Epilepsy

The different surgical approaches used for mesiotemporal epilepsy are standard anterior temporal lobectomy, anterior temporal (also known as key-hole resection), extended lesionectomy, and transsylvian and subtemporal selective amygdalohippocampectomy. Regardless of the selected surgical technique, each and all of them resulted in similar epileptological and neuropsychological results, as well as complication rates. The surgical approach for an individual patient should be tailored according to not only the specific localization of the epileptogenic area, but also based on the experience of the surgeon (Engel et al., 2003; Lopes et al. 2017).

MANAGING PATIENTS TREATED WITH SURGICAL PROCEDURES

Movement Disorders

Postoperative MRI to locate the electrode contacts and/or lesions is obtained only 1 month after the procedure so that any pneumatocele or hemorrhage is absorbed, reducing the risk of brain shift (Figure 3).

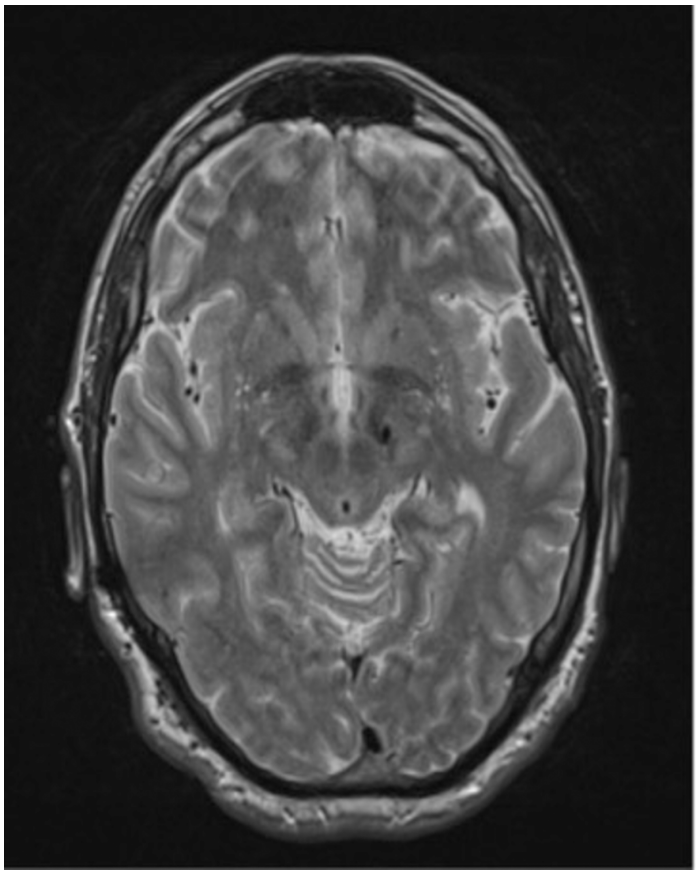
Postoperative T2-weighted brain MRI, axial plane, showing the electrode suitably positioned in the left STN topography.

Epilepsy

Approximately two-thirds of patients become seizure free after anterior temporal lobectomy, except for simple partial seizures, whose effects on the patient's quality of life are so mild, that their persistence is acceptable, with no further clinical compromise. This outcome was found in a large number of Class IV series, and was confirmed in a randomized, controlled trial of surgery versus antiepileptic drug therapy. However, ten to 15% of refractory patients remain unimproved after surgery (Engel et al., 2003; Lopes et al., 2017).

For those patients who persist with seizures after resective epilepsy surgery, further available surgical options have insufficient evidence to make firm conclusive statements on their efficacy and safety. These new techniques are all functional, stimulation-based techniques, such as hippocampal deep brain stimulation (DBS), centromedian thalamic DBS, nucleus accumbens DBS and cerebellar stimulation. There is a need for more, larger and well-designed randomized controlled trials to validate and optimize the efficacy and safety of any of these invasive intracranial neurostimulation treatments (Sprengers et al., 2017).

Figure 3. Postoperative MRI to locate the electrode contacts.



FUTURE RESEARCH DIRECTIONS

In studies conducted on non-human primates, researchers have identified that the ideal activity would be related to monitoring a neuron in the motor cortex (Rosin et al., 2011), as this cortical neuron firing would then trigger a reflex stimulus in the GPi of these animals, and the final result seems to be much more effective when compared to the use of continuous stimulation in this model. This is particularly difficult in clinical practice as the stimulation lead is already located in given neuron of a certain structure of the basal ganglia, so that the recording of the neuronal activity that would trigger the stimulation would start in the very structure that was being stimulated. The neurophysiological pattern of beta-oscillations (ranging from 13-30 Hz) has a high correlation with the symptoms of PD and these oscillations are restricted to the territory corresponding to the dorsolateral portion of the STN.

In a recently published clinical trial, Little et al. (2013) evaluated patients who underwent implantation of electrical stimulation electrodes in the STN and who were left with their electrodes externalized for detailed neurophysiological analysis. All patients had the expected improvement in motor symptoms. However, in situations where stimulation was triggered by beta band oscillations from the subthalamic nucleus, stimulation was not only statistically more effective, but there was also a documented reduction in battery consumption. These systems have been known in the field of epilepsy for some time.

Alternatively, in recent years there has been a growing interest in the development and application of techniques that, through the infusion of trophic factors, genetic and cellular therapies seek to modify the dysfunctional neuronal circuitry in patients with PD. Several attempts were performed using different techniques such as the use of neurotrophic factors such as neurturin (Marks et al., 2010), enzymes such as glutamic acid decarboxylase (GAD) (LeWitt et al., 2011) and dopaminergic cell transplantation (Freed et al., 2001; Olanow et al., 2003). These studies failed to demonstrate the expected effect on the evaluation of the primary endpoint at a given planned time when compared to the control groups. However, after some time there was some degree of improvement, which came with associated side effects, such as in cases of dopaminergic cell transplantation that led to worsening of previously existing dyskinesia. If on the one hand there is a strong appeal to treat degenerative diseases such as PD by using strategies that try to correct their basic biochemical changes, on the other hand we are faced with the challenge of demonstrating safety and efficacy comparable to electrical stimulation of brain structures, which currently stands as the surgical method of choice.

CONCLUSION

Despite all the knowledge about the pathophysiology of the basal ganglia, many patients who are submitted to deep brain stimulation do not have adequate therapeutic results. It may be possible to identify these intriguing situations even in cases of well-selected patients, with leads precisely located in the target structure and with optimized stimulation parameters. Neurodegenerative symptoms fluctuate a lot during the day and our therapeutic stimulation regime is fixed, creating an imbalance between what the organism needs and what the neuromodulator device really offers. This imbalance would be responsible for less than expected results and for possible premature drainage of batteries. As for other movement disorders, such as essential tremor and dystonia, although there are still no devices that are fully internal with such programmed pacing ability as those for patients with PD, the results of DBS are promising. The key point is to identify some sign of brain neuronal activity that cannot only trigger an immediate and coherent change in the parameters of stimulation, but also accurately translate the driving symptomatology at that specific moment.

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