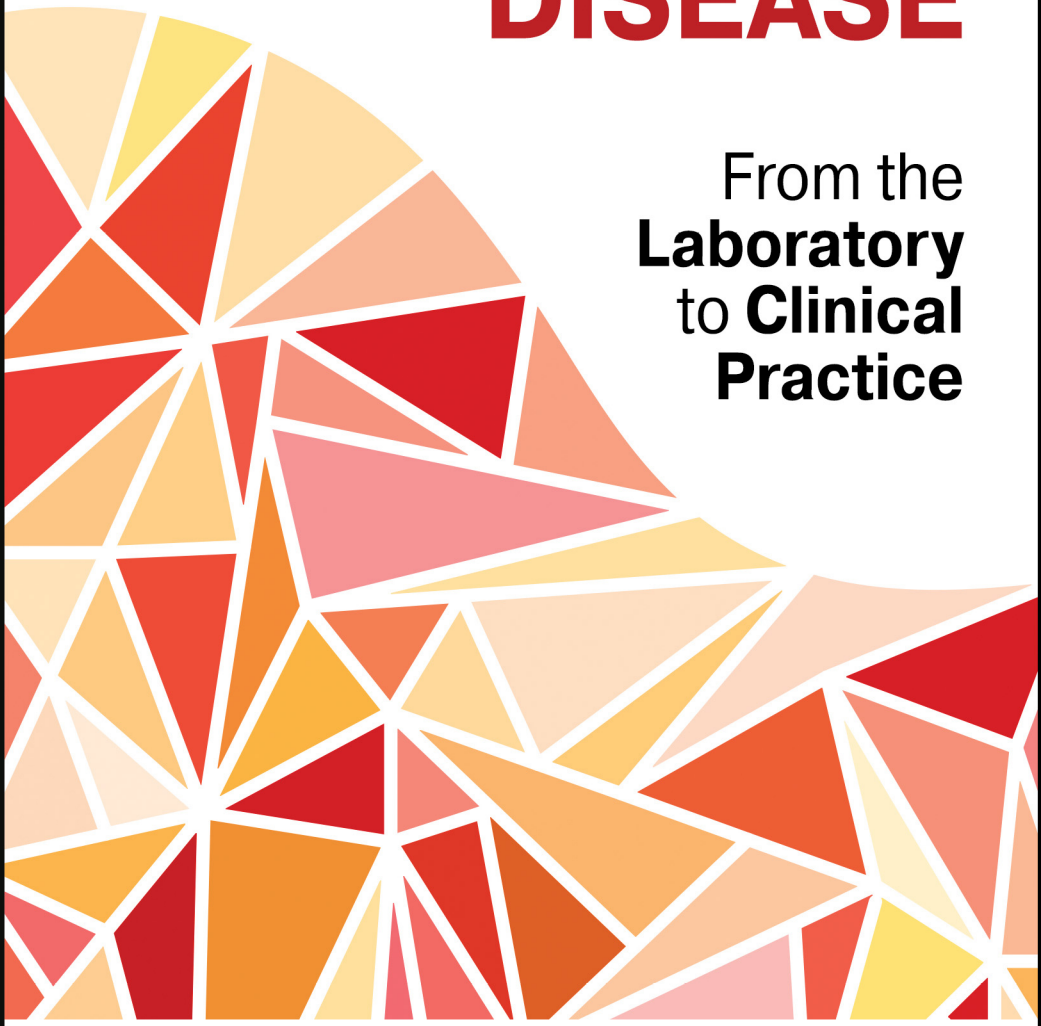
SICKLE CELL DISEASE

From the **Laboratory** to **Clinical Practice**



Edited by **Christopher Olutayo Alebiosu**

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The book is dedicated to the populations plagued with the menace of Sickle Cell Disease

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PREFACE

The Centre for Disease Control (CDC), USA stated that "Sickle cell disease (Sickle Cell Disease) affects millions of people throughout the world and is particularly common among those whose ancestors came from sub-Saharan Africa; Spanish-speaking regions in the Western Hemisphere (South America, the Caribbean, and Central America); Saudi Arabia; India; and Mediterranean countries such as Turkey, Greece, and Italy" (CDC, August 9, 2017). It was estimated that about 100,000 Americans suffer from Sickle Cell Disease. About 1 out of every 365 Black or African American births have Sickle Cell Disease, while it is 1 out of every 16,300 Hispanic American births. The sickle cell trait occurs at a more alarming rate of 1 in 13 of Black or African American babies.

The commonest haemoglobinopathy in the world is SS gene in terms of distribution and the population affected. Sickle cell disease is majorly a disease of black Africa with 25-30% having sickle cell trait AS and 2-3% being homozygous SS in Nigeria.

Sickle cell disease poses a huge burden on the economic, psychological and social well-being of not only the patients but their families and the nations of the world.

The disease is therefore of great public health importance globally even as people continue to migrate due to security, economic, educational and other sundry reasons.

With advances in knowledge of the pathophysiology of the disease and the advent of drugs to ameliorate its effect, affected individuals tend to achieve near normal life expectancy for age, sex and environment. Gene replacement therapy and stem cell transplantation offer cure but both are not readily available across the world in terms of expertise and cost. Even where they are available, there are other issues to contend with. Stem cell transplantation has its risks (including death) and complexities and many sick patients cannot stand the processes and procedure, moreover some may reject the donor cells. Therefore, cure is still a mirage.

The dissemination of knowledge that this book offers is needed at this time to increase awareness, improve preventive strategies and be abreast of current advances in treatment and cure of the disease.

The book has chapters on all the organs and systems affected in the body, written by people with in-depth knowledge and expertise.

This laudable project, its conception and execution by the authors, is a noble idea.

I recommend this book to everybody interested in sickle cell disease.

Patience Olayinka Akinwusi FWACP, FAHA, FESC, FNCS
Professor of Medicine/Cardiology
College of Health Sciences,
Osun State University, Osogbo

FOREWORD

Sickle cell disease is a generic terminology used for a group of disorders in which there is an inheritance of the sickle β – globin gene (HbS) which results in abnormal haemoglobin production. It comprises homozygous Sickle Cell anaemia (HbSS), Sickle Cell haemoglobin C disease (HbSC), Sickle Cell thalassaemia (HbSThal). Others are compound heterozygous conditions with rarer combinations of SD, SE, SO, and hereditary persistent fetal haemoglobin.

The HBSS is the most troublesome form and is most common among African descent. Though it was first discovered in 1907 and first published in America, history has it that the first symptoms were seen in a Ghanaian family back in the 16th century. Epidemiologically, the prevalence is highest in Sub Saharan Africa especially among Nigerians (about 2% of the population), Congolese, Cameroonians and then the Asians. It is also very common in malaria-endemic zones because of the protective effect of the heterozygous groups on malaria.

It is a disorder that affects every system and organ in the body because it is a form of blood disorder. In as much as it is hereditary, no cure has been found. This makes it a very disturbing disease of public health significance as an estimated 4.4 million people were affected by 114,800 deaths recorded in 2015. In 2018 "the global meta-estimate for the birth prevalence of homozygous sickle cell disease was 112 per 100 000 live births and a birth prevalence in Africa of 1125 per 100 000 compared with 43.12 per 100 000 in Europe." [Wastnedge E et al. J Glob Health. 2018; 8(2): 021103]

This disease can be classified as hereditary and non-communicable. The only way to reduce its prevalence is by having increased knowledge and awareness of its occurrence, which this book has attempted to achieve.

The authors of this book have delved into what is known to be the current concept within the time and period of writing this book. The writers are collaborating professions, teachers and health practitioners from institutions in Nigeria. The book gives in-depth knowledge on all the

systems in the body such as eyes, kidneys, hearts, bones, the pregnancy and delivery state, the mental and psychological states of a person. It also talks about the state, prevention and occurrence in children. The writing of this book went through scientific research processes of review and plagiarism tests and so makes it a scientifically sound and standard academic write up.

The book, therefore, is a very good source of information for health workers and practitioners, students, teachers, policymakers and the African populace in general as a way of caring, preventing and treating sickle cell diseases. It is highly recommended to enlighten the youths, particularly as a counselling guide in the preparation of their marital life.

We, however, look forward to a day we can find a cure to this disease and make SCD placed among the NCD of the global SDG prevention strategies. The mortality of the under-fives is also going to be reduced being one of the global health priorities.

I wholeheartedly and strongly recommend this book to every person of African and Non-African descent.

Professor Michaeline Asuquo ISAWUMI,
Immediate Past Ag. Provost, College of Health Sciences,
Osun State University, Nigeria
November 2019

LIST OF ABBREVIATIONS

ABG:	Arterial Blood Gas
ACS:	Acute chest syndrome
AIDS:	Acquired immune deficiency syndrome
AKI:	Acute kidney injury
ALA:	δ-Amino Levulinate
ALT:	Alanine aminotransferase
AP:	Alkaline Phosphatase
ASS:	Acute splenic sequestration
AST:	Aspartate aminotransferase
ATP:	Adenosine triphosphate
AVN:	Avascular necrosis
BCAM:	Basal Cell Adhesion Molecule
BMI:	Body Mass Index
BNP:	Brain natriuretic peptide
BTL:	Bilateral tubal ligation
CAN:	Cardiovascular autonomic neuropathy
CBC:	Complete Blood Count
CBT:	Cognitive behavioural therapy
CD:	Cluster of Differentiation
CDC:	Centre for Disease Control
CHCM:	Comprehensive Health Care Management
CO:	Carbon monoxide
CO_2:	Carbon dioxide
COPD:	Chronic obstructive pulmonary disease
CPAP:	Continuous positive airway pressure
CRP:	C-reactive protein
CT:	Computerized Tomography
CTEPH:	Chronic thromboembolic pulmonary hypertension
CVA:	Cerebrovascular accident
CVS:	Chorionic Villus Sampling
DMPA:	Depo-medroxyprogesterone acetate
DNA:	Deoxyribonucleic acid
EBT:	Exchanged blood transfusion
ECG:	Electrocardiogram
ED:	Erectile dysfunction

ELISA:	Enzyme Linked Immunosorbent Assay
EmeA:	European Medicines Agency
eNOS:	Endothelial NO synthase
ESRD:	End stage renal disease
ET-1:	Endothelin-1
FIO_2:	Fraction of Inspired Oxygen
FLACC:	Face, Legs, Activity, Cry and Consolability
FSH:	Follicular Stimulating Hormone
FVC:	Forced vital capacity
G-6-PD:	Glucose-6-Phosphate Dehydrogenase
GFR:	Glomerular filtration rate
GIT:	Gastrointestinal tract
GM-CSF:	Granulocyte macrophage colony stimulating factor
GVHD:	Graft versus host disease
Hb:	Haemoglobin
HbA_{1C}:	Glycated haemoglobin
Hb A:	Haemoglobin A
Hb AS:	Haemoglobin AS
Hb F:	Foetal haemoglobin
Hb S:	Haemoglobin S
Hb Sthal:	Haemoglobin Sickle cell thalassaemia
HCG:	Human Chorionic Gonadotropin
HDL-C:	High density lipoprotein cholesterol
Hib:	Haemophilus influenzae type b
HIV:	Human Immunodeficiency Virus
HLA:	Humal Leucocyte Antigen
HPLC:	High performance liquid chromatography
HRSA:	Health Resources and Services Administration
HRV:	Heart rate variability
HSC:	Haematopoietic stem cells
HSCT:	Haematopoietic stem cell transplantation
HU:	Hydroxyurea
ICAM:	Intercellular adhesion molecules
IEF:	Iso-electric focussing
IFN-γ:	Interferon-γ
Ig:	Immunoglobulins
IL:	Interleukins
INR:	International Normalized Ratio
IST:	International Stroke Trial
IUGR:	Intrauterine growth restriction
LAE:	Left Atrial Enlargement

LDL-C: Low density lipoprotein cholesterol
LFT: Liver function test
LH: Luteinizing Hormone
LV: Left Ventricle
LVH: Left Ventricular Hypertrophy
LVNC: Left ventricular non-compaction
MAC: Myeloablative conditioning
MACSS: multicenter acute chest syndrome study
Mb: deoxygenated myoglobin
MbO_2: Oxygenated myoglobin
MCH: Mean corpuscular haemoglobin
MCHC: Mean corpuscular haemoglobin concentration
MCV: Mean corpuscular volume
MI: Myocardial infarction
MMF: Mycophenolate mofetil
MOD: Multi-organ dysfunction
MPAP: Mean pulmonary artery pressure
MPI: Myocardial Performance Index
MRA: Magnetic Resonance Angiography
MRI: Magnetic Resonance Imaging
MSH: Multi-center Study of Hydroxyurea
MTD: Maximum tolerable dose
NBS: Newborn screening
NCD: Non communicable diseases
NEMLIST: National Essential Medicine List
NGCMSCD: National guidelines for the control and management of SCD
NGO: Non-Governmental Organization
NHLBI: National Heart Lung & Blood Institute
NHR: National Haemoglobinopathy Registry
NIH: National Institute of Health
NK: Natural Killer
NMAC: Non-Myeloablative conditioning
NO: Nitric oxide
N-PRS: Numerical Pain Rating Scale
NSAIDS: Non-steroidal anti-inflammatory drugs
NSCDN: Nigerian Sickle Cell Disease Network
NYHA: New York Heart Association
O_2: Oxygen
OCD: Obsessive-compulsive disorders
OSAS: Obstructive sleep apnoea syndrome

PAH:	Pulmonary arterial hypertension
PCI:	Percutaneous coronary intervention
PCR:	Polymerase chain reaction
PCV 13:	13-valent pneumococcal-conjugated vaccine
PGF:	Placenta growth factor
PHC:	Primary Health Care
PHT:	Pulmonary hypertension
PMN:	Polymorphonuclear
PNH:	Paroxysmal nocturnal haemoglobinuria
PO_2	Partial Pressure of Oxygen
PT:	Prothrombin time
PTTk:	Partial thrombopastin time
PVT:	Pulmonary venous hypertension
RAE:	Right Atrial Enlargement
RBC:	Red blood cell
RDW:	Red cell distribution width
RES:	Reticuloendothelial system
RHC:	Right heart catheterization
RTA:	Renal tubular acidosis
RV:	Right Ventricle
RVH:	Right Ventricular Hypertrophy
SaO_2:	Arterial Oxygen Saturation
SCA:	Sickle cell anaemia
SCD:	Sickle cell disease
SCCLD:	Sickle cell chronic lung disease
SCI:	Silent cerebral infarction
SCN:	Sickle cell nephropathy
SCT:	Sickle cell trait
SCTA:	Sickle Cell Treatment Act
S_PO_2:	Peripheral Oxygen Saturation
SS-RBC:	Sickled red blood cells
STRs:	Short tandem repeat allele mutations
TCD:	Transcranial Doppler
TIA:	Transient Ischaemic Attack
TLC:	Total lung capacity
TMA:	Thrombotic microangiopathy
TNF:	Tumor necrotic factor
TRV:	Tricuspid Regurgitant Velocity
TSP:	Thrombospondin
UK:	United Kingdom
USA:	United States of America

US-FDA:	United States Food and Drug Administration
UTI:	Urinary tract infection
VCAM-1:	Vascular cell adhesion molecule-1
VEGF:	Vascular endothelial growth factor
VLA-4:	Very late antigen-4
VOC:	Vaso-occlusive crisis
VTE:	Venous thromboembolism
WBC:	White Blood Cell
WB-PRS:	Wong-Baker Faces Pain Rating Scale
WHO:	World Health Organization

HAEMOGLOBIN: STRUCTURE, SYNTHESIS AND OXYGEN TRANSPORT

OLADOKUN OO AND ATERE TG

Introduction

Haemoglobin is a word that was coined from two words “haemo” which means blood and “globin” meaning protein. Globin is a protein substance of four different polypeptide chains that have amino acids ranging between 141 to 146. Haemoglobin is a conjugated globular protein having a molecular weight of about 64500 (1). There are two important oxygen-binding proteins in vertebrates namely haemoglobin (Hb or Hgb) and myoglobin. (1) Haemoglobin supplies oxygen (O_2) to tissues.

Haemoglobin’s function is to transport oxygen (O_2) in the blood from the lungs to other tissues of the body and provide cells with the oxygen they need for foodstuff oxidative phosphorylation. Haemoglobin is found in the blood within erythrocytes (red blood cells (RBC)) and is the most common family of carriers of O_2. (1) Haemoglobin is the main component of red blood cells which number about 250 million per cell and its combination with iron (Fe) and oxygen forms the bright red colour of RBC. Haemoglobin comprises more than 95% of the erythrocyte, it also carries nitric oxide, which controls vascular tone and blood pressure. (3) Haemoglobin is equally involved in the transport of respiratory carbon dioxide (about 20–25% of the haemoglobin as carbamino-haemoglobin) in which carbon dioxide is bound to the globin protein. (4) Erythrocytes further contain carbonic anhydrase, an enzyme that rapidly interconverts carbon dioxide and bicarbonate allowing the efficient transport of carbon dioxide, produced by respiration in the peripheral tissues, to the lungs, where it is exhaled. The haemoglobin combination with O_2 and CO_2 is reversible and this forms the basis for the gas-transport capability of hemoglobin. However, the combination of Hg with carbon monoxide (CO) is irreversible. This reduces the cell capacity to transport O_2 during carbon monoxide poisoning. (5) Myoglobin, the other

O_2-binding protein, stores oxygen in body tissues until cells need it. The highest levels of myoglobin are found in cardiac muscles and skeletal muscle, which require large amounts of oxygen during contraction. (6)

Catabolism of haemoglobin splits off the globin portion into an amino acid pool while the haem portion is converted into biliverdin. In humans, biliverdin is converted to bilirubin and secreted in the bile. Iron from haem is however reused for haemoglobin synthesis. (3, 6)

Haemoglobin is known to have an O_2-binding capacity of 1.34 cm^3 of dioxygen per gram which increases the total oxygen capacity in the blood by 70 times compared to dissolved oxygen in the blood. (6) For normal level tissue oxygenation, an optimum haemoglobin level must be maintained. The normal Hb level for males is 14 to 18 g/dl, and for females it is 12 to 16 g/dl. (7) A low level of haemoglobin results in anaemia, while a level above the normal is called erythrocytosis. A complete blood cell (CBC) test which expresses the level of haemoglobin is clinically used to diagnose anaemia, dehydration, and malnutrition. (7) Myoglobin and haemoglobin describe both protein structure-function relationships and the molecular basis of genetic diseases such as hereditary persistence of foetal haemoglobin, thalassaemias and sickle cell anaemia. (8, 9)

Structure

Haemoglobin has a quaternary structure, it is a tetrameric protein with two α chains and two β chains (α2β2), each with a haem unit as a prosthetic group, each polypeptide chain having a very strongly three-dimensional structure similar to the unique polypeptide chain in myoglobin. However, their amino acid sequences differ by 83%.

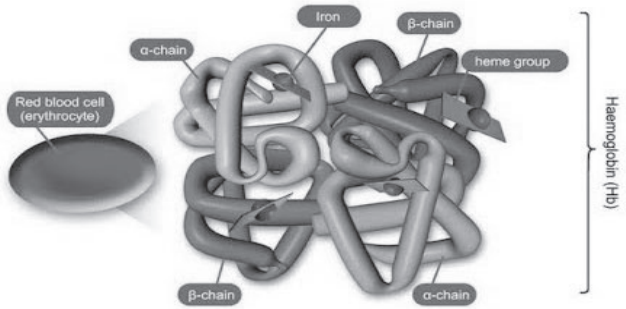

Figure 1: Structure of haemoglobin (10)

The globular protein units of haemoglobin comprise two identical pairs of polypeptide chains, i.e. two identical alpha (α) chains containing 141 amino acids and two identical non-α chains (beta (β), gamma (γ), delta (δ) or epsilon (ε) chains).

The main type of haemoglobin present in adults (HbA) consists of the α chain, which contains 141 amino acid residues, and the β chain, which consists of 146 amino acid residues ($\alpha_2\beta_2$, Figure 1). Each chain, comprises eight α helices and each group contains a prosthetic haemic group (Figure 1). As a result, haemoglobin can bind to four O_2 molecules. The four polypeptide chains, two α chains and two β chains are tightly grouped into a tetrahedral set to form a globally spherical molecule held together by several non-covalent interactions. (6) The two dimers are held tightly primarily by hydrophobic interactions. Ionic and hydrogen bonds also occur between the members of the dimers. Two dimers are able to move with respect to each other being held together primarily by polar bonds. The weaker the interaction between these mobile dimers results in the two dimers occupying different relative positions in deoxyhaemoglobin compared to oxyhaemoglobin. (11)

The tetrameric structure of common haemoglobin follows that found in an adult. However, there are other variations. For instance, the combination of two alpha chains and two gamma chains ($\alpha 2\gamma_2$) forms foetal haemoglobin, called haemoglobin F; sickle cell anaemia HbS (α_2S_2); and HbA_2 ($\alpha 2\delta 2$) (a minor haemoglobin A variant found in about 2.5% of adults). In a normal adult, with HbA, the α chain has 141 amino acid residues, while β has 146 amino acid residues, some minor haemoglobin types are shown in Table 1.

Table 1: Some minor haemoglobin types

Haemoglobin type	Chain composition	Fraction of total haemoglobin
HbA	$\alpha_2\ \beta_2$	90%
HbA_2	$\alpha_2\delta_2$	2-5%
HbA_{1c}	$\alpha_2\ \beta_{2\text{-glucose}}$	3-9%
HbF	$\alpha_2\delta_2$	<2%

Myoglobin, a haemoprotein present in skeletal and heart muscle, functions as both a reservoir and carrier of oxygen. Unlike haemoglobin that is tetrameric in structure, myoglobin is of a single polypeptide chain.

Foetal haemoglobin

In the foetus, there is another type of haemoglobin, haemoglobin F (HbF), which, unlike adult haemoglobin (HbA, $\alpha_2\beta_2$), consists of two α chains and two γ ($\alpha_2\gamma_2$) chains. HbF has a greater affinity for O_2 than HbA under physiological conditions, optimizing the transmission of oxygen from the maternal circulation to the foetal circulation through the placenta. The molecular basis of this difference in affinity for O_2 is that HbF 2,3-bisphosphoglycerate binds less strongly than HbA. Near birth, the synthesis of the γ chain is deactivated and the β chain (HbA) is activated (Figure 2). (6)

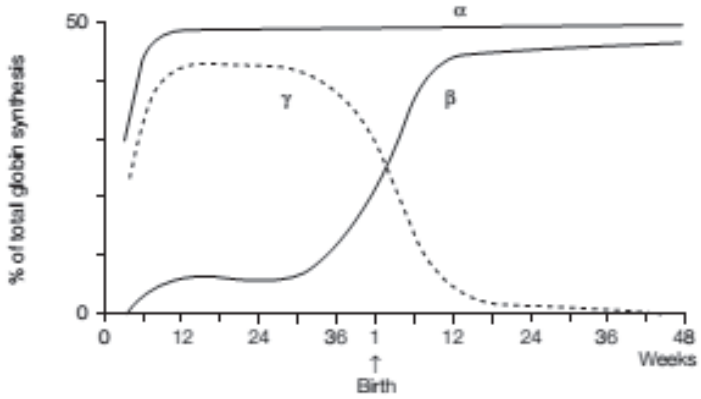

Figure 2: The transformation of human globulin synthesis at birth (6)

The different types of chains in haemoglobin are encoded by different genes. The genes encoding alpha globin chains are located on chromosome 16. The genes encoding non-alpha globin chains are on chromosome 11 in humans. Many human haemoglobinopathies result from inadequate expression of globin genes, and attempts to modulate globin gene expression are a fundamental approach to seek novel avenues to therapy. (12, 13)

Haem

Haem is a complex protoporphyrin IX and Fe^{2+}. Porphyrins are cyclic compounds formed by linking four pyrrole rings via methenyl bridges. A characteristic of porphyrins is the formation of complexes with nitrogen ions bound to metal ions (archive.org) of pyrrole rings. (14)

The iron is held in the centre of the haem molecule by bonds to the four nitrogens of the porphyrin ring. The Fe^{2+} of the haem can form two more bonds. In myoglobin and haemoglobin, one of these positions is coordinated to the side chain of the histidine residue of the globin molecule, while the other position is available for the binding of oxygen. (2)

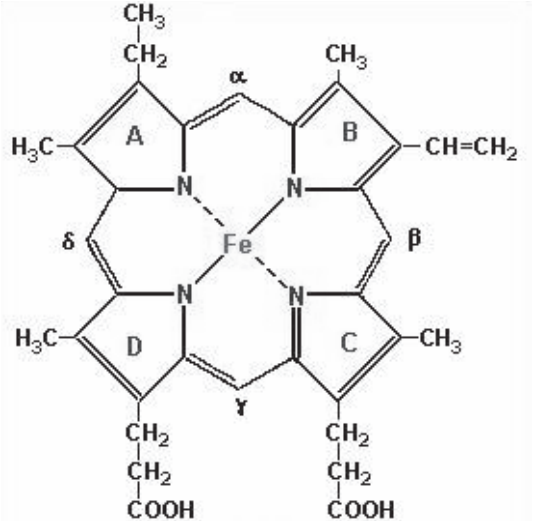

Figure 3: Structure of haem (https://www.namrata.co/structure-of-hemoglobin-an-overview/)

Synthesis of Haemoglobin

Synthesis of Haem

Acetic acid in the Krebs cycle changes into α-keto glutaric acid which combines with glycine to form pyrrole compound, and pyridoxal phosphate is necessary to activate glycine.The product of the condensation reaction between succinyl CoA and glycine is α-amino-β-ketoadipic acid, which is rapidly decarboxylated to form δ-aminolevulinate (ALA). The reaction is catalyzed by ALA synthase, which is the rate limiting enzyme in porphyrin biosynthesis. Two molecules of ALA condensed to form one porphobilogen (PBG) and two molecules of water. This reaction is catalyzed by ALA dehydratase. The formation of tetrapyrrole/porphyrin occurs by condensation of four PBG molecules. This reaction is catalyzed by PBG deaminase. Porphyrin biosynthesis occurs in the mammalian liver. (15, 16)

Four PBG molecules condenses to form linear tetrapyrrole, hydroxymethylbilane. The hydroxymethylbilane cycle spontaneously forms uroporphyrinogen I or it is converted to uroporphyrinogen III by the combined action of uroporphyrinsynthase and uroporphyrinogen III co synthase. (15, 16) In the presence of uroporphyrinogen decarboxylase, uroporphyrinogen III is decarboxylated of all the acetate substituents to methyl substituents to form coproporphyrinogen III. Coproporphyrinogen III is then transported into mitochondria from where it is transformed to protoporphyrinogen III, then to proporphyrin III in the presence of mitochondrial enzyme coproporphyrinogen oxidase while protoporphyrinogen oxidase is needed in the conversion of proporphyrinogen III to protoporphyrin. (15, 16)

The incorporation of Fe^{2+} into the protoporphyrin by the action of haem synthase or ferrochelatase is the last step in the biosynthesis of haem. The iron is held in the haem centre molecule with bonding to the four nitrogens of the porphyrin ring. In myoglobin and haemoglobin, the side chain of histidine residue coordinates the position of Fe^{2+} available for oxygen bonding. (15, 16)

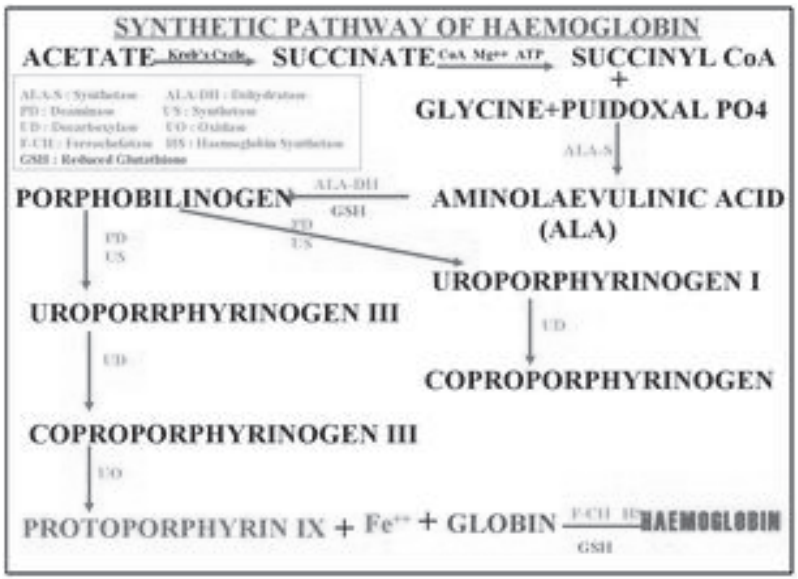

Figure 4: Synthetic pathway of haemoglobin (21)

The synthesis of globin chains α, β, δ, ε, γ and ζ, is controlled by structural genes of chromosomes 16 (α; ζ) (archive.org) and 11 (ζ). The rate of synthesis and the location vary through embryo to foetus to neonatal and to adult (17). The expression of alpha and non-alpha genes is precisely balanced by an unknown mechanism. Normal function of red blood cells requires balanced gene expression. A disturbance of balance leads to thalassaemia. (17, 18)

Binding of oxygen to haemoglobin

The deoxy form of haemoglobin is known as the "T" or taut (tense) form. In this form, the two αβ dimers interact through a network of ionic and hydrogen bonds that constrains the movement of polypeptide chains. This form is the low oxygen affinity form of haemoglobin. The binding of oxygen to haemoglobin causes the rupture of some of the ionic bonds and hydrogen bonds between the dimers. This leads to the "R" structure, or relaxed form, in which the polypeptide chains have more freedom of movement. The R form is the high oxygen affinity form of haemoglobin. (16)

Haemoglobin binds one oxygen molecule (O_2) at each of its four haem groups. The percentage of saturation of oxygen binding sites on haemoglobin molecules can be represented graphically on the oxygen dissociation curve for haemoglobin (Figure 5).

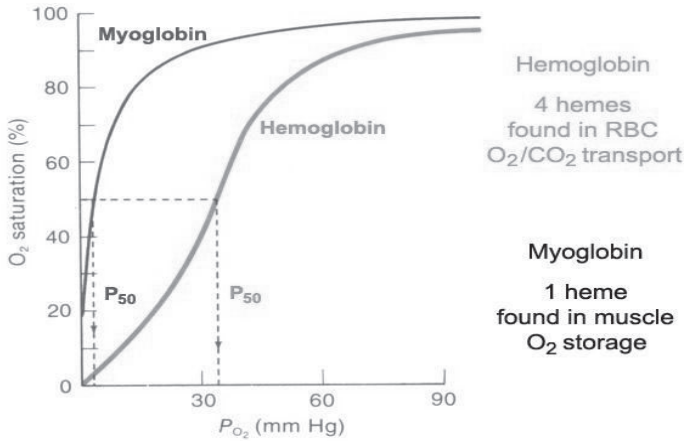

Figure 5: The oxygen binding curve (22)

The partial pressure of oxygen needed to achieve half saturation of the binding sites (P_{50}) is approximately 1 mmHg for myoglobin and 26 mmHg for haemoglobin. This shows that myoglobin has a higher affinity for oxygen. PO_2 in the lung capillary bed is 100 mmHg, myoglobin could effectively be loaded up with oxygen in the lungs. PO_2 of active muscle is about 20 mmHg. Myoglobin cannot deliver a large fraction of its bound oxygen even at 20 mmHg. It cannot serve as an effective vehicle for the delivery of oxygen from the lungs to peripheral tissue but is a better store of oxygen. The oxygen dissociation curve for myoglobin has a hyperbolic shape. This reflects the fact that myoglobin reversibly binds a single molecule of oxygen. The oxygenated myoglobin (MbO_2) and deoxygenated myoglobin (Mb) exist in simple equilibrium. (11, 12)

$Mb + O_2 \quad MbO_2$

Myoglobin therefore releases its oxygen during the deprivation that accompanies severe physical exercise that lowers the PO_2 of muscle tissue to as about 5 mmHg.

Haemoglobin binds $4O_2$ molecules per tetramer (one per subunit of haem) and the oxygen saturation curve is sigmoidal. The facility with which haemoglobin binds O_2 depends on whether other molecules are present at the same tetramer. If O_2 is present, binding of subsequent O_2 is achieved more readily because the binding of oxygen molecules at one haem group increases the oxygen affinity of the remaining haem group in the same haemoglobin molecule i.e. haemoglobin exhibits cooperative binding kinetics – a property that permits it to bind a maximal quantity of O_2 at the respiratory organ (PO_2) 100 mmHg and to deliver a maximal quantity of O_2 at the PO_2 of peripheral tissue (20 mmHg).

$Hb_4 + O_2 \quad Hb_4O_2$

$Hb_4O_2 + O_2 \quad Hb_4O_4$

$Hb_4O_4 + O_2 \quad Hb_4O_6$

$Hb_4O_6 + O_2 \quad Hb_4O_8$ (fully saturated haemoglobin)

These changes profoundly alter haemoglobin's secondary, tertiary and quarterly structure. One pair of α/β subunits rotates with respect to the other α/β pair, compacting the tetramer and increasing the affinity of the haem for O_2. Oxygenation of haemoglobin makes iron atoms of

deoxyhaemoglobin (which lie about 0.06 nm beyond the plane of the haem ring) move into the plane of the haem ring. This motion is transmitted to the proximal (F_8) histidine, which also moves towards the plane and to residues attached to $HisF_8$. (11, 12, 19)

Haemoglobin binds CO_2

Haemoglobin binds CO_2 directly when oxygen is released and about 15% of the CO_2 carried in blood is carried directly on haemoglobin molecules. CO_2 reacts with the amino terminal α-amino group of haemoglobin, forming a carbonate and releasing protons that contribute to the Bohr effect

$$CO_2 + Hb\text{-}NH_3^+ \qquad \overset{H}{2H^+ + Hb - N - COO^-}$$

Conversion of the amino terminal from a positive to a negative charge favours salt bridge formation between α and β chains so that the taut T state is stabilized resulting in a decrease in its affinity for oxygen. (19)

Increase in the partial pressure of CO_2 and/or increase in H^+ concentration or a decrease in pH enhances the release of oxygen from haemoglobin that is a decrease in Hb affinity for O_2 and the oxygen dissociation curve shifts to the right.

Sources of protons that lower pH

The concentration of both CO_2 and H^+ in the capillaries of metabolically active tissue is higher than that observed in alveolar capillaries of the lungs. As CO_2 is absorbed in blood, the carbonic anhydrase in erythrocytes catalyzes the formation of carbonic acid. Carbonic acid rapidly dissociates into bicarbonate and a proton.

$$CO_2 + H_2O \qquad H_2CO_3 \qquad HCO_3^- + H^+$$

Haemoglobin binds protons for every four oxygen molecules released and thus contributes significantly to the buffering capacity of blood.

In the lungs, the process is reversed. Oxygen binds to deoxyhaemoglobin and protons are released. The protons combine with carbonate forming carbonic acid. Carbonic anhydrase helps to form CO_2 which is exhaled. This reversible reaction is called the *BOHR EFFECT*. (11, 12)

The protons responsible for the Bohr effect are generated by the rupture of salt bridges during the binding of oxygen to the T structure. The protons released from the nitrogen atoms of β-chain residues drive carbonate toward carbonic acid which is released as CO_2 in alveolar capillaries. The Bohr effect can be represented as:

HbO_2^+ HbH^+ + O_2

oxyhaemoglobin deoxyhaemoglobin delivered

2,3 diphosphoglycerate (2,3 DPG) also affects the affinity of haemoglobin for oxygen

2,3 DPG is very plentiful in red cells. It is formed as an intermediate of the glycolytic pathway. It is a highly charged anion that binds to the β-chain of deoxyhaemoglobin. One molecule of deoxyhaemoglobin binds one of 2,3 DPG, in effect,

HbO2 + 2,3-DPG Hb-2,3DPG + O_2

The binding of 2,3-DPG to deoxyhaemoglobin stabilizes the taut conformation of deoxyhaemoglobin and favours the liberation of O_2 from haemoglobin. Haemoglobin from which 2,3-DPG has been removed has a high affinity for oxygen. The presence of 2,3-DPG therefore reduces the affinity of haemoglobin for oxygen thereby shifting the oxygen dissociation curve to the right to release O_2 at the peripheral tissue. (6, 11)

The preferential binding of 2,3-DPG to the β-globin chain is important and in foetal haemoglobin where the β-chain is replaced by the ϑ-chain that binds 2,3-DPG weakly, the affinity of haemoglobin to oxygen is high. This high affinity facilitates the movement of O_2 from mother to foetus despite the hypoxic (anaerobic) environment of the foetus. (20)

2,3-DPG concentration in red blood cells increases in response to chronic hypoxia and anaemia. In conditions like obstructive pulmonary emphysema or high altitude and chronic anaemia, intracellular levels of 2,3-DPG increase. However low pH reduces 2,3 DPG because acidosis inhibits red cell glycolysis. Thyroid hormone, growth hormone and androgens increase 2,3-DPG and the P_{50}. (6,11,12)

Conclusion

Hundreds of haemoglobins have been previously characterized to establish haemoglobinopathies. The best characterized haemoglobinopathy is probably sickle cell anaemia (sickle cell haemoglobin, HbS). The molecular basis of this disease is the substitution of a glutamic acid residue, a polar residue to a valine, a hydrophobic one at the 6-position of the β-chain, resulting in the substitution of a polar residue for a hydrophobic residue. (6) Sickle cell disease is a genetically transmitted haemolytic disease. The crescent-shaped RBCs are more fragile than the normal erythrocytes, they lysate easily and have a shorter half-life, leading to severe anaemia. Sickle cell anaemia is prevalent among people of African descent.

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History of Sickle Cell Disease

Omisore AG and Oguns O

This chapter examines the history and epidemiology of Sickle Cell Disease (SCD). Although SCD probably originated outside of America (speculations have suggested Africa or Asia as the true origin), it was first discovered in the United States. The discovery was incidentally made by a Surgeon (Herrick JB) and his resident (Irons E) from the blood of one Mr WC Noel, a dental student then who is now acclaimed to be the "first" Sickle Cell Anaemia (SCA) patient. Many scientists including physicians who play significant roles in the discovery and the confirmation of the pathology and science of SCD are mentioned in this chapter. SCD is a global phenomenon, although it is commoner in the tropical regions of Africa and Asia with about 80% of newborns who develop it coming from sub-Saharan Africa especially from Nigeria and the Democratic Republic of Congo, with the former responsible for almost one-third of cases worldwide. SCD especially SCA is associated with huge health and financial burdens and its history and epidemiology are vital areas that should be given the desired priority by all relevant stakeholders, with a view to achieving significant reduction and control globally via adequate preconception counselling and screening.

History of Sickle Cell Disease: The Discovery of the Sickle Red Cell and Subsequent Developments

In 1904, Walter Clement Noel, a 20-year-old man, from a wealthy Black family in the Caribbean Island of Grenada went to the United States to study dentistry at the Chicago College of Dental Surgery (1). A few months later he was admitted to the Presbyterian Hospital in Chicago on account of severe respiratory distress and a leg ulcer, which are now known as part of the symptoms of sickle cell disease. Dr Earnest E Irons, the intern who was on duty that day, did a routine blood test for Noel and was the first to observe these "pear shaped, elongated" sickled blood cells (1). He was on admission a number of times within the next few years before completing his studies.

In 1910, Dr James Herrick, who was Dr Irons' supervisor, published his article describing the "unique stretched out and sickle shaped red blood cells associated with severe anaemia" (1, 2). This was the first documented and recorded case of Sickle cell in Western medicine (1). Dr Noel went back to Grenada in 1907 and ran his dental practice in St. Georges, the capital city, until he died in 1916 at the age of 32 from acute chest syndrome (2, 3). The third case of Sickle cell was reported in 1915 by Cook and Meyer in a 21-year-old woman. Blood samples from both the patient and her father, who had no symptoms, showed the sickling deformity of the red cells and three of her siblings had died from severe anaemia. These observations suggested a genetic basis for the disease (4, 5).

In 1917, Victor Emmel using an in-vitro culture showed that the normal red cells of the father of a patient became sickle after in-vitro culture (2). Hence, the sickle red cells represented a physical change in the morphologically normal red cells released from the bone marrow. That is, these sickle red cells were not released from the marrow as sickle cells. In the 1920s, Hahn and Gillespie attributed the sickling to the deoxygenation of red blood cells (6). Some people's red cells were found to sickle when deoxygenated, but they did not manifest with anaemia or other classical symptoms. This became known as "sickle cell trait (SCT)". In 1945, the American novel prize-winning chemist, Linus Pauling, who later received a Nobel prize, observed that sickle haemoglobin has 2 to 4 more net positive charges than normal haemoglobin and with his colleagues in 1949, demonstrated electrophoretic differences between haemoglobins from normal, SCT and sickle cell anaemia subjects (6, 7). Dr Mason, who observed the fourth reported case of Sickling of RBC, was credited with first using the term "sickle cell anemia (SCA)" and also noticed the similarities between the cases (2). Hahn and Gillespie demonstrated that the red cell sickling occurred with low oxygen tension and low pH in 1927 and they were able to revert sickled cells back to their normal discoid shape by simply providing the cells with oxygen (6).

The protective role of foetal haemoglobin (HbF) was discovered in the 1940s by Dr Janet Watson who suggested a link between HbF levels and the presence of disease symptoms in 1948 (6). In 1945, the American chemist, Linus Pauling, who later received a Nobel prize, observed that sickle haemoglobin has 2 to 4 more net positive charges than normal haemoglobin. In 1949, Pauling tested the haemoglobin samples from normal individuals, sickle cell patients and people having SCT using electrophoresis, which separated proteins based on their size and electrical

charge. Normal individuals had haemoglobin of one type distinguishable from the haemoglobin from patients with SCA, and the individuals with the SCT had both. Around the same time, the autosomal recessive inheritance of the disease was demonstrated by Dr James V Neel (2, 6). In the 1950s, researchers noticed a high prevalence of sickle cell gene among people living in or originating from areas with high malaria prevalence (8). It was later observed that the sickle cell trait offers some protection against malaria especially in childhood. This explains why the prevalence of the sickle cell gene is high in sub-Saharan Africa, the Middle East and India (8). In 1950, Watson et al. predicted the importance of foetal haemoglobin (Hb F) by suggesting that its presence could explain the longer period necessary for sickling of newborn red blood cells, compared with those from mothers who had "sicklemia" (6). The globin chain of the red cell haemoglobin was sequenced by Vernon Ingram and JA Ingram in late 1956 (4, 6). This revealed the replacement of glutamic acid at position 6 by valine on the beta globin chain in SCD, making SCD the first genetic disease with a known molecular basis. Studies that analysed the structure and physical properties of Hb S, which formed intracellular polymers upon deoxygenation were thereafter published. In 1971, the then US President, Richard Nixon called for enhanced funding for SCD diagnosis, prevention through genetic counselling, and treatment and in 1972, he signed into law the SCA Control Act (2). In the eighties, bone marrow transplantation in a child with acute leukaemia was done to cure the acute leukaemia, and was later found to result in a cure of the SCD as a side-event (4). This was the first reported cure of the SCD. Bone marrow transplantation has not been put into wide usage because of challenges related to it which include finding a suitable donor, costs and the risk of rejection with associated morbidities and mortalities.

Although the first recorded history of SCA was in America, symptoms of sickle cell anaemia could be traced back to 1670, in one Ghanaian family. (9) Sickle cell anaemia has probably existed in Africa, at least as far back as 5000 years and known by a lot of names in their native languages, but there has been no record of it, until it was discovered in America in 1904 and subsequently published (10).

The discovery of the molecular basis of SCD was an important landmark in molecular medicine. It has also paved the way for research into future therapeutic agents that will benefit SCD patients.

Global Epidemiology of Sickle Cell Disease

Inherited haemoglobin disorders, particularly thalassaemias and sickle cell disorders (SCD) were previously considered as a problem of the tropics and subtropics, but due to migration, they are now common worldwide. SCD is a group of inherited autosomal recessive blood disorders which constitutes significant public health concern globally especially among blacks in sub-Saharan Africa (11-14). In a published map the global distribution of the haemoglobin S allele confirms the hypothesis that the sickle cell trait offers some protection against malaria, as the prevalence of the Hb S gene is highest in malaria endemic regions (8). Globally, SCD accounts for 80% of the inherited haemoglobin disorders and an almost similar proportion of all affected births occur in Africa (11, 12). SCD is a group of disorders and in sub-Saharan Africa it commonly manifests as SCA (HbSS – with inheritance of the haemoglobin gene S from both parents who have sickle cell traits), Sickle haemoglobin C disease (HbSC) and Haemoglobin S beta Thalassaemia disease (HbSBetaThal). (13).

SCA is responsible for approximately 5% of under-five mortality in Africa, and in high prevalence countries like Nigeria it may be in excess of 15% with just half of the under-five children living beyond this age (11, 15). Although, SCD is majorly found in sub-Saharan Africa, the Middle East and Asia, significant migration from these regions to Europe and other western nations have led to SCD almost becoming the leading inherited disorder in some countries, at least in terms of prevalence (11, 16). SCD has no sex predilection since it is not an x-linked disease. The male-to-female ratio is 1:1.

Globally, it is estimated that SCD occurs in about 300,000 births annually and is most prevalent in the malaria endemic regions of the world with10-40% of the population carrying the Hb S gene resulting in an estimated SCA prevalence of 2% (12). Though other authors quote 25-30% instead of the 10-40% (16). Worldwide sickle cell births per year are in excess of 300,000 with about 80% of the births occurring in sub-Saharan Africa and Nigeria where the largest burden of the disease is borne having in excess of 90,000 births (17). It is projected that by 2050, annually there will be over 400,000 newborns with almost half of these coming from only two sub-Saharan countries – Nigeria and the Democratic Republic of Congo while it is expected that India which currently leads the pack in Asia would have a significantly decreased incidence between 2010 and 2050 (17).

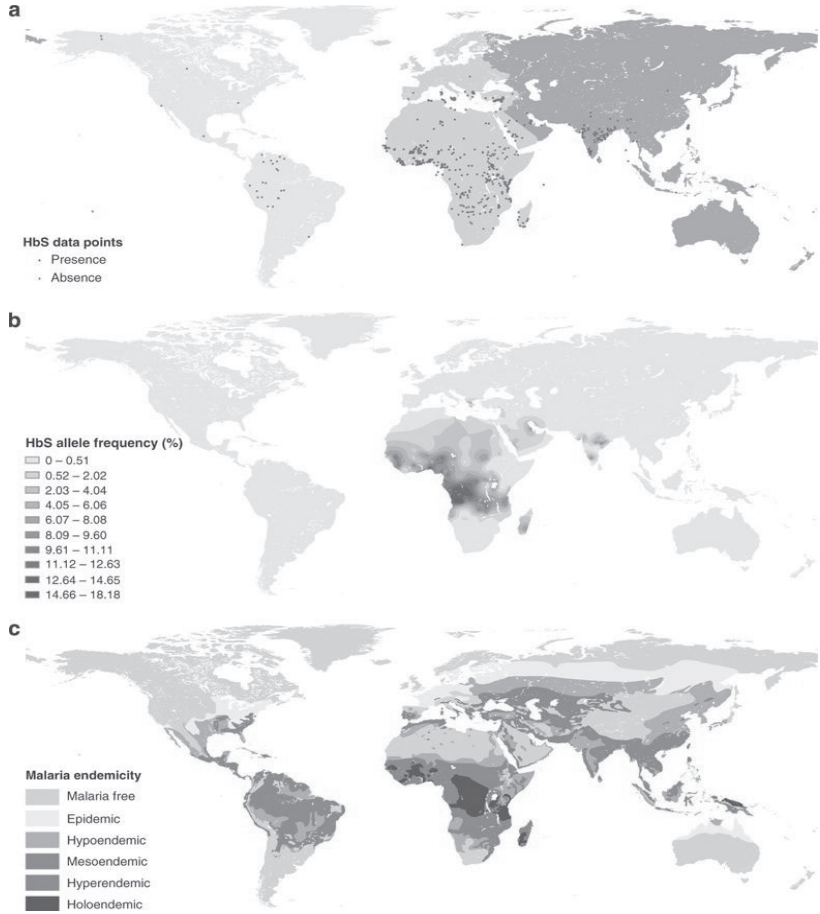
As of 2015, about 4.4 million people have SCD with about 80% occurring in sub-Saharan Africa. In 2015, SCD accounted for 114,800 deaths (18). SCD is a global phenomenon and increasingly SCA is found worldwide, even in the Caribbean and America, however Nigeria remains the most challenged country in the world when it comes to SCD and SCA.

Epidemiology of Sickle Cell Disease in Nigeria

The reported prevalence of SCA in Nigeria is between 2 and 3% with about 25% of the population having the carrier state (HbS gene) and this proportion has been quite consistent, even over decades (19). Nigeria remains the country with the largest number of people with SCA worldwide, partly due to its large population and perhaps also due to the lack of clear-cut policies and/or poor implementation regarding preconception counselling and screening for SCD.

The prevalence of SCD in Nigeria and in fact other populations is not unrelated with the overall prevalence of malaria in the country and the high proportion of carriers of the sickle cell gene (Hb S) in the country which has been reported to be protective against falciparum malaria in sub-Saharan Africa (8).

Concerning the pattern of Sickle Cell Trait in Nigeria, HbS appears evenly distributed across geo-political zones in the country while HbC is apparently commoner in western Nigeria (some studies documenting as much as 5% or more of the populace) and declines as one shifts from the west towards the east. In a specific study done among preschool children in eastern Nigeria, the prevalence of the carrier state (HbS) was 22.5% while HbSS was 1.6% and HbC was 0.1% AC.



a. Red dots show the presence of the Hb S gene and blue dots show its absence.
b. Hb S allele frequency in different parts of the world.
c. Malaria endemicity.

Figure 1a-c: Maps showing the global epidemiology of sickle cell disease and its relationship with malaria endemicity [Source, Piel et al(8)].

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INHERITANCE OF SICKLE CELL DISEASE/ SICKLE CELL HAPLOTYPES

OLUFEMI-AWORINDE KJ, ONI O AND AKINWUSI PO

Inheritance of Sickle Cell Disease

Sickle cell disease (SCD) is a result of a single amino acid substitution in the gene encoding the β-globin subunit. (1) A sickle cell gene is inherited by the baby from both parents. When both parents have the genetic defect, there is a 25% chance that each child will be born with sickle cell disease.

If a child inherits only one copy of the defective gene (from either parent), there is a 50% chance that the child will carry the sickle cell trait. People who only carry the sickle cell trait typically do not get the disease, but can pass the defective gene on to their children. When both parents have the defective gene, there is a 25% chance that a baby will be born with normal haemoglobin.

Sickle cell disease is an autosomal recessive disorder and inheritance is by simple Mendelian rule as illustrated by the family tree. (2)

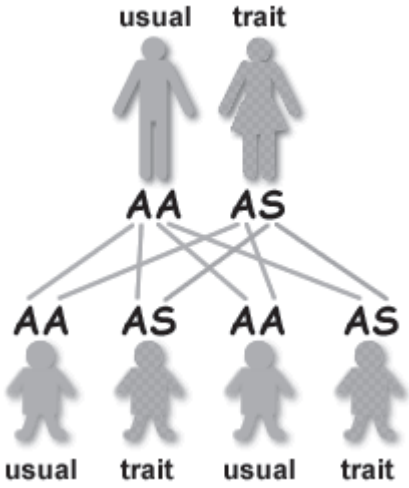

Figure 1 Inheritance pattern (Courtesy of the Sickle Cell Society via www.sicklecellsociety.org/resource/inheritance-sickle-cell-anaemia/)

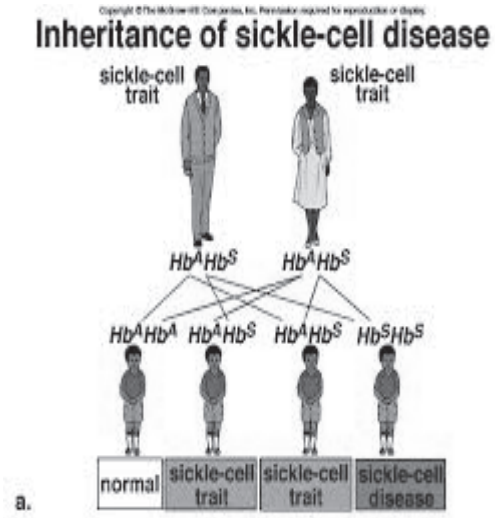

Figure 2 Inheritance pattern

A child born by a parent without the defective gene and the other parent with the defective gene has a 50% chance of having usual/normal

haemoglobin and a 50% chance of being a carrier of the defective haemoglobin per each pregnancy called sickle cell trait (Fig. 1). A sickle cell trait and another sickle cell trait parent have a 25% chance of a child with normal haemoglobin, a 50% chance of a child with sickle cell trait and a 25% chance of a child with sickle cell anaemia per each pregnancy (Fig. 2).

Sickle Cell Haplotypes

A haplotype is a set of genetic determinants located on a single chromosome or it refers to an individual collection of short tandem repeat allele mutations (STRs) within a genetic segment. (3)

Homozygous patients for the HbS allele have a similar genotype but the clinical presentation and disease severity among affected individuals can be extremely variable. (4) The type of haplotype inherited has been associated with the clinical severity of the sickle cell anaemia. (3)

The mutations that occurred in HbS have been described distinctly on five haplotypes based on the presence or absence of different restriction enzyme sites in the β-globin gene region located at the 5' and the two restriction enzyme sites at the 3'end on the β gene. (5,6)

The different haplotypes include:

1. Senegal haplotype
2. Bantu/Central African republic haplotype
3. Benin haplotype
4. Cameroon haplotype
5. Arabian/Indian haplotype.

The first four are the types of haplotypes found in Africa, named after their group and ethnic origin. (7)

The different haplotypes can occur in pure homozygous form or as compound heterozygous forms which may be associated with the clinical differences seen in patients. (8)

When the different polymorphic sites of the β gene cluster are analysed, it is of genetic and clinical interest which is useful in predicting the prognosis of the disorder and to plan the best form of treatment. (8)

The Senegal and Arabian/Indian haplotypes have been associated with a mild clinical form of sickle cell anaemia and less organ damage whereas the Bantu haplotype is associated with a severe clinical form and the Benin and Cameroon haplotypes are in-between. (3) This observation has been found to have correlation with the level of foetal haemoglobin in the circulation of the patients with different haplotypes. The Arabian/Indian haplotype had an average of about 17% foetal haemoglobin and the Senegal haplotype had an average of about 12.4% whereas the Benin and Cameroon haplotypes had an intermediate value of foetal haemoglobin. (9, 10) The Bantu haplotype is associated with the lowest value of foetal haemoglobin and thus patients with this haplotype have a three-fold increase to development of renal failure, stroke, chronic lung disease and young adult death. (11,12) However, risk of acute chest syndrome, infections and painful crises is similar in Benin and Bantu haplotypes. (12,13)

Conclusion

HbS patients present with different clinical manifestations ranging from mild to severe forms in which haplotypes are found to be associated with the severity of the disease, and the haplotype effect on phenotypes highly correlates with foetal haemoglobin expression. (14,15) However, the severity of the disease remains variable within the same haplotypes even in the homozygous form, indicating that more molecular, genetic and external factors should be considered before associating a haplotype type with severity. (8)

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PATHOPHYSIOLOGY OF ANAEMIA IN SICKLE CELL DISEASE

ABAYOMI TA AND ADELEKE SO

Sickle cell disease is a blood ailment usually caused by aberrant haemoglobin inherited from one's parent. The aberrant haemoglobin causes red blood cells to misshapen (sickle). The sickled red blood cells are easily destroyed and thus often predispose to rupture. Sickle cell anaemia results when the total number of red blood cells in the whole blood significantly decreases as a result of haemolysis (ruptured red blood cells).

Sickle cell disease is an increasing global health problem. Estimates suggest that every year approximately 350,000 infants are born with Sickle cell anaemia, which is defined as homozygosity for the sickle haemoglobin (HbS) gene i.e. abnormality in the amino acid sequence of the β-globin chain, and that this number could rise to 400,000 by 2050.

Better understanding of the precise molecular mechanisms of HbS polymerization and a pathophysiological understanding of the disease in general are essential to the development of new therapeutic hypotheses which will eventually help in early prevention of severe complications which will reduce morbidity, increase the amount of time one is expected to live and improve life quality. Thus, this chapter aimed at analyzing the pathophysiologic basis of anaemia in Sickle cell disease.

Haemoglobin (Hb) is the protein located in red blood cells that assists in the distribution of oxygen to the tissues. To make sure adequate oxygen reaches the tissues, an adequate haemoglobin level must be maintained. The quantity of haemoglobin in whole blood is expressed in grams per decilitre (g/dl). The normal Hb level for males is 14 g/dl to 18 g/dl; that for females is 12 g/dl to 16 g/dl. When the haemoglobin level is low, the patient has anaemia (1).

Anaemia is a common dietary insufficient disorder and global public health problem which affects both developing and economically stable nations. Its resultant effects are felt on human health, social development and the economy of the affected nations (2). According to the WHO (2018) definition, anaemia is a condition in which the number of red blood cells or their oxygen affinity is not enough to meet physiologic needs (3).

Anaemia is a functional inability of the blood to supply the tissue with adequate oxygen for proper metabolic function. Anaemia is not a disease, but rather the expression of an underlying disorder or disease. Anaemia is usually associated with decreased levels of haemoglobin and/or decreased packed cell volume (haematocrit), and/or a reduction in red blood cell (RBC) count (1). Deficiency of iron in the blood has been linked to the major cause of anaemia globally, although deficiency in some nutrients like folate, Vitamin A and B12 while some disease conditions such as parasitic infections, chronic inflammation and inherited disorders are also implicated as a causative of anaemia (3).

The World Health Organization (WHO) in the year 2004 reported that one-third of the global populations are anaemic due to imbalance in their nutritious food intake (4). The WHO has estimated that approximately 1.6 billion people have anaemia while Africa is the most affected region (5). Anaemia is most prevalent among expectant mother and toddlers and is particularly prevalent during the first two years of life. Around 60% of African children below the age of five have anaemia (5).

Morphological Classification of Anaemia

There are several types and classifications of anaemia. The occurrence of anaemia is due to the various red cell defects such as production defect (aplastic anaemia), maturation defect (megaloblastic anaemia), defects in haemoglobin synthesis (iron deficiency anaemia), genetic defects of haemoglobin maturation (thalassaemia) or due to the synthesis of abnormal haemoglobin (haemoglobinopathies, sickle cell anaemia and thalassaemia) and physical loss of red cells (haemolytic anaemia's) (6).

Sickle Cell Anaemia

Sickle cell disease is a blood ailment usually caused by aberrant haemoglobin inherited from one’s parent. The aberrant haemoglobin causes red blood cells to be misshapen (sickled). The sickled red blood

cells are easily destroyed and thus often predispose to rupture. Sickle cell anaemia results when the total number of red blood cells in the whole blood significantly decreases as a result of haemolysis (ruptured red blood cells). The uneven shape of the blood cells (sickled cells) can cause obstruction in the blood vessels thereby resulting in pain, tissue and organ damage (7).

Sickle cell disease is an increasing global health problem. Estimates suggest that every year approximately 350,000 infants are born with sickle cell anaemia, which is defined as homozygosity for the sickle haemoglobin (HbS) gene i.e. abnormality in the amino acid sequence of the β-globin chain, and that this number could rise to 400,000 by 2050 (8).

The prevalence of sickle cell anaemia has been reported to be directly proportional to the development of a country. In most developed countries, sickle cell anaemia patients have easy access to sophisticated and intensive medical care which will proffer solutions to varying degrees of complications associated with Sickle cell anaemia. In a developed country like the United States, between 90,000 and 100,000 Americans are evaluated to be afflicted with sickle cell anaemia with the disease being more common among African Americans (7). Statistically, 30% of African countries have sickle cell trait while the sickle cell disease has been reported to be most prevalent in sub-Saharan Africa (9). SCD has been reported to affect up to 2% of the population living in Nigeria, the Democratic Republic of Congo and India with 90% of people living with SCD located in these countries (9). Nigeria has about 150,000 newborns born with SCD per annum, though this figure is challenging because of the lack of federal newborn screening programs (10).

Pathophysiology of Sickle Cell Anaemia

Sickle cell anaemia is caused by a point mutation in the β-globin chain of haemoglobin, causing the amino acid glutamic acid to be substituted with the hydrophobic amino acid valine at the sixth position. The β-globin gene is seen on the chromosome short arm (11). The association of two mutant β-globin subunits forms haemoglobin S (HbS). Under low-oxygen conditions, the lack of a polar amino acid being substituted for by hydrophobic amino acid valine at position six of the β-globin chain fosters the non-covalent polymerization of haemoglobin, which misshapens red blood cells into a sickle shape and lowers their elasticity. Reduction in the red blood cell elasticity is the core key to the pathophysiology of sickle

cell disease. Normal red blood cells are stretchable and this makes the cells change their shape at any time, especially when passing through capillaries. In sickle cell disease, low oxygen tensions enhance red blood cell sickling and several series of sickling damage the cell membrane, thereby reducing the cell's elasticity. After the restoration of normal oxygen tension, these cells fail to return to their normal shape and consequently, the blood cell becomes rigid. These rigid blood cells are unable to change shape as they pass through narrow capillaries, leading to the blockage of blood vessels and Ischaemia (11). The actual anaemia illness is caused by haemolysis, the destruction of the red cells (deformed red blood cells) inside the spleen. Although, the bone marrow will try to remunerate destroyed red blood cells by creating new red cells, but RBC production from the bone marrow does not usually match the rate of destruction (12). Healthy red blood cells' half-life is between 90 and 120 days, but sickle cells only survive 10 to 20 days.

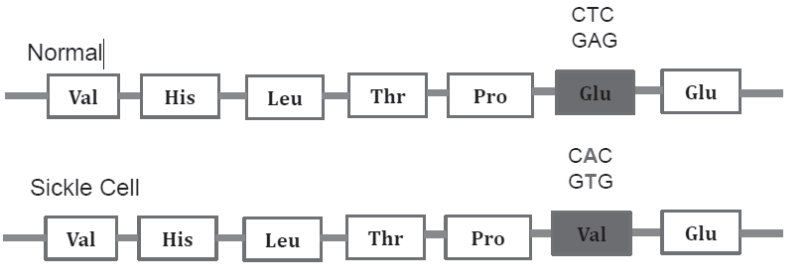

Fig. 1: Normal Haemoglobin - Two alpha globin chains and two β-globin chains. **Haemoglobin S –** Point mutation changing the sixth amino acid in the β haemoglobin chain from glutamic acid to valine (11).

Furthermore, when RBCs are deformed (sickled), they gain Na^{+} and K^{+}. Membrane permeability to Ca^{++} increases, possibly due in part to impairment in the Ca^{++} pump that depends on adenosine triphosphatase (ATPase). The intracellular Ca^{++} concentration rises to four times the reference level. The membrane becomes inelastic as a result of changes in cytoskeletal protein interactions; however, these changes are not seen to be consistent. It is thus not clear if calcium is responsible for the cell membrane stiffness is not clear (13).

When membrane vesicle formation occurs, the lipid bilayer will be unsettled, thereby making the outer leaflet increase the amounts of phosphatidyl ethanolamine and phosphatidylserine. Phosphatidylserine

may play a role as a contributor to thrombosis, acting as a catalyst for plasma clotting factors. Membrane rigidity can be reversed in vitro by replacing HbS with HbA, which implies that HbS interacts with the cell membrane (13).

Haemolytic Crisis

Premature destruction of sickle erythrocytes occurs both extravascularly and intravascularly. Extravascular haemolysis results from abnormalities of the sickle cell that permit its recognition and phagocytosis by macrophages and from impaired deformability of sickle red cells, enabling their physical entrapment (14). Elevations of free plasma haemoglobin in patients suggest that one-third of the total haemolysis in sickle cell anaemia is intravascular. One mechanism of intravascular haemolysis is sickling-associated exo-vesiculation of vesicles rich in phosphatidy linositol anchored membrane proteins (15), depleting the cell of the complement of regulatory proteins DAF and MIRL and leaving the cells susceptible to complement-mediated intravascular lysis (16). Another component of intravascular haemolysis is increased mechanical fragmentation of sickle cells; (17) which accounts for the accelerated haemolysis of sickle cell patients during exercise (17). Haemoglobinuria and oliguria may be present. Pallor develops rapidly and icterus is common. Frequently the pallor, listlessness and mild icterus develop more insidiously. The urine may be dark in colour due to the presence of excess urobilinogen. The anaemia is usually ortho chromic but it may be either normocytic or macrocytic. Reticulocytosis is often marked and there may be many erythroblasts in the peripheral blood (18).

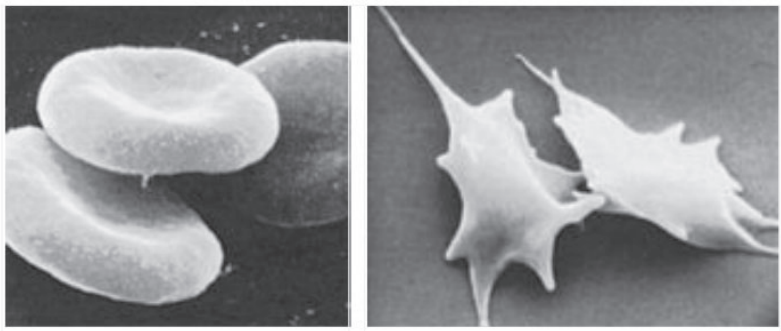

Fig. 2 Normal Red Blood Cell Sickle Red Blood Cell (11).

The basic pathophysiological mechanism: haemoglobin S polymerization and red blood cell alterations

During the deoxygenation which follows the passage of RBCs in the microcirculation the Hb molecule undergoes a conformational change. In HbS, replacement of the hydrophilic glutamic acid at position 6 in the β-globin chain by the hydrophobic valine residue results in the latter establishing hydrophobic interactions with other hydrophobic residues on the β-globin chain of another deoxy-HbS molecule. A polymer forms and lengthens in helical fibres which, grouped together, stiffen, and induce the deformed characteristic red blood cell shape, i.e. sickled red blood cells (SS-RBCs) (19). This process needs a certain time to be primed, the so-called "delay time", which is inversely proportional to the intracellular concentration of HbS. The formation of these long polymer fibres triggers a cascade of several other cellular abnormalities which participate in the overall pathophysiological mechanism. Dysregulation of cation homeostasis resulting from the activation of some ion channels, such as the K-Cl co-transport system and the Ca-dependent K-channel (Gardos channel) leads to a loss of potassium and cellular dehydration which, in turn, by increasing the intracellular Hb concentration, favours deoxy-HbS polymerization. Hb becomes denatured and haemichromes concentrate at the internal side of the membrane together with proteins of the cytoskeleton, in particular protein band 3. This process comes along with the loss of haeme and with the liberation of $Fe3^{+}$ which promotes the existence of an oxidizing microenvironment. The normal asymmetry of membrane phospholipids is disrupted with the exposure of anionic phosphatidylserine at the cell surface. Anti-band 3 IgGs accumulate on the protein band 3 aggregates, inducing erythrophagocytosis by macrophages (20). Finally, all these membrane changes give rise to the production of microparticles. The stiffening and fragility of SS-RBC explain vaso-occlusion and haemolytic anaemia, respectively. However, if these mechanisms indeed constitute the pathophysiological bases of SCD, they do not explain what triggers vaso-ocular crisis (VOCs). In basal conditions, the delay time, necessary for the polymerization of deoxy-HbS is longer than the time of passage of RBCs in the microcirculation. Recent data provide additional elements on various mechanisms that, by slowing down the blood flow in the microcirculation, are likely to precipitate VOCs.

In the 1980s and 1990s the teams of R.P.Hebbel and N. Mohandas showed the existence of an increased adhesion of the SS-RBCs to the endothelium

(21). Unexpectedly, it turned out that rather than the distorted RBCs, the main actors of this abnormal adhesion process are a population of young RBCs, referred to as “stress reticulocytes”. These stress reticulocytes, coming out prematurely from the bone marrow because of the anaemic stress, express on their surface adhesion proteins that normally maintain them in the marrow. Thus VOC seems to be composed of two consecutive steps. The first one involves adhesion of the stress reticulocytes to the endothelium of post-capillary venules, slowing down the blood flow and thereby inducing and propagating sickling of mature SS-RBCs that are maintained for a longer time in a hypoxic environment. This first step leads to a second one which corresponds to the entrapment of irreversible sickle cells and to the complete occlusion of the micro-vessels (22).

The first molecular partners identified as the actors in these abnormal interactions on RBCs were the α 4 β 1 integrin or very late antigen-4 (VLA-4) which directly binds to the vascular cell adhesion molecule-1 (VCAM-1) on the endothelial surface, and CD36 which interacts with another CD36 molecule on the endothelium through a molecular bridge formed by a molecule of plasmatic thrombospondin (TSP). Since then, the picture has considerably complexified, with the identification of numerous other receptor/ligand couples on the RBCs, on one side, and on the endothelium on the other, of the involvement of various plasma proteins in addition to TSP, and with the description of an intricate network of probably co-operative and sometimes redundant interactions (23). Clearly, the situation varies according to the vascular territories, for example VCAM-1 is specific to the endothelium of the microcirculation whereas von Willebrand factor probably mediates abnormal cell-cell interactions in large vessels. The endothelium is altered as witnessed by circulating endothelial cells (ECs) and accordingly subendothelial structures are exposed that are also involved. For instance, the basal cell adhesion molecule (Lutheran blood group) Lu/BCAM antigen at the SS-RBC surface interacts with laminin in the subendothelial matrix (24).

Even though these advances are remarkable, in particular the discovery of the major implication of stress reticulocytes, the SCD basic mechanism, namely deoxy-HbS polymerization, should never be forgotten. Even though other haemolytic anaemia’s come along with the presence of circulating stress reticulocytes as is the case, for example, of pyruvate kinase deficiency, none of these come along with VOCs. Thus, it is clear that, even though complex abnormal phenomena are at play, HbS is indeed the basic and the sole defect responsible for the SCD pathology, and in fact of the vaso-occlusive events.

All the cells in the blood vessel are implicated

Over the past few years, it has become more and more clear that SS-RBCs and ECs are not the only actors of VOCs. For instance, plasma Thrombospondin (TSP) is secreted by activated platelets. Polymorphonuclear neutrophils (PMN) also seem to be essential actors (25).

Hyperleukocytosis is almost constant in SCD patients, and a high PMN count is a pejorative element. The presence of adherent leukocytes in post-capillary venules suggests strongly that leukocytes, because of their cell volume, are major participants in the circulatory slowing down that initiates VOCs. In addition, it was shown that SS-RBCs are capable of abnormally interacting with leukocytes and particularly with PMNs. All these interactions take place in a subintrant inflammatory context maintained by a set of additional mechanisms (26).

Phosphatidylserine abnormally exposed at the SS-RBC surface and tissue factor expressed by activated circulating ECs participate in a borderline activation of the coagulation system. The resulting production of thrombin, even at a minimal level, added to ischaemia-reperfusion injury is probably at the origin of these inflammatory phenomena (27).

These result in the production of pro-inflammatory cytokines that maintain a state of generalized cell activation. Furthermore, haemolysis leads to the liberation of free iron from the haeme which is at the origin of an oxidative stress which in turn, via the activation of transcription factors such as nuclear factor-kappa β (NFk β) and activator protein-1 (AP-1), participates in the endothelial expression of VCAM-1, inter-cellulae adhesion molecule-1 (ICAM-1), and E-selectin, all proteins that are involved in the adhesion of stress reticulocytes and in leukocyte recruitment. Finally, cell activation induces the production of micro particles. In addition to the micro particles of erythrocytic origin already mentioned, circulating micro particles of endothelial, platelet, and leukocytic origins are observed in SCD patients and are increased in number at the time of VOCs. Very significantly, these micro particles are not only passive witnesses of cell activation, but these are probably important actors through activating properties conferred to them by their reorganized membrane (28).

Sickle red blood cells can be triggered and activated

For a long time considered as simple “hemoglobin bags”, RBCs have been shown to express on their surface a variety of receptors susceptible to induce signalling pathways that modify their functional properties. This aspect is particularly relevant to the pathophysiology of SCD. Cytokines and hypoxia modulate signalling pathways involved in the regulation of ion transport and RBC hydration, the influence of which on HbS polymerization has already been discussed.

Some extracellular stimuli are also capable of activating adhesion mechanisms. Epinephrin for example, by inducing the activation of the protein kinase A-dependent (PKA) signalling pathway leads to the phosphorylation of Lu/BCAM, and this phosphorylation is indispensable for the expression of Lu/BCAM adhesion properties (29).

All these data have brought a new vision of factors that participate in the initiation of the VOC. We now perceive better the precarious balance of the steady state of the SCD patient and how this can tip over towards the initiation of a VOC for example, during an infection which increases inflammation, or because of a stress that activates adhesion proteins on the RBCs.

Haemolysis alters nitric oxide metabolism and vessel biology

For a long time, VOC has been the focus of researchers trying to decipher the intimate mechanisms of SCD pathophysiology and haemolysis was rather a neglected aspect left in the second rank. Still, over the last decade, the work of the group of M.T. Gladwin outlined the potential importance of haemolysis as one of the primary pathophysiological factors in SCD (30).

Regulation of the vascular tone depends on a subtle balance between mediators produced by the endothelium such as endothelin-1 (ET-1), with its vaso-constrictive action, and nitric oxide (NO), with its strong activity as a vaso-dilator. In SCD, plasma NO is low and ET-1 is increased, particularly during VOCs.

The normal balance is thus shifted towards a vaso-constrictive state that is also susceptible to slowing down the blood flow and leading to the precipitation and perpetuation of VOCs. Haemoglobin is the most

powerful NO scavenger known. Free Hb destroys NO and generates free radicals one thousand times more quickly than Hb in the RBC. The originality of Gladwin's work was to connect haemolysis and the resulting liberation of Hb in plasma and a decrease of NO bioavailability in SCD. This depletion of NO is still majored by the fact that haemolysis also releases erythroid arginase in plasma where this enzyme degrades L-arginine, the substrate of the NO producing enzyme, i.e. the endothelial NO synthase (eNOS) (31). Thus the mechanism of NO depletion is double: destruction of NO by free Hb and reduced NO production by depletion of its precursor. Haemolysis-induced NO depletion is responsible for a set of abnormalities, the first of which being the essential loss of the vasodilator potential, incapable of counteracting the vasoconstrictive action of ET-1, but also a facilitation of platelet activation and an endothelial dysfunction with an abnormal expression of adhesion molecules. From these data, the authors suggested distinguishing two sub-phenotypes in SCD, one referred to as "hyperviscosity – vaso-occlusion" and the other one "hemolysis-endothelial dysfunction", each associated with different complications of the disease. They proposed that the first one was preferentially associated with VOC, acute chest syndrome and femoral head osteonecrosis and the second one with a greater risk of developing arterial pulmonary hypertension (APHT), a complication with a severe prognosis and relatively underestimated until then in SCD, leg ulcer, priapism, and possibly stroke. These sub-phenotypes, however, are overlapping and simultaneously present in all the patients, but certain patients would express preferentially a sub-phenotype with regard to the other one and would develop preferentially the complications specifically associated to this sub-phenotype. This attractive hypothesis led to a whole series of new therapeutic hypotheses to restore NO bioavailability. Various clinical assays to test these hypotheses were realized, none of which with very convincing results at the moment, but other assays are still in progress. One should note however, that the relevance of Gladwin's hypothesis was recently challenged (32).

Certainly, NO scavenging by free Hb has been documented in some other haemolytic diseases as for example, paroxystic nocturnal haemoglobinuria (PNH). But SCD and PNH do differ on several important aspects: the level of free plasma Hb which is 10 times higher in PNH than in SCD, the acute character of intravascular haemolysis in PNH versus a most frequently chronic and primarily extravascular haemolysis in SCD, the erectile abnormalities: impotence in PHN versus priapism in SCD. Recent data also suggest that the APHT is a complication, certainly very severe, but rare in SCD, contradicting the initial data of Gladwin's group. Thus, the

relative importance of the abnormalities of NO metabolism in the pathophysiology of SCD still remains to be defined with more precision (32).

Conclusion

The first molecular disease to be described, SCD remains an unprecedented model. The elucidation of the precise molecular mechanisms of HbS polymerization represented, at the time, an absolutely remarkable achievement. Even though it still remains valid, this scheme does not explain, by itself alone, the factors triggering VOCs. In this domain, considerable progresses were realized over the last few years which gave a new version of SCD. These factors are complex, still controversial for some of them, but clearly very intricate, sometimes redundant and probably complementary and synergistic. Clearly, the pathophysiological understanding of diseases in general is essential to the development of new therapeutic hypotheses to be tested. It is indeed the case for SCD for which the remarkable progress realized in terms of reduced morbidity, improved quality of life, and increased life expectancy is essentially the fact of early follow up after neonatal screening and early prevention of severe complications. A single drug, hydroxycarbamide (or hydroxyurea), has definitely been proven to be efficient at improving the patients' quality of life, but its mode of action is still poorly defined. The development of new therapeutic approaches applicable in countries where SCD is endemic is an absolute necessity. Much is thus still to be done. The recent technological advances of biology now allow global approaches without a preconceived idea. In science, the new "omic" technologies: genomics, transcriptomics, proteomics, metabolomics... now prevail. Simultaneously, biocomputing, biomathematic, and modelling tools necessary for the interpretation of the huge mass of generated data are being rapidly developed. The so called "system biology" emerges, that encompasses the analysis of the functioning and dysfunctioning of the signalling pathway networks and of their interactions globally.

Because it is relatively simple in its complexity, SCD could indeed continue to serve as a model for the application of these new approaches and concepts to the understanding of diseases in general.

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Leucocytes in the Vaso-Occlusive Process

Olufemi-Aworinde KJ,
Oni O and Akinwusi OP

Red blood cells in the vaso-occlusive processes

Traditionally, sickle cell anaemia has been described as a haemoglobinopathy, caused by the substitution of valine for glutamic acid at position 6 of the β-globin chain. Hydrophobic interactions within mutated molecules of haemoglobin S lead to their polymerization and alteration of their shape from the normal bi-concave disc to a sickle shaped cell. (1) This abnormal shape causes the plugging of blood vessels within the microcirculation and undue aggregation of red blood cells.

Studies have been done to explain the abnormal interactions within red blood cells in sickle cell patients and the endothelium of blood vessels. Kaul et al., using the suspension characteristics of red blood cells (RBCs) and the intracellular mean corpuscular haemoglobin concentration (MCHC) classified RBCs into four (4) categories – fractions 1 to 4. (2) Those with moderate MCHC, comprising essentially of reticulocytes (fraction 1) and discocytes (fraction 2) behave as normal cells. Fractions 3 and 4, which are rigid discocytes and irreversible sickle cells respectively, have abnormally elevated MCHC and are responsible for the higher flow resistance in shear flow. (3)

Formerly, irreversible sickle cells were thought to occlude capillaries as they transit, causing ischaemia in regions distal to the point of occlusion. However, it has been revealed that the post capillary venules are those commonly occluded, corresponding to the period where the red blood cells will have been thoroughly de-oxygenated (2). This may explain the micro-vascular injury that is observed in people with sickle cell, manifesting as retinopathy, leg ulcers and nephropathy.

Apart from platelet activation, there appears to be activation of the coagulation cascade in sickle cell anaemia. This is evidenced by the apparent protein S deficiency and elevated fibrin d-dimers noted by Francis Jr. et al. (4) A study by Adewoye et al. also showed that heat shock protein–70, a pro-inflammatory mediator, is released during vaso-occlusive crises and perpetuates an inflammatory state. (5) These studies suggest that the pathology seen in SCA is due to a complex interaction of red blood cells, white blood cells and other inflammatory mediators.

Leucocytes in the vaso-occlusive process

Leucocytosis has been traditionally associated with inflammation and infection. (6) However, studies have also shown that leucocytosis is an acute phase reactant and a marker of poor prognosis across myriads of clinical conditions, including ischamic heart disease and stroke. (7-9) Leucocytosis was found to be an independent predictor of leukaemic transformation and venous thrombosis during follow up in patients with polycythaemia vera and has been found to be associated with poor prognosis and vaso-occlusive event in patients with SCA. (10)

Polymorphonuclear (PMN) cells have been found to be both acutely and chronically activated in patients with SCA. A study showed that sickled cells are preferentially recognized by PMN cells and bind to them via multiple receptors. (11) This study was also able to demonstrate that sickled cells that are pre-incubated with autologous plasma triggered more avid binding to PMN cells but this did not occur with haemoglobin A cells, suggesting an amplification of binding due to interaction with immunoglobulins and or complement. This may contribute to the occlusion of the microvasculature by the sickled erythrocytes, causing infarction downstream from the point of occlusion. This is supported by Lachant et al., who observed that polymorphonuclear cells exhibit enhanced aggregation during crises in a group of SCA patients with pain as compared to those who were pain free. (12)

Leucocytosis and activated monocytes are also observed in patients with sickle cell anaemia, in the absence of diagnosed infection and vaso-occlusive crises. (13) Monocyte chemotaxis also has been shown to be induced by placenta growth factor (PlGF) as a contribution to the inflammatory process. (14) This has also been found to be related to the severity of the vaso-occlusive crises, with those having more than 3 VOC episodes per annum having higher levels of PlGF and the associated

inflammatory cytokines like VEGF, monocyte chemoattractant protein-1, Interleukin 1-beta and interleukin 8. Granulocyte colony stimulating factor, a cytokine that is released to stimulate leukocytosis in response to bacterial infections, has been found to be low in patients with SCA as compared to controls (splenectomized patients with hereditary spherocytosis and haemoglobin A subjects). (15) This generally suggests that the leukocytosis in patients with SCA is not due to bacterial infection. However, in that same study, though other markers of inflammation like interleukin-3 and macrophage colony stimulating factor were raised, only granulocyte macrophage colony stimulating factor (GM-CSF) was found to correlate positively with leukocytosis in patients with SCA .This suggests that leukocytosis in SCA is triggered by a non-bacterial cause, possibly by a chronic inflammatory state. This is supported by a study that showed elevated TNF-α, Interleukin 8 and prostaglandin E2 in patients with SCA. (16)

Hydroxyurea and its impact on sickle cell crises and longevity

Hydroxycarbamide (also known as hydroxyurea) has come to stay as an agent that reduces the frequency and severity of crises in patients with sickle cell anaemia. Known mechanisms of action include its anti-angiogenic and Haemoglobin F-inducing effects. (17) However, hydroxyurea has also been found to inhibit the production of leucocytes and also depletes white blood cells. This presumably may be one of the mechanisms through which it improves quality of life of sickle cell patients. Hydroxyurea has also been found to reduce TNF-α and increase an anti-inflammatory cytokine, Interleukin-10. (16)

Conclusion

Leucocytosis seen in SCA is more of an acute phase reactant and chronic inflammatory process than due to an infection process. Through a complex process via interactions with other cytokines, PMN contributes to occlusion of the microvasculature by the sickled red cells. Leucocytosis is now known to be a marker of severity in SCA and it carries a bad prognosis.

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INFECTIONS AND THE SICKLE CELL DISEASE

ALEBIOSU CO, OKUNOLA OO
AND OYEBISI OO

In sickle cell disease (SCD), infection is a significant contributor to morbidity and mortality since the sickle gene confers an increased susceptibility to infection, especially to certain bacterial pathogens, and at the same time infection provokes a cascade of SCD-specific pathophysiological changes. Globally, infections remain the leading cause of death, particularly in less developed nations. In developed countries, measures to prevent and effectively treat infection have made a substantial contribution to improvements in survival and quality of life, and are continually being developed. (1)

In this era of effective antibiotics and vaccines, there is a tendency to see infection as a minor and treatable problem. In SCD, although these measures have been a huge step forward in preventive care, infection remains a major cause of morbidity and mortality in the developed world and even more so in the developing world. A better understanding of the mechanisms behind the increased susceptibility to infection in these patients may enable interventions addressing the underlying cause.

Splenic dysfunction has a key role in the increased susceptibility to bacterial infections seen in children with sickle cell disease (2), and pneumococcal and haemophilus infections seem to be important, suggesting that penicillin prophylaxis and vaccinations, could lead to substantial improvement in survival among patients with sickle cell disease in lower-income countries, just as such interventions have done in high-income countries. (3)

Infection also contributes significantly to morbidity and mortality among patients with sickle cell disease, particularly as a cause of death in children (Streptococcus pneumoniae) and as a cause of diseases such as osteomyelitis (salmonella, Staphylococcus aureus, gram-negative bacilli, and Mycobacterium tuberculosis) and the acute chest syndrome

(chlamydia, mycoplasma, and viruses), regardless of age. (4) Although the spectrum of infections may vary across environments, the effect is greatly modified by the availability of facilities for prophylaxis and treatment, including access to antibiotics and safe blood transfusion.

Malaria is the other infection that is widely believed to contribute to excess mortality among patients with sickle cell disease in Africa. (5, 6)

The effect of sickle cell disease on infection

Impaired splenic function

In explaining the increased susceptibility to certain bacterial infections seen in SCD the spleen has a key role. Ordinarily, the organ has a phagocytic function, removing and also producing antibodies. Activation of B and T lymphocytes in follicles and periarteriolar lymphatic sheaths enables initiation and expansion. There is an accompanying slowing down of blood flow enabling splenic macrophages to remove defective RBCs and bacteria and to present antigen to lymphocytes. (7)

Opsonized bacteria are removed efficiently by macrophages in the spleen or liver. Many bacteria require opsonization (coating of the microbial surface by complement components (especially C3b, or other molecules) before being recognized and removed by macrophages. (8) The spleen synthesizes tuftsin, an immunostimulatory peptide, and properdin, which participates in complement activation. (9) Poorly opsonized bacteria are cleared effectively by the spleen. Such pathogens include encapsulated bacteria, especially Streptococcus pneumoniae (pneumococcus), Haemophilus influenza, Neisseria meningitidis, and salmonellae. Clearance of these bacteria requires anti-polysaccharide IgM antibodies, which facilitate phagocytosis either directly or via deposition of complement over the capsule itself. (10)

In SCD the sluggish circulation through the spleen, high rates of O^2 extraction, and local acidosis cause deoxygenation of HbS, promoting sickling, which leads to congestion and engorgement of the sinusoids with sickled cells – hyposplenism. This can cause diversion of blood via intrasplenic shunts, bypassing the normal filtering mechanisms.

Macrophage phagocytosis may become “blocked”, impairing their phagocytosis of other particles that are initially reversible by blood transfusion, bone marrow transplant, or hydroxyurea treatment. (9)

Multiple infarcts of spleen tissue result over time, the spleen becomes scarred and atrophied, resulting in “autosplenectomy”.

(11) In HbSS this situation develops between the ages of 6 months and 3 years. (9) Hyposplenic and asplenic individuals lack IgM memory B cells and cannot mount a rapid specific response to encapsulated organisms. Simple infections can readily become systemic and this, in combination with the loss of the spleen’s filtering function, can permit overwhelming sepsis to develop.

Septicaemia can develop rapidly resulting in shock, disseminated intravascular coagulation, adrenal haemorrhage, and mortality within 24 to 48 hours. (12)

Defects in complement activation

Patients are also predisposed to other infections, such as Escherichia coli urinary tract infection, Mycoplasma pneumoniae or Chlamydophila pneumoniae respiratory infections, and dental infections and cholecystitis caused by anaerobes, possibly due to complement system malfunction (classical or alternative system pathway). The complement system involves a large number of plasma proteins that are cleaved sequentially by protease enzymes to generate active fragments, which function as opsonins or chemoattractants – the terminal components can kill some pathogens directly by creating pores in their membranes. (8)

Inadequacies in micronutrients

Low levels of Zinc in SCD have been proposed as a contributory factor in defencelessness to disease since it is known to be imperative for immune function. Zinc insufficiency is related with lymphopenia, and is connected with decreased creation of interleukin (IL)-2, reduced natural killer (NK) cell lytic activity, and a reduced CD4:CD8 ratio. (13) Zinc insufficiency may be seen in 60–70% of SCD patients.

Mechanical factors

Sluggish circulation and increased haematopoiesis render bone vulnerable to vaso-occlusive episodes and infarction. Staphylococcus aureus is the main pathogen causing osteomyelitis in children not affected by SCD with necrotic bone acting as the foci for infection. (14) Salmonella is the most

common agent causing osteomyelitis in SCD, followed by S. aureus then Gram-negative enteric bacteria. (15) This might be due to increased gut permeability and biliary sludging (16, 17) of Edwardsiella tarda (an enterobacterium) in SCD. SCD also carries an increased risk of acute chest syndrome due to Mycoplasma, Chlamydia and other pathogens. SCD patients may be predisposed to certain iatrogenic infections also.

The effect of infection on sickle cell disease

Infection is one of the most common precipitants of crisis in SCD. Vaso-occlusive crisis is a complex process involving active interaction between adhesion molecules on the vascular endothelium, vascular cell adhesion molecule-1 (V-CAM1), and a5b3 integrin and both RBCs and leukocytes. RBCs attach via surface ligands including a4b1integrin, basal cell adhesion molecule (BCAM), phosphatidylserine, and sulfated glycans. (18) Leukocyte adhesion may be the initiating event in vaso-occlusive episodes, as microvascular occlusion occurs in post-capillary venules, rather than pre-capillary arterioles. Steady-state neutrophil count correlates with the severity of SCD, and treatment with hydroxyurea, which lowers neutrophil numbers, reduces the frequency of crises, painful episodes, and hospital admissions. (19)

These observations suggest a central role for leukocytes in the vaso-occlusive process. Narrowing of the vessel lumen by attached leukocytes may enable the accumulation of RBCs, platelets, and further leukocytes, with increasing occlusion. Local hypoxia in areas of poor flow promotes RBC sickling and propagation of the blockage, culminating in a crisis.

During infection, changes occur at a cellular level, which predisposes to crises. Levels of circulating leukocytes and inflammatory cytokines increase, with elevated expression of adhesion molecules on both the vascular endothelium and leukocytes themselves. This occurs locally in infected tissues and systemically. Neutrophils, basophils, and monocytes attracted to sites of inflammation produce cytotoxic proteins such as proteases, collagenase, and elastase and generate reactive O^2 radicals, which cause oxidative damage. This promotes further endothelial activation and cell adhesion. (20)

In addition, infections can have more non-specific effects on the host physiological milieu, which increase the risk of sickling. Fever with water loss due to sweating, anorexia, and nausea with reduced oral fluid intake, diarrhoea, and vomiting all contribute to dehydration. Renal impairment in

SCD causes poor urinary concentrating ability, so plasma osmolarity can rise, promoting RBC dehydration. The stress and emotional response, accompanied by neural and hormonal changes, may also play a role.

Miscellaneous

The relationship between SCD and malaria is interesting. The presence of HbS is related with a diminished parasitic intrusion of erythrocytes, impaired multiplication, and accelerated clearance of parasites by the spleen, as RBC infection produces intracellular hypoxia, provoking sickling and hence splenic filtration of parasitized cells. (21)

The spleen assumes an essential job in the control of malaria, expelling harmed and parasitized RBCs from the circulation, “pitting” tainted cells (evacuating parasites and returning the cells to the circulation intact), and creating explicit B and T cell reactions. Splenectomized people with P. falciparum have diminished clearance of parasitized RBCs, however, it is unclear whether they endure progressively serious malarial symptoms. (22)

Regarding the impact of coexistent of SCD and HIV infection, there is inadequate information of the impact. Whether the progression of HIV disease is attenuated by SCD, there is no proven scientific observation.

Table 1 Common pathogens associated with infection in sickle cell anaemia with underlying mechanisms for predisposition

Pathogen	Predisposing factors
Encapsulated bacteria (e.g., Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis, Salmonella spp.)	Impaired splenic function
Salmonellae	Impaired opsonization
	Recurrent vaso-occlusion with intestinal infarct, necrosis and increased gut permeability
	Decreased neutrophil killing
Malaria	Decreased deoxyhaemoglobin solubility
Parvovirus	Increased red cell turnover
Hepatitis B, C	Multiple blood transfusion
Chlamydophila	Unknown
Yersinia enterocolitica	Iron overload
Mycoplasma	Unknown
Edwardsiella tarda	Increased intestinal permeability and biliary sludging

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Clinical Features of Sickle Cell Disease in Children

Adegoke SA and Ologun BG

Clinical presentation of children with sickle cell disease (SCD) varies widely between and within patients and is influenced by sociodemographic, environmental, molecular and genetic factors. An acute intermittent painful episode remains the hallmark of sickle cell disease and the leading cause of hospital admissions. In addition to acute vaso-occlusive episodes, a significant number of adolescents also experience chronic pain. Severe anaemia commonly resulting from hyperhaemolytic crisis, acute chest syndrome and severe infections such as meningitis, pneumonia and sepsis are frequent causes of mortality.

Manifestations are pansystemic and may be associated with multiple organ dysfunctions. Stroke is a devastating, although a preventable complication of SCD, which may be seen even in very young children. It has a reported incidence of 0.61-0.76 events per 100 patient-years. In the first decade of life, about one-third of children with SCD, especially those with homozygous SCD may also develop at least one silent cerebral infarct. Cholelithiasis, retinopathy and chronic leg ulcers are relatively uncommon in children compared to adults. For the effective care of children with SCD, an individualized treatment approach is recommended because of the clinical pleotropism.

Sickle cell disease (SCD) exhibits phenotypic variability attributable to nature (several genetic, environmental or geographical modifiers) and nurture (sociodemographic and nutritional influences). (1) The spectrum of clinical manifestations therefore varies widely both between patients and even within the same individual at different times. The disease spectrum ranges from an asymptomatic or mild disease state to a persistent, severe or debilitating condition commonly associated with multiple organ dysfunction. (2) Children with severe disease need frequent hospitalization, while those with an asymptomatic or mild condition may never require this in their lifetime. The severity of the disease tends to be worse generally in patients with the homozygous state compared to those

with the heterozygous state. Clinical manifestation also differs with age. Infants less than six months old are rarely symptomatic as this can be explained by the relatively higher level of foetal haemoglobin.

The health status of patients with SCD alternates between steady clinical state and crises periods. Steady state is commonly defined as a period during which the patient has no acute event such as pain, fever or infection in the last four weeks and no transfusion in the previous four months. (3) Crisis is defined as the point of rapid deterioration from the apparently stable healthy state. This state poses a significant threat to patients and requires urgent attention.

For the purpose of simplicity, clinical features of SCD in infants and children are discussed under three subheadings: physical habitus, crises state and systemic complications.

Physical habitus

Typically, children with SCD have one or more characteristic physical features referred to as sickle cell habitus. These include:

1. Craniofacial alterations such as bossing of the skull, flattening of the nasal bridge and gnathopathy. These alterations occur due to hyperplasia and compensatory expansion of the bone marrow because of increased and continuous haemolysis, resulting in exaggerated growth or protrusion of the midface, expansion or protrusion of the maxilla and or retrusion of the mandible. (4) Bossing involves frontal, parietal or occipital portions of the skull. Occasionally, a child may have bossing of all the four quadrants of the skull, referred to as caput quadratum.
2. Long and thin extremities: Affected children have a reduced trunk-to-total-length ratio.
3. Shorter stature: Most children with SCD have growth failure, i.e. they tend to have reduced weight and height for age.
4. Protuberant abdomen due to enlarged abdominal organs – the spleen and liver.
5. Clinical jaundice and pallor.

Manifestation in early life

Neonates and young infants (aged 0–6 months) are usually asymptomatic. A small percentage may however present with neonatal jaundice or sepsis. Although some earlier studies observed that SCD may be more prone to nenonatal jaundice, the exact mechanism to explain this in the absence of known causes of jaundice in the newborn period is not clear. (5) Also, children in this age group may manifest with progressively worsening anaemia usually after the age of three months due to the replacement of foetal hemoglobin by sickle haemoglobin.

Manifestation in late infancy up to the age of 2 years

1. Dactylitis and or hand-foot syndrome.
2. Acute painful/vaso-occlusive crises.
3. Anaemic crisis.
4. Predisposition to infections.
5. Growth failure.

Manifestations in older children

Apart from dactylitis which is not common after the age of 2 years, clinical features of SCD in older children are similar to those of late infants and toddlers. The two main sickle cell crises are vaso-occlusive and anaemic crises, with the latter being subdivided into hyperhaemolytic, sequestration, aplastic and megaloblastic crises.

Manifestations in adolescents

In addition to the above manifestations, adolescents with SCD tend to present with a lot of psychosocial issues such as impairment in attention, memory, executive functions and sensori-motor skills. They may also have a reduction in intelligent quotient, lower academic performance, feelings of anxiety, self-hate and depressive symptoms including low self-esteem and feelings of hopelessness. (6)

Vaso-Occlusive Crisis

Acute vaso-occlusive crisis is the commonest clinical phenotype in children with SCD, affecting between 50 and 75% of patients in most studies. (7) Pain, the cardinal presentation of VOC, usually starts

manifesting from infancy as dactylitis or hand-foot syndrome, however as the child grows older, pains in the long bone predominate. Severity of VOC ranges from mild to severe pain episodes. Significant pains are defined as acute painful episodes requiring a hospital visit and treatment with analgesics. (3)

Dactylitis and or hand-foot syndrome: This is defined as painful non-pitting swelling of the hand/foot/digit. Figure 1 show a child with dactylitis. It is the first symptom in up to 33% of affected children in this age group, particularly in areas where severe disease is more prevalent such as the Central African Republic, West Africa and Jamaica. (7, 8) The syndrome results from vascular obstruction in the bone marrow of small distal bones. The presence of dactylitis in infancy means a three-fold increase in the risk of an adverse outcome and is predictive of patients that will run a turbulent course of illness when older. (9)

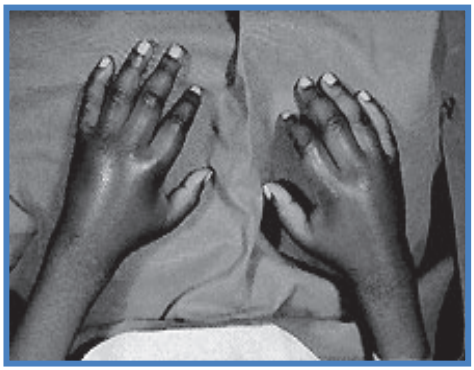

Fig. 1. Picture of a child with dactylitis (Photo courtesy of Prof. Maria Stella Figueiredo, UNIFESP, Brazil).

Bone pain episodes

Bone pains are usually diffuse and could involve different parts of the bone. Sickle cell pain is described as unremitting, burning, tingling, drilling, pounding, throbbing or aching discomfort that initially increases in intensity, plateaus and later remits. Some individuals may feel electric shocks, numbness or cutaneous pain that may be aggravated with slight skin pressure or cold temperatures. (10) An acute episode of pain may last for a few hours to a few weeks. In addition to the bones, pain could affect any other part of the body.

Chest pain: Chest pain can occur in isolation or may be associated with difficulty in breathing (dyspnoea), fever, cough, hypoxaemia and pulmonary infiltrate on chest radiograph, in a condition referred to as acute chest syndrome (ACS). It is associated with significant morbidity and mortality. ACS is a form of vaso-occlusion of the lungs and has been linked with lung infarction, infection and thromboembolic phenomenon. The reported prevalence of ACS varies with age (children of 2–4 years have the highest incidence of about 25.3 episodes/100 patient-years), season of the year and geographical locations. (11-13) Repeated events of ACS have been associated with chronic lung diseases such as pulmonary hypertension, chronic interstitial lung disease and abnormal lung function. This portends a poor prognosis. (14)

Abdominal pain: Mesenteric infarction is the leading cause of abdominal pain which can sometimes be confused with a surgical cause of acute abdomen. Abdominal pain may however be due to stretching of the liver or splenic capsules from the pooling of blood, splenic abscess, hepatitis, cholecystitis, gall stones, peritionitis and urinary tract infections.

Other parts of the body: In older children and adolescents, back pain, hip pain and headache are also common features.

Chronic pain: About 40% of children and adolescents with SCD regularly complain of chronic pain and up to one-third in this age group complain on a daily basis. (15) Table 1 summarizes pain expressions according to age group in children with sickle cell disease.

Table 1: Pain expression according to age of children with sickle cell disease

Age range	Pain phenotype
Infancy (0–23 months)	Dactylitis or hand-foot syndrome Minimal bone pain or acute intermittent mild to severe pain
Toddler (2–4 years)	Commonly experience acute, mild to severe intermittent pain
School age (5–12 years)	Patients continue to have acute, mild to severe intermittent pain
Adolescence (13–18 years)	Acute pain events increase in frequency, duration and severity. They begin to experience chronic pain (almost daily pain that occurs irrespective of an acute vaso-occlusive crisis)
Adulthood (≥19 years)	Daily chronic pain becomes the norm They also continue to have acute intermittent pain crises which superimpose on chronic pain

Assessment of pain episodes

Severity of pain is assessed with an age-dependent pain rating scale. For children younger than three years, the expressions on their faces, the positioning of the legs, activity, cry and consolability are used as seen in Table 2. The Wong-Baker Faces Pain Rating Scale (WB-PRS) is used for children aged three to five years. This scale consists of six cartoon faces showing a smiling face for "no pain" to a tearful face for the "worst pain". The Numerical Pain Rating Scale (N-PRS) is used for children older than five years who are able to count numbers and understand a number in relation to other numbers. On the scale, zero represents "no pain" while 10 denotes the "worst possible pain".

Table 2: The Face, Legs, Activity, Cry, Consolability (FLACC) pain rating scale for young children (≤2 years)

Categories/ Score	0	1	2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn or disinterested	Frequent-to-constant quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless or tense	Kicking or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid or jerking
Cry	No cry (awake or asleep)	Moans or whimpers; occasional complaints	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging or being talked to, distractible	Difficult to console or comfort

NB: Each category is scored from 0–2 resulting in a total score of 0–10; significant pain ≥4/ 10

Adapted from Voepel-Lewis T, Zanotti J, Dammeyer JA, et al. Reliability and validity of the face, legs, activity, cry, consolability behavioral tool in assessing acute pain in critically ill patients. Am J Crit Care. 2010;19:55–61.

Anaemic Crisis

Hyperhaemolytic crisis

Although children with SCD haemolyze chronically, the hyperhaemolytic state occurs when the red blood cells (RBCs) are broken down at a more rapid rate below their steady state haematocrit. Hyperhaemolysis is usually precipitated by infections such as malaria or sepsis, or seen in patients

with concomittant Glucose-6-Phosphate Dehydrogenase deficiency. The affected child manifests with worsening pallor and jaundice and features of cardiac decompensation (heart failure) such as significant tachypnoea, tachycardia, soft tender hepatomegaly and gallop rhythm. Although, a greater proportion of haemolysis takes place in the reticuloendothelial system, those with significant intravascular haemolysis present with haemoglobinuria which shows as the passage of dark-brown urine and may subsequently develop acute kidney injury. Laboratory evidence of haemolysis such as low haematocrit, hyperbilirubinaemia, reticulocytosis, haemoglobinuria, increased lactate dehydrogenase enzyme and a low serum level of haptoglobin may be present.

Sequestration crisis

It is a potentially life-threatening condition in which there is a sudden pooling of red blood cells into the spleen. This is characterized by sudden onset of anaemia with evidence of cardiovascular collapse. There is a sudden enlargement of the spleen with associated abdominal pain. The patient may also present with cold clammy extremities, restlessness, weak thready pulse, low or unrecordable blood pressure and severe pallor. Usually, there is no noticeable worsening jaundice. The characteristic history is that of an apparently well child in the morning, who becomes weaker as the day goes by and severely pale and restless at noon. Rarely, sequestration may occur in the liver. (16)

Aplastic crisis

This is characterized by a progressive weakness from the sudden cessation of erythropoiesis following vague upper respiratory tract infection. This has been associated with parvovirus B19 infections. The affected child presents with bleeding, a progressive drop in haematocrits (usually with no evidence of hyperhaemolysis); fever, leucopenia, thrombocytopenia and reticulocytopenia, the hallmark of the condition in the early phase. The disease is self-limiting and recovery occurs in 2 to 3 weeks.

Increased predisposition to infections

There is high incidence of bacterial infections in SCD particularly those with sickle cell anaemia. Pneumonia, urinary tract infections (UTI), osteomyelitis, meningitis and pneumococcal septicaemia occur mainly in younger patients. (17) The commonly implicated organisms are

encapsulated bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenza*, *Neisseria meningitides,* and *Salmonella spp. Others are Staphyloccus aureus* and *Mycoplasma*.

Functional hyposplenia or asplenia, defective opsonization, an impaired alternate pathway of the complement system, and impaired leucocyte function are established reasons for increased susceptibility to infection. Other reasons include multiple micro infarcts that serve as a nidus for bacterial organisms, low levels of immune boosting micronutrients such as zinc and elevated serum iron that enhance bacterial multiplication and elevated serum bilirubin which is a favourable medium for *Salmonella species* to thrive. (18, 19)

In the tropics, one of the major threats to patients with SCD is malaria parasite infestation. A previous hospital based study in a sub-Saharan African country showed that although the frequency of malaria infection in the Out-patient Department is similar between children with SCA and those without SCA, severity (associated morbidities and mortality) tended to be greater among patients with SCA. Therefore, protection against malaria in this group of patients is highly desirable. (20)

Complications in Different Organ Systems

Since SCD is pleiotropic, several other features in children manifest as complications in different organs/ systems of the body such as the central nervous system (CNS), musculoskeletal system (bones, joints, skin and muscles), eyes, the hepatobiliary system, lung, heart, and genito-urinary and immune systems.

Central Nervous System

The most important complication in the CNS is cerebrovascular accident (CVA) due mainly to ischaemia of the cerebral vessels. Common clinical presentations include severe headache, hemiplegia, slurred speech, seizure, altered sensorium, abnormal posturing, coma and transient ischaemic attack (TIA). In the paediatric age group, about 11% and 20% will have either overt or silent strokes respectively before the end of the second decade of life. The risk of overt stroke increases to 15% and 25% by the end of the third and fourth decades of life respectively, and between 3 and 17% of the affected children with stroke will experience recurrence. (21, 22) The peak age of stroke in children is between 2 and 9 years.

Children with overt stroke present functionally with focal neurologic deficit lasting more than 24 hours, and may have T2 weighted Magnetic Resonance Imaging (MRI) features of cerebral infarct. (22) In about 75% to 88% of cases, stroke is ischaemic in nature compared to the haemorrhagic type that is more commonly seen in adults. In silent cerebral infarct, the patient has a clinically silent area of hyperintensity on T2-weighted MRI, but with no feature of overt stroke, or neurological symptoms.

Risk factors for stroke in children with SCD include:

1. Low steady state haematocrit
2. Hyper leucocytosis
3. Elevated systolic blood pressure
4. Previous episode of stroke or transient ischaemic attack
5. Previous episodes of acute chest syndrome
6. Abnormally high cerebral blood flow velocities on non-imaging Transcranial Doppler ultrasonography (the timed averaged mean maximum velocity ≥200 cm/sec). The medium-sized arteries such as the middle cerebral, anterior cerebral and internal carotid arteries are usually affected.

Bone and Joint Manifestations

i. **Osteomyelitis:** Infection of the bone is common in children with SCD because of recurrent vaso-occlusion to the bone causing ischaemic necrosis. The commonest causative agent is staphylococcus aureus, but salmonella osteomyelitis is commoner than in the general population. It is commonly seen affecting the tibia, femur and humerus. Patients usually present with pain, swelling, fever and inability to use the affected part of the body. It may be difficult to differentiate osteomyelitis from VOC. Some predictors of osteomyelitis include prolonged pain and fever before presentation, swelling of the affected limbs, pain involving only one site, diaphyseal involvement and elevated leucocytes. (23) Radiograph shows periosteal reaction and bone destruction, culture of bone aspirate is diagnostic and blood culture is supportive.

ii. **Avascular necrosis:** It commonly affects the femoral head since it is supplied by the end artery and the joint is designed to bear heavy weight. It occurs in about 30% of patients by adulthood. The usual presentation is hip pain that worsens with walking and is often associated with impaired gait. Radiologic features range from a normal X-ray film in the early stage to the destruction of articular cartilage of the joint in the later stage. Another site of involvement is the humeral head which runs a milder course because of the absence of weight bearing.

Hepatobiliary manifestations

The hepatobiliary system has some peculiar complications in children because of chronic haemolysis and high serum bilirubin levels. Recurrent blood transfusions and direct intrahepatic sinusoidal and extrahepatic sickling also contribute to these manifestations. (24) They include hepatomegaly, elevated liver enzymes, hepatic sequestration, sickle cell hepatopathy, viral hepatitis, transfusion hemosiderosis and hepatic infarction.

Cholecystitis, cholestasis, cholelithiasis and choledocholithiasis are also seen in some patients. Frequency of cholelithiasis increases with age and varies in different geographical locations. (25) Sickle cell hepatopathy is a potentially fatal clinical condition in which intrahepatic sickling of RBC leads to cholestasis and may manifest with features of extrahepatic bile duct obstruction and thus may pose a diagnostic dilemma. (26)

Lung manifestations

Children with homozygous SCD have significantly lower lung function indices compared with matched haemoglobin AA controls. (27) Lung function test shows reduced lung values and diffusion capacity secondary to restrictive lung disease. Repeated episodes of vaso-occlusion, recurrent pneumonia, ACS, chronic anaemic state and pulmonary fat embolism have been linked to impaired lung function. (28) Children with SCD may develop chronic lung diseases such as pulmonary hypertension, chronic interstitial lung disease and abnormal lung function.

Pulmonary Hypertension

Pulmonary hypertension (PHT) occurs when the pulmonary wedge pressure is greater than 25 mmHg. It is a major risk for death in older children or adults with SCD. Its association with other haemolytic conditions suggests chronic haemolysis, and reduced nitric oxide availability which contributes to airway remodelling, thus resulting in pulmonary hypertension. The exact pathophysiologic mechanism of PHT in SCD is unknown, but has been linked to several factors including SCD-related vasculopathy, recurrent chest infection, chronic hypoxia and fat embolism. (29) Chronic hypoxia leads to irreversible remodelling of the blood vessels with consequent smooth muscle proliferation and fibrosis. (29) Other risks for PHT include recurrent pulmonary thromboembolism, increased blood viscosity and pulmonary scarring from repeated episodes of ACS.

Patients with mild PHT and those in the early stages are usually asymptomatic. Those with moderate and severe pulmonary hypertension present with chest pain, dyspnoea and hypoxaemia even at rest. PHT ultimately predisposes to impairment in exercise tolerance and right heart failure, pulmonary thromboembolism, systemic hypotension, cardiac arrhythmia and sudden death. (29)

Renal Manifestation

SCD has a significant effect on both the renal function and structure. Patients manifest a defect in urinary concentration and acidification, renal papillary necrosis, haematuria, proteinuria, nephrotic syndrome, and acute and chronic renal failure. Increased GFR has been ascribed to impaired renal concentrating ability from medullary hypotonicity. This can present as enuresis, polyuria and nocturia in younger children. Haematuria results from obstruction in the renal medulla vessel, papillary necrosis and the nut cracker phenomenon in which the left renal vein is compressed as it passes between the superior mesenteric artery and the abdominal aorta. This results in the development of chronic kidney disease. (30)

Priapism

Priapism is a persistent, usually painful, erection that lasts for more than four hours and occurs without sexual stimulation. This results from sickling and obstruction of venous drainage from the corpora cavernosa.

About 20% of patients between 5 and 20 years of age report having at least one episode of priapism. (31) The corpora cavernosa are rigid, but the glans penis is soft. It often starts at night or an early hour of the day in association with a full bladder.

Types of priapism: stuttering and refractory priapism

1. Stuttering priapism is characterized by multiple intermittent episodes of self-limiting penile erection over a time period.

2. Refractory priapism: the patient experiences prolonged priapism lasting beyond several hours. The refractory form is usually associated with cumulative damage and causes partial or complete impotence/erectile dysfunction.

Priapism may involve only the paired cavernosa body (bicorporal priapism). This has a better prognosis unlike when there is affectation of the corpus spongiosum which has a poor prognosis. (31)

Growth and development

Patients with SCD have a characteristic delay in physical and sexual development. Though they are usually delivered with normal anthropometry at birth, various studies have shown reduced mean height and weight when compared with age- and gender-matched haemoglobin AA controls. (32) This may manifest as failure to thrive from infancy and a progressive decrease in growth velocity up to adolescence. In addition, they exerience delay in bone maturation, and epiphysis fusion during puberty.

Delayed sexual maturation is also common in children with SCD. Females may present with delayed menarche, puberche and telarche, although this does not preclude pregnancy. Males have been shown to have a lower mean testicular volume and delayed genital pubic hair stages of development in comparison with the control. (33) Possible reasons for delayed growth and sexual development include chronic anaemia, low hormonal production especially growth hormone and deficiency of nutrients such as folate, zinc, 25-hydroxyvitamin D, selenium and retinol.

Leg ulcers

Although not frequently seen in young children, adolescents may develop leg ulcers. The pathogenesis of leg ulcers in SCD is not well understood but is most likely multifactorial, with local vasculopathy and chronic inflammation as the most important. (34) Ulcers are usually located in the peri-malleolar region, though the distal third of the leg, foot or digits may be affected. The lesion may be solitary or multiple and is often very painful.

Ocular manifestations

Ocular manifestations are not very common in children but severe and sudden blindness may occur if present. The emergence of proliferative sickle retinopathy is usually insidious with onset in the first decade of life. The condition remains asymptomatic until complications such as vitreous haemorrhage or retinal detachment occur typically between 20 and 30 years of age. These conditions are associated with irreversible blindness.

Assessment of the clinical severity of sickle cell disease in children

Several methods are available to determine the clinical severity of SCD in children. (1, 2, 35, 36) In many developing countries, where sophisticated facilities are limited, basic clinical and or haematological parameters are used in the assessment. (2) However in developed countries, several molecular or genetic markers and imaging results such as cranial magnetic resonance angiography and transcranial Doppler ultrasonographic findings are incorporated into the scoring system. (34) Rates of pain episodes, blood transfusion and hospital visits are common to most of the methods. Other parameters include the extent of liver and splenic enlargement, the level of steady state haematocrit and leucocytes, and the presence and severity of the lifetime cumulative incidence of SCD-related complication(s).

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SICKLE CELL DISEASE IN OLDER ADULTS

ADEKOMI DA

In past centuries, little is known about the lives of older adults affected with sickle cell disease (SCD). SCD is an inherited haemoglobin anomaly linked with recurrent painful episodes, progressive haemolytic anaemia, and progressive damage of many organs in the body. At the expiration of the 19th century, survival beyond the fourth decade for a patient with SCD was considered unusual and prompted case reports. However, in today's world, in countries with developed health care systems, more than 90% of newborns with SCD survive into adulthood. Nevertheless, their life expectancy is still shortened by more than two decades compared to the general population. With an increasing life expectancy, SCD has now evolved into a debilitating disorder with substantial morbidity resulting from progressive sickle cell vasculopathy and multi-organ damage. Limited data on the health care issues of older adults with SCD pose multiple socio-economic challenges to affected patients. In this chapter, implications of SCD on older adults are addressed and discussed.

Sickle cell disease is a severely advancing, debilitating and deleterious disease. In 1994, Platt and colleagues (1) observed and reported that the median age of survival of male patients with SS was 42 years, while for females, it was 48 years. Subsequently, the National Institute of Health (NIH) also reported that the median age for individuals with SS is now in the late 50s gradually approaching the early 60 years. Older subjects with SCD are much at risk of developing comorbid disorders that often occur in the general population at large.

The hallmark of SCD is haemolytic anaemia and pain. (2) Depending on the mode of inheritance of the disease, sickle cell disorder is sometimes expressed as sickle cell anaemia, sickle haemoglobin C disease, or sickle cell thalassaemia disease. (3-5) SCD is caused by a gene mutation that produces defective haemoglobin. (6-7) This genetic mutation may eventually cause damage to every organ-system in the body of affected

individuals. Patients with SCD may suffer from a lifelong disorder characterized by anaemic crises, haemolytic anaemia, infections, pulmonary disorders, recurrent and unpredictable episodes and incidences of pain, renal disturbances, and stroke, as well as numerous problems associated with organ dysfunction of varying severity leading to hospitalization. (8, 4) The pain experienced by SCD patients occurs from the lack of oxygen that arises when sickle-shaped red blood cells occlude the vascular structures. Fatigue, nausea, and tenderness of the joints are some of the signs and symptoms associated with the prodromal phase of a vaso-occlusive episode. The onset of pain may be gradual; however, it often occurs suddenly. (9-10) The peaks of the "throbbing" and "stabbing" pain experienced by the aged SCD adults do not subside until about the end of the fifth day after hospitalization. (9, 10, 11)

The death rate in adult individuals with SCD has greatly decreased due to advancement in modern medicine, early detection, and recent improvements in effective, comprehensive treatment. (12, 13) Advancement in clinical practices has positively affected the mortality rate of adult individuals with SCD. Advancement in the Doctor/Nurse care plan as well as the production and use of pharmacological agents such as the use of prophylactic penicillin to prevent pneumococcal infections, preoperative transfusions, multidisciplinary pain management, adrenergic agonist anti-androgen therapy for the treatment and prevention of priapism, and the use of angiotensin-converting enzymes to inhibit proteinuria and subsequently prevent renal disease is on the increase in reducing the mortality-rate of adult individuals with SCD. (12) Despite this development, many adults who are currently 45 years of age or older did not have the benefit of these recent advancements in medical management. In a 1995 report published by Charache and colleagues, it was shown that hydroxyurea is the first agent of use to prevent complications of sickle cell anaemia (e.g. acute chest syndrome, vaso-occlusion, and painful crises/episodes).

When a chronic illness like SCD has been diagnosed, managing symptoms and complications, and maintaining control over the course of the disease, while assisting the affected individual to achieve an acceptable quality of life, should be major foci of interventions from healthcare providers. (14, 15, 5) Interventions must support the coping strategies of individuals with SCD, who have reported that during a painful episode, diversion activities (e.g. praying), are beneficial. (16-18, 5) The body of literatures in several health care journals suggests that prayer and religious-belief in the supreme-being are cherished "healing and/or spirituality" practices within

the African American community. (19-21) The healthcare manager/providers must importantly acknowledge the gravity of religion and spirituality to adult subjects with SCD. (5)

Old age in the general population usually refers to the life expectancy of people beyond what is presumed to be the life expectancy of human beings. The specific definition of old age, however, varies greatly among countries, cultures, races, genders, habitats, sociologists and gero-psychiatrists. Thus there are official definitions, popular definitions, sub-group definitions, etc. Gerontologists define sub-group definitions in a number of ways. (22, 23) The sub-group definitions that seem to be in common use define young-old (65-74 years), middle- or older-old (75-84 years) and oldest old (≥85 years). (23)

Treating older patients could be challenging. Patient-physician communication barriers may occur. Assessment of patients' complaints is often difficult resulting in under- or overtreatment especially in patients who have irrational fears about therapeutic agents and/or cognitive changes. Providers may have difficulty in differentiating the signs and symptoms due to SCD from other comorbid conditions or side effects of medications to treat them. (24-26) Moreover, with aging, physiologic changes occur that influence the pharmacodynamics and pharmacokinetics aspects of therapeutic medications. (27)

With aging the fat-muscle ratio increases thus altering drug distribution, the gastrointestinal motility decreases causing longer transit time, the cardiac output and renal clearance decrease as well. In addition, protein binding of drugs decreases thus increasing drug availability and senescence in the central nervous system associated with decreased resilience and increased side effects of medications. (27)

Comorbidities in Older Adults with SCD

Acquired immune deficiency syndrome

Acquired immune deficiency syndrome may occur concomitantly in patients with SCD. (28-33) It is associated with several pain syndromes (34), but the types of pain syndromes that may arise when SCD and acquired immune deficiency syndrome coexist are not well characterized. At least in some patients, it appears that SCD may ameliorate the human immunodeficiency virus infection, due to host factors of which asplenia before infection may be one. (29)

Chronic pulmonary complications

These complications include asthma, chronic obstructive pulmonary disease (COPD), pulmonary restrictive (also known as fibrotic) lung disease, obstructive sleep apnoea and pulmonary hypertension. The hallmark of these pulmonary complications is the presence of hypoxia and/or hypoxaemia. Accordingly, this set of complications could be due to SCD itself or comorbidities due to factors associated with the environment and aging. This dual causality may explain why these complications in SCD are not exactly the same as those in the general population.

Asthma

Asthma is a chronic inflammatory disorder characterized by repeated attacks of airway obstruction and symptoms of increased airway responsiveness (35). It improves symptomatically in children and young adults but often it persists in adults and worsens with age. It is more rampant among children (approximately 20–70%) than adults (about 20–30%) and is more common in African Americans. (36) It is associated with increased morbidity and mortality in people with sickle cell anaemia. (37, 38) Its diagnosis is based on the clinical picture and spirometry showing decreased forced expiratory volume in one second (FEV1).

Chronic obstructive pulmonary disease (COPD)

Chronic obstructive pulmonary disease is a common lung disease with two main types: chronic bronchitis and emphysema. The former type is the one that usually complicates SCD. It is characterized by airflow limitation that is not fully reversible but is usually progressive and associated with an abnormal inflammatory response to noxious particles or gases. (39) It is diagnosed by post-bronchodilator spirometry showing a reduction in the ratio of FEV1/FVC (<0.70).

Chronic restrictive lung disease

Chronic restrictive (also known as fibrotic) lung disease is characterized by persistent reduction in total lung capacity (TLC) with or without interstitial lung disease accompanied by a reduction in forced vital capacity (FVC) and functional residual capacity, but little change in residual volume. It is diagnosed by spirometry showing FVC <80% of predicted value or total lung capacity (TLC) <90% of predicted value. (40)

Patients with a history of recurrent acute chest syndrome tend to have a lower TLC consistent with pulmonary fibrosis/restrictive disease similar to the restrictive lung disease in patients without SCD. (40)

Obstructive sleep apnoea

Obstructive sleep apnoea (OSA) is recurrent off (stopping) and on (restarting) breathing during sleep. It occurs when the muscles that support the soft tissues of the throat, such as the tongue and soft palate, temporarily relax and also when there is lymphoid proliferation. When these muscles relax, the airway is narrowed or closed, and breathing is momentarily cut off. Signs of OSA include snoring, morning headache, daytime sleepiness, etc. It is more common (about 4 times) in children with SS than in controls. Treatment includes a continuous positive airway pressure (CPAP) machine and surgery in severe cases. (41, 42)

Pulmonary hypertension

Pulmonary hypertension is increased blood pressure in the pulmonary vasculature (both the micro and macro vasculature). Clinical manifestations include dyspnoea, palpitations, chest and abdominal pain, syncope, cyanosis, oedema, fatigue and heart failure. Among these, pulmonary arterial hypertension (PAH) and pulmonary venous hypertension (PVH) are the most common and most important in SCD. The pathophysiology of PAH includes two mechanisms: vascular obstruction and intimal hyperplasia. The vasoconstriction is due to decreased nitric oxide bioavailability and increased production of vaso-constrictors such as endothelin. (43) Intimal hyperplasia is the result of the hypoxia response pathway. (44) Specifically, hypoxia induced factors α and β (HIF-α and HIF-β) translocate to the nucleus across the cell membrane. The α/β complex activates the transcription of genes that increase cell proliferation and inflammation thus causing intimal hyperplasia and vaso-occlusion. The PVH, on the other hand, is due to left ventricular failure. Pulmonary hypertension is technically defined by a mean pulmonary artery pressure (MPAP) ≥25 mmHg which can be determined by echocardiography. In order to determine whether it is PAH or PVH, however, depends on the mean pulmonary capillary wedge pressure which cannot be determined by echocardiography but requires right heart catheterization (RHC).

Treatment of pulmonary hypertension depends on its aetiology. Thus the treatment of PVH targets the management of left ventricular failure. Treatment of PAH includes the use of vasodilators. This worked in PAH in the general population but not in PAH in patients with SCD. For now, management of PAH in SCD includes blood transfusion and hydroxyurea. More studies and controlled trials are needed to determine the appropriate treatment of the PAH of SCD.

Fibromyalgia, rheumatoid arthritis and osteoarthritis

The signs and symptoms of these disorders overlap with those of SCD especially in the case of fibromyalgia. (45) The occurrence of fibromyalgia may be mistaken for sickle cell pain. Fibromyalgia pain is typically persistent, severe, and disabling and afflicts females approximately five times more often than males. (46, 47) In the United States, approximately 5 to 6 million individuals suffer from fibromyalgia. The characteristic patient is a woman of 20 to 45 years of age who has diffuse chronic pain and chronic fatigue syndrome. Physical examination reveals no abnormalities, except for scattered tender points that are painful on palpation. Traditionally, the pain is subdivided into localized and diffuse. Interestingly, fibromyalgia is not an inflammatory disease, and primary central sensitization is thought to be the pathophysiologic mechanism of pain. (48) In a retrospective study (45), a rheumatologist reviewed the charts of nine SCD affected patients and eleven in-patients with other forms of anaemia and assessed them for fibromyalgia. Eight of the nine patients with SCD fulfilled the classification criteria for fibromyalgia, compared to one of the eleven patients without SCD ($p < 0.001$). Except for this retrospective chart review, fibromyalgia has not been reported in association with SCD. Again, its occurrence may be mistaken for sickle cell pain. Those patients with intractable chronic VOC pain may suffer from chronic fibromyalgia with superimposed acute VOCs. Such a possible combination needs further explanation and study. Thorough history, physical exam and radiological studies could differentiate rheumatoid arthritis and osteoarthritis from sickle cell pain.

Gout

The increased purine turnover of accelerated erythropoiesis in SS causes increased production of uric acid (49) in amounts proportional to the severity of haemolysis. However, in most patients, increased production of uric acid is balanced by increased renal excretion. (50, 51) Consequently,

most patients with SCD have a normal or moderately elevated serum uric acid level. Reports of clinical gout are infrequent (52, 53) but usually involve the knees, wrists, and small finger joints rather than the big toe, as is typical of classical gout. (54) Gout may be underdiagnosed in a disease associated with recurrent joint pain and may be mistaken for the usual VOC of SCD. Hyperuricaemia alone is not sufficient to establish diagnosis, which requires the demonstration of uric acid crystals in joint fluid. (55, 56)

Viral hepatitis

The clinical, laboratory, and liver findings of patients with SS and viral hepatitis appear to be more complicated, more prolonged, and associated with significantly greater bilirubin levels than in control groups. (56, 57) Viral hepatitis occurs as frequently as in the general population. (58) Hepatitis C, and to a lesser extent hepatitis B, occur more often because of blood-product exposure. Improved blood-product testing has reduced the incidence of these infections, but they still occur. Patients with chronic hepatitis B or hepatitis C should be treated as any other patients. There has been some concern regarding the use of ribavirin because it may cause haemolytic anaemia. If a patient on ribavirin develops worsening anaemia, placing the patient on chronic transfusion would allow therapy to continue and would decrease sickle cell and anaemia symptoms. A recent article reported good results in treating patients with SCD for chronic hepatitis C. (59) Liver transplant is as successful in patients with SCD as in other patients needing allograft liver transplant. (60-63)

Autoimmune hepatitis

Autoimmune hepatitis has been reported in patients with SCD. (64-67) Associated features of autoimmune hepatitis include rashes, skin ulcers, and joint disease. The aetiology, natural course, and treatment of autoimmune hepatitis in SCD are unclear. If a patient has persistent liver symptoms and antibody titers to smooth muscles, a therapeutic trial of prednisone and azathioprine may be required. Referral to a hepatologist is important and crucial.

Solid tumours

Solid tumours have been reported in patients with SCD including SS and haemoglobin (Hb) SC disease. Reported cancers included alveolar cell

carcinoma (68), breast cancer (69-72), pheochromocytoma (73-75), renal medullary carcinoma (76, 77), testicular carcinoma, gastric cancer and poorly differentiated adenocarcinoma of unknown origin. (72) The age range of adult patients with solid tumours was 18–79 years with a mean age of 28.8 years. The mean age at death due to cancer, the survival rate and the cancer incidence rate are not well defined due to the relatively small number of patients reported. In one institution the estimated cancer incidence rate was 1.74 per 1000 patient years and the mortality rate was 1.04 per 1000 patient years. (72) Renal medullary carcinoma was reported more often in sickle cell trait than in SCD. (78-82) There is concern that long-term use of hydroxyurea may be associated with increased incidence of malignancy. Moreover, the use of allogeneic stem cell transplantation is on the increase and this also is a risk factor for the development of cancer. (83) To date however, there is no evidence that either of these therapeutic approaches is associated with malignancy.

Haematologic malignancy

Acute leukaemia, chronic leukaemia, Hodgkin and non-Hodgkin lymphoma have been reported in patients with SCD. (84-87) Haematologic malignancies tend to be more common in children than in adults with SCD with the exception of multiple myeloma. The combination of SCD and multiple myeloma is a bad combination. Both are characterized by hyper-viscosity, renal failure, bone involvement, and sepsis, due to suppressed immunity. (88-93) Unfortunately, the diagnosis of multiple myeloma may be missed initially since the presenting signs and symptom of multiple myeloma are often attributed to SCD.

Cataract

Cataract is progressive clouding of the lens of the eye resulting in blurred vision. It could be unilateral or bilateral. The word cataract is derived from the Latin *cataracta* meaning waterfall, cascade or white water. The simile indicates the difficulty to see clearly through waterfalls. Typically, cataract occurs in older patients (94) and hence, is often referred to as senile cataracts. Cataracts in SCD were first reported in 1976 in two patients while receiving sodium cyanate for treatment of SS (95). Ophthalmologic examination revealed bilateral posterior subcapsular cataracts in both patients. After discontinuation of cyanate therapy, the lens opacities regressed in one of the patients.

The first case of senile cataract was first reported in a 62-year-old man with SS. (96) His cataracts were also bilateral and posterior subcapsular. Cataract extraction from both eyes showed clear but thick, tenacious and mucoid aqueous humour unlike that seen in other senile cataracts without SCD. Like other ophthalmologic complications, cataracts seem to be more common in Hb SC disease than SS. (97)

Glaucoma

The glaucoma reported in SCD is mostly secondary glaucoma. (98-105) Causes of secondary glaucoma include medications, trauma, physical injury, inflammation or eye surgery. In SCD, glaucoma is most often associated with traumatic hyphaemas causing obstruction of the anterior chamber outflow tract. Less often, it may be associated with retinopathy. Glaucoma has been described in both SCD and sickle cell trait. In primary glaucoma the cause of obstruction of the aqueous humour flow is unknown. In older patients, the aqueous humour flow may be less efficient leading to glaucoma. Anecdotally octogenarians with SCD and glaucoma have been described (94) but it is not known if their glaucoma is primary or secondary.

Dental comorbidities

Caries are the most common dental comorbidity globally and in patients with SCD. Whether some of these complications are pathophysiologic manifestations of SCD or comorbidities in addition to SCD is controversial. (106, 107) Some authors indicate that poor oral hygiene maintenance may be the major cause of dental complications in SCD. Thus, it is imperative that dental follow-ups every 6 months should be emphasized for patients with SCD. Aseptic necrosis of teeth has been described in some patients. The hallmark of this complication is the presence of dental pain in the absence of any dental pathology. (108-110) Other forms of dental comorbidities in SCD are dental erosions, infarctions, hypodontia, malocclusions, pulp necrosis, abnormal trabecular spacing, and infection.

Deafness

Hearing loss or deafness has been well described in patients with SCD. It is usually sensori-neural in nature. It could be unilateral or bilateral with sudden or gradual onset. Possible aetiologies include infection especially

in children, tumours (neuroma or Schwannoma), labyrinthine haemorrhage or *labyrinthitis ossificans*. (111-114) Unlike the dental complications, three prospective, controlled, cross-sectional studies reported the effect of age on the prevalence of inner ear involvement. The first found mild sensory neural hearing loss (SNHL) in three of 80 (3.8%) Nigerian children with SS aged 4–15 years old. (115) In the second study, the SNHL occurred in seven of 52 (13.5%) Nigerian children with SS aged 6–19 years old. (116) The third study was of 167 Nigerian adults of 15–56 years of age with SS in whom the prevalence of SNHL was 66%. (117) Similarly, in a Brazilian prospective controlled study (118), the prevalence of SNHL in 28 adults with SS was 21.4% compared to 3.6% in control subjects ($p = 0.05$); moreover, the prevalence was greater among patients ≥25 years old than younger patients ($p < 0.05$).

In Guadeloupe (France), the prevalence of SNHL was 47.22% among patients with Hb SC disease and 43.5% among those with SS, and the majority of the patients had the Benin βs haplotype. (119) The prevalence in these countries is greater than that reported in the UK and the US. (120, 121) Moreover, in Nigeria, Brazil, and Guadeloupe (France), the prevalence of SNHL was relatively high in control groups, albeit lower than that among patients with SCD; in comparison, the prevalence of SNHL in the control group of the UK study was nil. These findings suggest that the tropics may be a predisposing factor for SNHL, possibly as a malarial effect in some countries. (121, 122) SNHL is bilateral in most patients with SCD; when it is unilateral, it is more frequent on the left side. It seems to be more common in males and in patients with Hb SC disease. (115, 117, 119-121, 123)

Tinnitus

Tinnitus is the perception of sound in one or both ears the source of which is not external. It is often described, among other things, as buzzing, ringing, humming, hissing, etc. It usually lasts for a relatively short period but it may recur on and off. In a few persons it may be prolonged. Tinnitus has been described in patients with SCD but always in the presence of deafness. (118, 120, 124)

Conclusion

The advent of newborn screening, antibiotic prophylaxis, better vaccines, safer blood transfusion, iron chelation and hydroxyurea has improved the

survival of patients with SCD. This improvement, however, introduced a third dimension of SCD, namely the older and elderly patients with SCD. There is concern that the improved survival may be offset by the comorbidities of the older patients in the general population. Thus it is important that providers become aware of these comorbidities and how to differentiate them from the complications of the disease so that appropriate therapies can be given.

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NEUROLOGIC MANIFESTATIONS OF SICKLE CELL DISEASE

ADEKOMI DA

Sickle cell disease is a blood-related disorder that alters the functional integrity of red blood cells. It is a haemoglobinopathy characterized by polymerization of haemoglobin, stiffening of erythrocyte, and vascular occlusion. These alterations can lead to microcirculation obstructions, tissue ischaemia, infarction, headache, neurocognitive impairment and acute stroke. In addition, chronic cerebral ischaemia and cerebral vascular anomalies are considered among the most disabling problems in sickle cell disease. Neurological manifestations of sickle cell disease include ischaemic stroke, haemorrhagic stroke, transient ischaemic attack, silent cerebral infarction, headache, occlusion of the Circle of Willis, and neuropathic pain. Early diagnosis and proper management of sickle cell disease require specialized neurological expertise.

Sickle cell anaemia and associated haemoglobinopathies are autosomal recessive haemoglobin disorder of the red blood cell. (1-3) This category of blood linked disorders includes sickle C disease, sickle cell disease (SCD) and sickle-β thalassaemia, and affected individuals (irrespective of gender) suffer damage to many vital organs (such as the organs in the central nervous system, the heart, the kidney, the lung, the spleen) by sickled erythrocytes, erythrocyte stiffening as well as occlusion of the vascular structure by the sickled erythrocytes. (4, 1, 3)

The pathophysiology is not completely understood, however, observations and reports have shown that the disease is associated with enhanced adhesiveness of red blood cells linked with heightened shear stress on the account of the anaemia initiating the damage of endothelial cells of the vascular systems including the cerebral arteries. This, in turn, triggers cascades of other deleterious processes such as aberrant vasomotor

regulation, exaggerated coagulation, inflammation, and oxidative injury of vascular walls. (5)

A crucial contributor to vascular occlusion may be the enhanced or heightened disposition of the sickle red cells to stick to the vascular endothelium. (6) When sickle-shaped red blood cells cleave to the vascular endothelium, blood flow is obturated thereby increasing the blood transit time in the capillary. Study has shown that an elevated level of cell adherence can trigger and increase vascular occlusion. (7) Some of the phenomenal causative factors of sickling include dehydration, hypoxia and metabolic acidosis. (8) Structurally deformed red blood cells hinder microcirculation, and cause localized necrosis of tissues.

In many life-threatening presentations associated with SCD, complications of the central nervous system ranging from silent cerebral infarcts, acute stroke, haemorrhagic stroke, and ischaemic stroke, acute and chronic headache, chronic cerebral ischaemia, neurocognitive deficits, hemiplegia, convulsion/seizure, coma/stupor and visual impairment/disturbances are some of the widespread clinical consequences of the disease. (9-12)

Epidemiological studies have shown that sickle cell disease is a leading public health concern affecting about 83% of the 330,000 live-births each year across the globe. Of the 20–25 million individuals living with sickle cell disease worldwide, about 12–15 million reside in Africa. (13) The disease is rampant in equatorial Africa and less frequently observed in Southern and Northern Africa. (14-15) The sickle cell gene is also discovered in countries and places such as India, Northern Greece, Turkey, Saudi Arabia, and Sicily. The sickle cell gene observed in Europe and Turkey is of a haplotype of the gene seen in African patients, whereas the gene in India and Saudi Arabia is a different and independent haplotype. In populations in which the statistical number of occurrences of the sickle cell gene's frequency is high, the carrier frequencies often range from 5 to 40%. (14, 16)

According to the National Institute of Health (NIH), the statistical prevalence of sickle cell disease in the United States is about 1 in 5000, mostly affecting Americans with sub-Saharan African origin. In the United States, approximately 1 in 500 black live-births have sickle cell anaemia.

Sickle cell disease persists as a public health challenge in African countries because of the lack of adequate national health coverage systems, inadequate or non-existing basic health-care facilities, low

population sensitization of the disease and its associated complications and poor access to proper diagnostic and screening procedures. (17) This poor access to appropriate healthcare explains the increased susceptibility and/or vulnerability of children affected with sickle cell disease to aggravated complications with resulting major neurological, psychological and socioeconomic outcomes for them and their families. (13, 17)

The disease continues to affect several million people worldwide. It is connected with life-threatening complications that have adverse effect(s) on the quality of life and survival of affected individuals. (18) In the past decades, the relative frequency of occurrence and the statistical prevalence of sickle cell disease in Africa have been on the increase. It is estimated that about 240,000 children are born with sickle cell disease per annum in sub-Saharan Africa and approximately "50–80% of these children die before the age of 5 years". (17, 13, 19) The numerical prevalence is highly multivariate across Africa countries. It is approximately 1–2% in Northern Africa and slightly less than 1% in Southern Africa. It is about 45% in Uganda, and 20–30% in Cameroon, Gabon, Ghana, Nigeria, and the Republic of Congo. (20-23)

The clinical hallmark of patients with sickle cell disease is extremely variable, with much variation in the clinical expression of the phenotype. Regrettably, complications of the central nervous system are frequently seen in sickle cell disease and the neurologic complications associated with sickle cell disease are linked to haemolysis and occlusion of the vascular systems. These neurologic complications are often evident as cerebral infarction, transient ischaemic attacks, intracranial haemorrhage, subsequent behavioural and cognitive deviations, and seizures and in some instances, aneurysms and arteriovenous anomalies are also seen in these patients. (1)

Neurological Manifestations Associated with Sickle Cell Disease

Headache

Headache is a frequent symptom in sickle cell disease. (24) It is unclear as to whether the headache is anaemia-related, stress-related, or a consequence of an as yet unknown factor that predisposes this population of patients to headache. (25) In the presence of poor cerebral vessel autoregulation seen in sickle cell disease patients, the cerebral vessels

vasodilate but do not increase the blood flow. (26) Such cerebral vasodilatation is known to cause headaches. In addition, abnormalities in the cerebral perfusion, as measured by perfusion magnetic resonance studies, have been shown to be correlated with several neurologic symptoms. Headaches are associated with the steady lower state of haemoglobin. (28)

Neuropathic Pain

Pain related to sickle cell disease is an unpredictable challenge; it could be due to the involvement of the nociceptive and neuropathic pathways. (29) Nociceptive pain is due to nociceptors sensory receptors activation by noxious stimuli. (30) Neuropathic pain is defined as persistent pain resulting from damage to the peripheral or central nervous system or abnormal communication within the nervous system. (31) Neuropathic pain is usually described as numbness, tingling, lancinating, spontaneous, shooting, needles sensation, hyperalgesia, and allodynia pain. (32) The finding of neuropathic pain in sickle cell disease patients is contrary to the common belief that this pain is only nociceptive, and this may have a profound impact on our understanding and treatment of sickle cell disease associated pain. Neuropathic pain in sickle cell disease could be the result of tissue damage after the vaso-occlusion of blood vessels of nerves. (16) The mechanisms of underlying neuropathic pain in sickle cell disease could be relevant to signalling mechanisms involving protein kinases. Some of these mechanisms may contribute to glial activation, pro-inflammatory or pro-nociceptive cytokines, chemokine receptors and transporters. (33, 34) Alterations in neuronal activity have also been observed in other chronic inflammatory linked with pain models presumably containing a neuropathic component such as SCD. (35, 36)

Haemorrhagic Stroke

Haemorrhagic stroke is an acute neurologic injury resulting from bleeding in the brain. Approximately 70–80% of all strokes are ischaemic and 20–30% are haemorrhagic in nature. There are two distinct types of haemorrhagic strokes: intra cerebral haemorrhage in the brain, and subarachnoid haemorrhage, that cause haemorrhage in the region between the brain and the meninges. Other causes of haemorrhagic stroke include aneurysms, medications such as aspirin or the anticoagulants. (37) The CT scan of the brain is the most important test used to confirm a brain haemorrhage. MRI scan can be done later for a better understanding of the

cause of the bleeding. Conventional angiography may be performed on affected patients to identify the aneurysms or the arteriovenous malformation, although CT and MRI are more often of use. (38) Haemorrhagic stroke in sickle cell disease could be associated with advanced sickle cell hepatopathy, where the coagulation profile is significantly impaired. (39)

Ischaemic Stroke

Stroke is described as a clinically severe neurological event or dysfunction. It occurs in 8 to 11% of children with SCD. (40) Frequent or typically presenting signs and symptoms include acute headache, aphasia or (dysphasia), cranial nerve palsy, hemiparesis, monoparesis, seizures, stupor, and coma. Stroke occurs as an isolated vascular event or as a sequence of other complications in SCD. (41) Ischaemic stroke is a common brain injury**.** The most common intracranial vessels affected are the distal internal carotid, proximal middle cerebral, and anterior cerebral arteries. The vasculopathy of these large vessels is most often associated with cortical infarction. (42) Sickle cell disease causes ischaemia of small vessels by erythrocyte sickling in microcirculation, but most clinical strokes are due to large vessel occlusions. The endothelial damage in large vessels is believed to promote a stenotic and obliterative process. When a vessel is stenosed, the thrombosis can occur by a similar mechanism as that known to occur in the microcirculation. (43) Several mechanisms predispose sickle cell disease patients to an increased risk of ischaemic stroke; these include sickling of large extracranial and intracranial vessels which occurs secondarily to fibrous intimal proliferation. (44) The large vessel, stenotic lesions can be identified by transcranial Doppler (TCD) ultrasound This technique is helpful in predicting patients that are at high risk of cerebral infarction, as in such patients, a program of exchange transfusion is beneficial. Prophylactic blood transfusion in sickle cell disease with abnormal TCD can reduce the incidence of stroke from 10% per year to less than 1% per year. (45)

Transient Ischaemic Attack

A transient ischaemic attack (TIA) is a focal neurologic deficit of acute onset lasting less than 24 hours (typically less than 1 hour), with no radiographic evidence of infarct. The 24-hour threshold to distinguish an overt stroke from a transient ischaemic attack has historical value. Cerebral infarcts also can be seen in individuals who have focal

neurological deficits that last less than 24 hours. (46) The absence of the focal neurological deficit on examination 24 hours after presentation does not mean that the patient has not had a cerebral infarct. (47) The TIA symptoms may be mimicked by other neurological disorders such as migraine, seizure, and global hypo perfusion that make the diagnosis sometimes difficult. There is often disagreement about TIA diagnosis, even among experienced neurologists. (48) In many instances, the primary cause of TIA is associated with an increase in the amount of cholesterol containing plaques in an artery or one of its branches that carry nutrients and oxygen to the central nervous system. Plaques can significantly impair the flow of blood in an artery and this could lead to the formation of a clot.

Silent Cerebral Infarction

Silent cerebral infarction (SCI) is a brain lesion that is presumably a result of vascular occlusion found incidentally by MRI or CT in otherwise healthy subjects or during autopsy. (49, 50) It is considered a precursor of symptomatic stroke and progressive brain damage (51) that may be associated with vascular dementia. (52) Patients who have suffered silent strokes usually experience numerous neuropsychological deficits and have marked impairment in many different aspects of cognitive performance. (53) Silent stroke is capable of altering the functional integrity of the central nervous system. It further subjects the affected individual to greater risk for both major stroke and transient ischaemic attack in the future. (54) The risk of silent stroke not only increases with age but could also affect relatively young adults. Women tend to be at higher risk for silent stroke, with current cigarette smoking and hypertension being amongst the susceptible factors. (55, 56) Identifying the basic cause of silent stroke is often made as incidental observations that are discovered as a result of clinical researches using various neuroimaging techniques. In SCD patients, silent strokes may be discovered by Magnetic Resonance Imaging (MRI) technique (57) and computerized axial tomography (CAT) scans. (58) The coarctation or narrowing of these vascular structures which is a risk factor for cerebral infarction is qualified by markedly higher blood flow velocity. (59) Silent infarcts were seen by MRI in about 17% of those with SCD. Patients with SCI are usually not managed as having had a stroke. (60)

Spontaneous Occlusion of the Arteries of the Circle of Willis (Moyamoya)

It is an uncommon cerebral vasculopathy, characterized by typical angiographic changes associated with subsequent clinical features. (61) In Moyamoya, with other chronic steno-occlusive cerebrovascular diseases; steno-occlusive changes in the main cerebral arteries and a decrease in the cerebral perfusion pressure, result in the development of a fine neurovascular network. (62) These collaterals are suggestive of stress associated with significantly higher continuous flow, including the assemblage of fragmented elastic lamina, thinned media in the wall of the vessel, and the presence of microaneurysms; these remarkable observations help to explain why some affected individuals are with haemorrhage. (63, 64) Other Moyamoya related vessels are collapsed, and their lumen thrombosis could cause ischaemic symptoms. (65) It is expected that treatment with chronic transfusion may also prevent new cerebral infarction in individuals with SCD who exhibit Moyamoya syndrome. (66) Moyamaya is found as a rare neurological complication in individuals with traits of sickle cell. Moyamoya is also more prevalent in SCD patients. (3) At the time of treatment, the neurological status prognosticates a long-term outcome, suggesting that early diagnosis and treatment are important to avoid irreversible neurological deficits. (67) Patients with a low stroke burden, or strokes limited to one hemisphere, may have a satisfactory long-term prognosis if further infarcts can be prevented. (68) The tendency of identifying the predictive factors for the development of Moyamoya in an at-risk population could lead to better outcomes for these patients through earlier diagnosis and treatment. (69, 70)

Brain Atrophy

The shrinking of the brain is referred to as brain atrophy. It is caused by loss of its neurons. Two types of brain atrophy can occur; generalized and focal. Generalized atrophy refers to neuron loss throughout the entire brain, and focal atrophy refers to neuron loss in a specific brain region. Normal aging causes generalized atrophy. (71) Brain atrophy has several aetiologies. Different mechanisms are involved including arterial occlusion, thrombosis, and embolism. (72) Cerebral infarction and atrophy could be a serious complication in SCD patients (73) caused secondary to occlusive vasculopathy developing in 5.5 to 17% of patients with SCD. (74, 75) Clinical manifestation in brain atrophy includes dementia,

seizures, loss of motor control, and difficulty with speaking, comprehension or reading. Dementia, which is marked by memory loss and an inability to perform daily activities, may be mild or severe and may worsen with increasing atrophy. Seizures can range from absence seizures to convulsive seizures. MRI is the procedure of choice for most brain disorders, as it creates images from multiple angles and provides a detailed view of many brain structures not visible by CT scan. There is no cure for cerebral atrophy. Once brain cells have been lost, the damage is permanent. Treatment for cerebral atrophy focuses on treating the symptoms and complications.

Brain Infection

Infection is a significant contributor to the relative incidence and ratio of deaths in SCD. The sickle gene confers an increased susceptibility to infection, especially to certain bacterial pathogens, and at the same time infection provokes a cascade of sickle cell disease-specific pathophysiological changes. (76) Splenic atrophy or functional hyposplenism which occurs in SCD also renders the patient with less immunity to infectious agents. (77) SCD heightens the probability of meningitis and brain infection secondary to viral or bacterial infections mainly the encapsulated bacterial organisms. (78, 68) Abscess is an accumulation of infectious material and offending microorganisms, and this can occur anywhere within the CNS. (79) Salmonella is frequently reported as causing brain abscess in SCD patients. (80) The majority of brain-related abscesses also occur in patients who are compromised by basic or fundamental medical conditions other than SCD such as patients who are placed on immunosuppressive therapy. (81, 82) In contrast, rhombocephalitis, a primary infection affecting the brain stem, is basically different since it is observed mainly in uncompromised adults. (83, 84) Brain abscess could be induced or stimulated by inflammation and collection of infected materials arising from local sources such as infections in the ear, dental, paranasal sinuses, mastoid air cells of the temporal bone. Brain abscess could be from remote sources such as the heart, kidney, lung, etc. Death occurs in about 10% of incidences and people do well about 70% of the time. There has been a large improvement since the 1960s due to an improved ability to image the head, better neurosurgery and better antibiotics. (85) Positive labelling in radionuclide imaging helps in differentiating abscess from tumor. (86, 87) In early phases the capsule will be difficult to visualize via conventional techniques, and often, double contrast CT is useful in defining the

encapsulation of abscess. (88) To a moderately sufficient extent, MRI features recognize pyogenic abscesses accurately. Usually "triple high dose" antibiotics intravenously for 2 weeks followed by four weeks of oral antibiotic therapy is recommended. Pyogenic intracranial abscess should be treated on an emergent basis. An abscess diameter of more than 2 cm needs surgical intervention and most of them show an excellent clinical and radiological response to single burr-hole aspiration. Craniotomy is required in selected cases and as a primary procedure in the cerebellar. (89) The long-term outcome is gratifying if prompt treatment is instituted in the appropriate time period. (90)

Neurocognitive Impairment

Observations from studies have shown a higher frequency of impairments on executive functions in children with SCD compared to the normal population. (91, 92) Among the executive functions, working memory deficits appear to be more prominent. (93, 94) Attention difficulties are commonly reported in children and adolescents with SCD, particularly sustained attention was suggested to be impaired in SCD affected children. (95, 96) The available literature on memory functions in SCD is relatively limited. (97) Sickle cell disease may impair intellectual activity; 25% of the SCD patients have a significant cognitive deficit. (98) An incidence of mild mental deficiency was increased by about 11-fold in a small sample of individuals with SCD with no clinical history of stroke. The full-scale intelligence quotient of these patients correlated with haematocrit. (99) Because SCD is a lifelong condition, age effects have also been examined. Cross-sectional studies have suggested that older children show greater neuropsychological impairment in reading achievement, spatial functioning, and sustained attention. (100, 101) Hypoxaemia was reported as a precipitating factor for vaso-occlusive events at the microcirculatory level (102) and for "silent" ischaemic cerebrovascular accident, which causes quite a number of neurocognitive deficits, such as learning problems, attention deficit and lack of executive functions, and short-term and long-term memory loss. (103) Several studies pointed out that SCD affected children have impaired cerebral blood flow autoregulation compared with age matched healthy subjects, independently from their haemolysis rate. (104) It was suggested that cognitive impairment in SCD affected children may be a function of chronic hypoxia on the central nervous system, most especially the brain. (105) Sickle cell disease children with overt strokes usually have neuropsychological complications that have been shown to relate to the location and size of the lesion in the

brain. However, other areas of dysfunction including learning deficits in reading and mathematics; have also been identified. (106) Lesion size in relation to intellectual functioning has been documented in children with silent infarcts. (107) Studies on neuropsychological complications in adults with SCD are limited, although cognitive impairment including dementia has been demonstrated, irrespective of normal or abnormal MRI results. (108) Evidence from SCD affected children shows that lesion size and related neuropsychological complications tend to increase with age (109) and could suggest similar problems in adults. In addition, frontal lobe abnormal blood flow has been shown in adult individuals with SCD. (110) This could indicate attention/concentration and executive function problems, and therefore should not be ignored by haematologists. (93)

Delirium

Delirium is an acute confusion state, characterized by psychological disorder of consciousness and modification in cognition that develop over a brief period. The disorder has a tendency to rise and fall during the day, and there are indications from the clinical histories and clinical examinations indicating that delirium is a direct outcome of systemic infection of the brain, chest, kidney, liver, and the side effect of fever medications, dehydration, cessation of drug or opioids, alcohol use, major surgery, epilepsy, and terminal illness. (111) Delirium is fairly common among hospitalized patients, with around 1 in 10 having a period of delirium. (112) It is more common among older people. (113) A comprehensive and detailed clinical history must be taken from the care giver of the affected individuals (114), and the following information should be specifically taken:

- history of alcohol use/abuse,
- full drug history including non-prescribed drugs,
- previous intellectual functional status,
- onset and course of confusion,
- previous episodes of acute or chronic confusion,
- sensory deficits associated with hearing, sight, and speech,
- symptoms suggestive of underlying cause,
- pre-admission and social circumstances.

In sickle cell disease it often exhibits tolerance to opioids due to repeated use of these agents. This results in the need for higher and higher doses of opioids to provide the same level of analgesia. (115) Clinical experience

and previous studies demonstrate that delirium susceptibility varies among individuals. (116)

Psychosis

Psychosis could be described as a symptom of neuropsychiatric disorder. (117) It is linked with experiencing false things and believing these experiences are real when they are not; in other words, losing contact with reality. This is classified into two broad forms:

a) Hallucinations – hearing, seeing or feeling things that are not there, and

b) Delusions – holding conventional beliefs not shared by other people.

Psychotic SCD patients could have silent infarction of brain tissue because of the pathophysiological processes the sickling red blood cells are undergoing. Isolated brain tissue in silent infarcts could indicate these aetiological factors associated with psychosis in SCD patients, and this often poses further treatment challenges in tackling this comorbidity. (118)

General Treatments for Neurological Complications Associated with Sickle Cell Disease

In SCD patients, both haematology and neurology specialists should be consulted in addition to the ICU team by the attending physician. If an acute ischaemic stroke is confirmed, exchange transfusion with Hb 10 g/dl, and % HbS <30% is recommended. Elevated intracranial pressure is considered an emergency in the setting of an acute change of neurological status, especially in stroke or infections such as meningitis. Antiepileptic medications may be used in the case of overt seizures or in non-convulsive status epilepticus which may occur in critically ill patients with hypoxia in sickle cell disease. (119-122) MRI/MRA should be carried out after exchange transfusion if not previously done. (123)

a. Red Blood Cell Transfusion

Red blood cell transfusions remain essential components of the medical management in SCD affected patients. Transfusions decrease the morbidity of acute complications, reduce the recurrence of sickle cell

disease associated complications, and prevent neurologic events in individuals with high-risk features. (124) As the indications for transfusion expand for this population, the incidence of RBC alloimmunization also increases. (125) Regular transfusions may be appropriate in this group if there is evidence of established or progressive cerebral-vasculopathy or other neurocognitive concerns. The time-course of treatment action in these cases should be decided by the clinicians responsible for the clinical care, taking into account individual circumstances and the diagnostic facilities available**.** Transfusions are often used to enhance the oxygen-carrying capacity of the blood and to decrease the concentration of cells with abnormal haemoglobin. (126)

b. **Hydroxyurea**

Hydroxyurea was first approved by the FDA in 1967 for the treatment of neoplastic diseases. In 1998, Hydroxyurea received a new indication, for the treatment of SCD. It was authorized for use in subjugating the relative frequencies of painful crises and the need for blood transfusion in adult SCD patients with re-occurring moderate to severe painful crises. (127) Hydroxyurea is the only modifying therapeutic agent approved for sickle cell disease.

c. **Aspirin**

Aspirin might prevent stroke, silent infarcts and cognitive impairment by mechanisms that include the reduction of inflammation and the antiplatelet effect. (128) The antithrombotic effect of aspirin results largely from irreversible inhibition of the cyclooxygenase-1 enzyme in platelets, leading to impaired platelet aggregation and activation. (129, 130) Aspirin therapy could reduce recurrent ischaemic events, but also could put the patient at risk of an intracranial haemorrhage. (131) Due to bleeding risk, aspirin is not recommended to be given within 24 hours of any thrombolytic therapy. (132) The International Stroke Trial (IST), a randomized trial, demonstrated that patients allocated to aspirin therapy had significantly fewer recurrent events measured 14 days later compared to the “avoid aspirin” group, with no significant increase in intracranial bleeds. (133) Aspirin is often empirically administered to children with idiopathic stroke, TIAs, recurrent strokes, and TIAs not previously treated with aspirin and who are not candidates for warfarin therapy. One risk of aspirin therapy is the possible development of Reye syndrome although

Roach et al. have treated three dozen children with aspirin without complications. (134-135)

Conclusion

Neurological complications and manifestations in SCD are diverse. A physician treating affected patients should be aware of the indicating neurological evidences. Early neurological consultation is required in order to avoid life-threatening complications. The physician, family and the affected patient should be educated on the available prophylactic measures for sickle cell patients. The future is promising with more agents which could work better than Hydroxyurea. Many studies are ongoing or planned to evaluate potential agents. Combination therapy may be more effective than single agents.

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SICKLE CELL DISEASE AND THE EYE

ISAWUMI MA AND HASSAN MB

Sickle cell disease is a generic terminology used for a group of disorders in which there is inheritance of the sickle B-globin gene (HbS) which results in abnormal haemoglobin production. It comprises homozygous sickle cell anaemia (HbSS), sickle cell haemoglobin C disease (HbSC), sickle cell thalassaemia (HbSThal), and other sickle cell traits which are uncommon e.g. Hb AC, Hb AS, and Homozygous C (CC).

There are other compound heterozygous conditions (rarer combinations of SD, SE, SO, and hereditary persistent foetal haemoglobin) which all have in common the inheritance of the sickle B-globin gene. (1)

Inheritance Disorders in Haemoglobinopathies

The mutant haemoglobinopathies (Hb) S, C or combinations are the most important ocular alleles of normal haemoglobin A. (1) At the molecular level, there is substitution of glutamic acid (as found in the normal chain) in the 6^{th} position of the Beta-polypeptide chain by other various amino acids depending on the genetic mutation e.g., valine substitutes glutamic acid in HbSS; in Hb C, lysine substitutes glutamic acid while in thalassaemia, there is a defect in the production of the entire globin chain which may affect the Alpha or Beta chains.

Homozygous SS disease gives the worst systemic pathology and mild ocular manifestations whereas the other heterozygous forms give the worst ocular manifestations and minimal systemic pathologies (refer to Chapter … for the systemic manifestations of SCD). (2)

This is a condition that is very prevalent in the black race all over the world especially in Central and West African sub-regions. (3)

Ocular manifestations of Sickle Cell Diseases can be divided into four broad categories namely ocular adnexae, anterior segment manifestations, posterior segment manifestations, and neuro-ophthalmological manifestations. (2, 4)

Ocular Adnexae (2, 4)

Ocular adnexae include eyelids, orbits and other facial structures surrounding the eye ball and its muscles. Common adnexae manifestations of SCD include the following.

1. Frontal bossing of the skull – prominence of the frontal bone,
2. Prominent malar bones, and
3. Protuberant teeth.
   All these are due to hyperplasia of the marrow in the fifth year of life which persists into adult life leading to the expansion of the marrow cavity in order to cope with the persistent anaemia from recurrent haemolysis.

Anterior Segment Manifestations

The anterior segment of the eye includes the conjunctiva; cornea; sclera; anterior chamber; iris and pupil; ciliary body and the zonular ligaments; the posterior chamber and the lens.

SCD can manifest in various forms in the anterior segment. The commonest manifestations include the following.

1. **Conjunctiva –** in homozygous SS disease, the commonest findings in the conjunctiva are multiple short comma-shaped capillary segments seemingly isolated from the vascular network; and jaundice.
2. **Iris –** features include circumscribed areas of ischaemic atrophy usually at the pupillary edge and extending to the collarette; and new vessel formation on the iris known as rubeosis iridis is also a common feature of SCD especially in the late stage of Proliferative Sickle Cell Retinopathy.

Posterior Segment Manifestations

The posterior segment of the eye extends from the anterior vitreous face all the way to the retina and optic disc and most of the pathology can be attributed directly or indirectly to vascular obstruction with attendant ischaemia. Most findings in the posterior segment can be grouped into Non-proliferative or Proliferative Sickle Cell retinopathy.

1. **Non-proliferative Sickle Cell retinopathy**

This includes both non-symptomatic and symptomatic lesions

a. Non-symptomatic lesions

i. Venous tortuosity – the first sickling retinopathy that was described and it occurs in 47% of SS and 32% of SC patients.

ii. Black sunbursts – this is an ophthalmolscopically observable pattern of melanin and haemosiderin deposits probably resulting from a reparative process as a result of a small blow-out type of preretinal, intraretinal or subretinal haemorrhage. Usually ovoid, 0.5 to 2 disc diameter and common at the equator with stellate or speculate borders.

iii. Refractile deposits – these are refractile, glistening, granular deposits that have been observed in 29% of SS and 36% of SC patients and they resemble cholesterol crystals.

iv. Silver wire arterioles – these are chalky white arterioles peripherally representing an area of arteriolar occlusions.

v. Salmon patch haemorrhage – a blow-out haemorrhage following arteriolar occlusion distal to the point of occlusion. They are initially red but as they undergo haemolysis they usually turn pink, then orange and later white.

vi. Retinal holes – usually located in equatorial or pre-equatorial areas. They are asymptomatic until causing complications like vitreous haemorrhage or retinal detachment.

b. Symptomatic Lesions

i. Central Retinal Artery Occlusion – this is a devastating complication of sickling and may result in permanent visual loss.

ii. Macular Arteriolar Occlusion – this can also result in severe visual impairment usually from tortuosity and micro aneurysm formation.

iii. Retinal Venous Occlusions – these may be central or branch though they are very rare.
iv. Choroidal Vascular Occlusion – this has also been observed though it is very rare due to an extensive anastomotic network in the choroid.
v. Angioid streaks – these are infrequent complications of sickling.

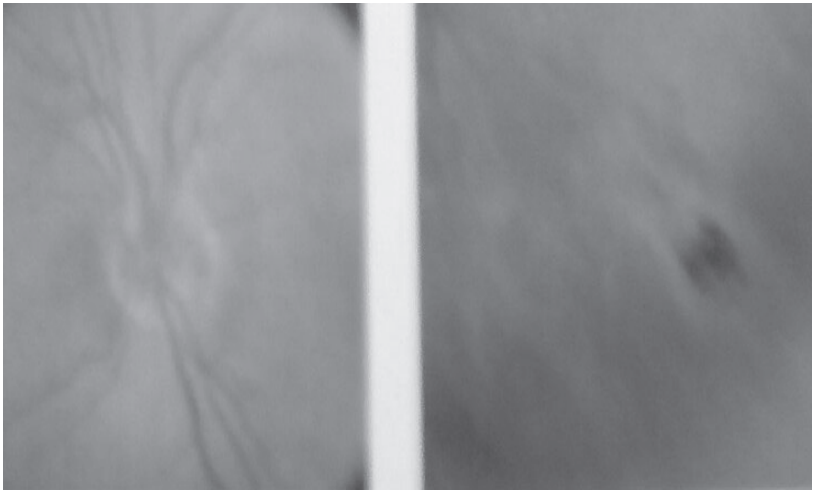
2. **Proliferative Sickle Cell Retinopathy**
This is characterized by actual vascular proliferation and is mainly seen in SC and S/Thal diseases. The underlying factor is retinal ischaemia from vascular occlusion which leads to the production of vascular endothelial growth factor (VEGF). This stimulates the production of new vessels in order to bypass the area of vascular obstruction. Through the use of Fluorescein angiography, this has been classified into five distinct stages namely – Goldberg staging (1):
I. Peripheral arteriolar occlusion;
II. Peripheral Arteriolar-Venular Anastomosis;
III. Neo-vascular proliferation;
IV. Vitreous Haemorrhage; and
V. Retinal Detachment.

Neuro-Ophthalmological Manifestations

These are symptomatology of SCD resulting from vascular occlusions involving the optic nerve, the intracranial visual pathway, the brain stem and the visual cortex. These manifestations include the following

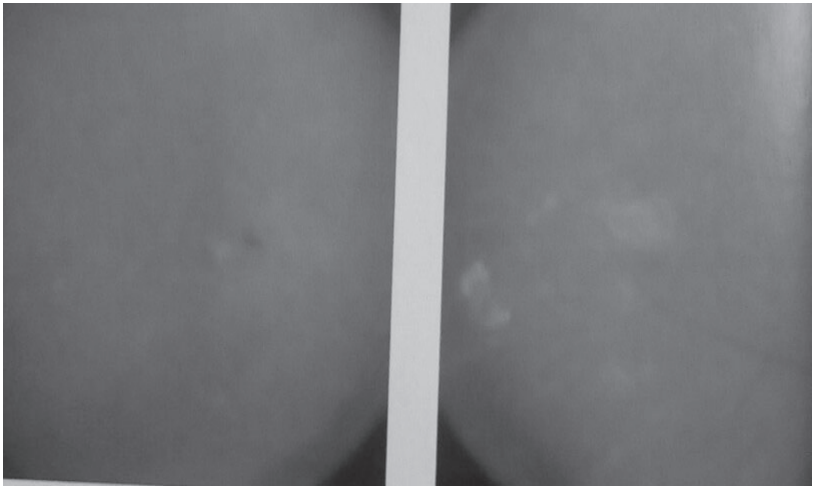
1) External Ophthalmoplegia;
2) Internal Ophthalmoplegia;
3) Optic Neuropathy;
4) Visual field defects;
5) Diplopia/Strabismus;
6) Gaze palsies;
7) Nystagmus;
8) Convergence and Accommodation paralysis; and
9) Cortical Blindness.

Figure 1 (3):



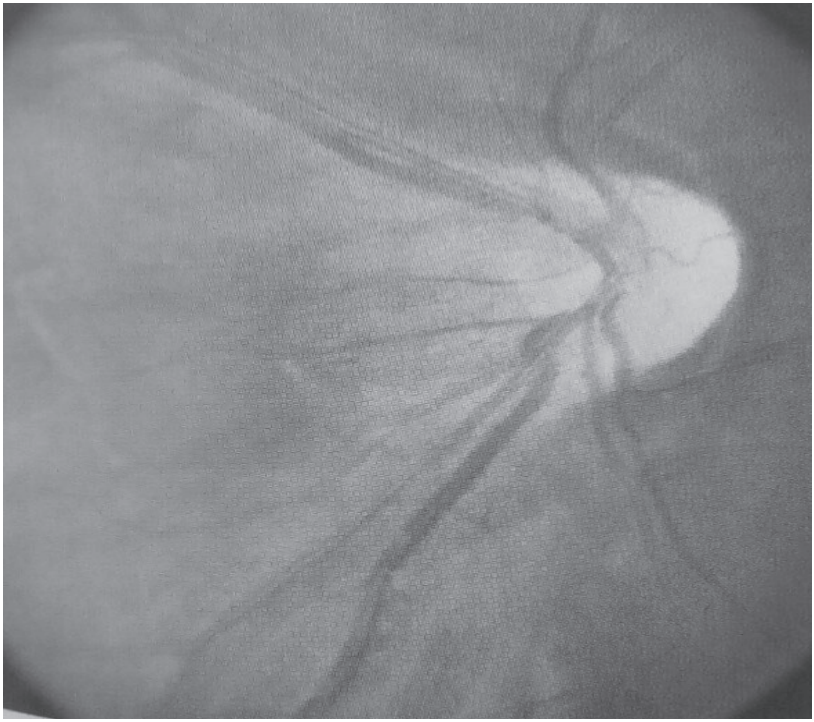
Vascular tortuosity (L) and Subretinal Haemorrhage in a Sickle Cell Thalassaemia Patient (R)

Figure 2 (3):



Arteriovenous Anastomosis (L) and Neovascularization (R) in Sickle Cell Thalassaemia Disease

Figure 3 (3):



Retinal Detachment in a Sickle Cell Disease patient – both tractional and rhaematogenous detachments coexisting

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PULMONARY COMPLICATIONS OF SICKLE CELL DISEASE

ODEYEMI AO. AND OJO OT

The lung is one of the major organs affected in sickle cell disease (SCD) and pulmonary complications of SCD are very common among these patients. They are a common cause of morbidity and mortality in this category of patient, being responsible for over 20% of mortality in these patients. (1, 2) These pulmonary complications are however often under-diagnosed by health care providers. Pulmonary complications of SCD can be acute or chronic.

Acute Pulmonary Complications of Sickle Cell Disease

Acute complications occur commonly among patients with SCD. They include asthma, thromboembolism and acute chest syndrome (ACS).

Acute Chest Syndrome

Acute chest syndrome (ACS) is defined as the appearance of a new pulmonary infiltrate on chest X-ray in a patient with SCD with the infiltrate involving a minimum of a whole lung segment and being consistent with alveolar consolidation rather than atelectasis in addition to one or more of the following clinical manifestations including cough, chest pain, fever, wheezing and hypoxaemia. (3, 4, 5)

15% to 43% of patients with SCD have been reported to develop ACS. (6, 7) ACS is the second most common cause of hospital admission among patients with SCD (8, 9) and it occurs in 10% to 20% of SCD patients admitted to hospital. (5, 10) Prior to the identification of pulmonary hypertension (PH), ACS was thought to be the most common cause of premature death among patients with SCD, being responsible for 25% of deaths in this category of patients in earlier studies. (1, 6, 9, 11, 12). Following the widespread use of hydroxyurea and more aggressive

transfusion therapy, the mortality associated with ACS has reduced. (10) More recently, mortality from ACS has been observed to be associated with underlying PH and acute cor pulmonale. (5) The risk factors for acute chest syndrome include lower haemoglobin F concentration, younger age, higher steady-state haemoglobin, higher steady-state white cell counts, history of asthma (in children) and cigarette smoking (active or environmental smoke exposure). (4, 5, 9, 13, 14, 15) Other factors associated with the development of ACS include avascular necrosis of the hips, previous pulmonary events, use of narcotics, major surgical procedures, pregnancy, acute anaemic events, and acute rib infarcts. (6, 16)

Aetiology of acute chest syndrome

There are three major causes of ACS including, fat embolism, pneumonia or systemic infection, and direct red blood cell intravascular sequestration leading to pulmonary infarction. (3, 5)

In adults and children with SCD, ACS is most commonly caused by pulmonary infection arising from a community-acquired pathogen, which induces an excessive inflammatory lung injury response. (5) Furthermore, over 80% of adult patients who have SCD give a history of hospitalization with "pneumonia" requiring intravenous antibiotics. (17) In the landmark multicenter acute chest syndrome study (MACSS) which reported findings from 671 episodes of ACS in 538 patients with SCD using rigorous techniques, infection was identified as the underlying cause in 54% of patients admitted for ACS. (5) The majority of the identified pathogens were atypical bacteria and viruses (Table 1). In less than 10% of the cases, community-acquired encapsulated bacteria were isolated despite the fact that normal phagocytic function of the spleen is rare in sickle cell disease.

Table 1: Infectious causes of acute chest syndrome

Causative agent	Number of cases (%)
Chlamydia pneumoniae	29%
Mycoplasma pneumoniae	20%
Legionella pneumophila	2%
Respiratory syncytial virus	10%
Parvovirus	4%
Rhinovirus	3%
Parainfluenza virus	2%

Influenza A virus	2%
Cytomegalovirus	2%
Epstein-Barr virus	1%
Herpes simplex virus	1%
Staphylococcus aureus	5%
Streptococcus pneumonia	4%

The second most common cause of ACS is fat emboli syndrome. The MACSS identified fat emboli syndrome in 16% of both adults and children with ACS. (5) This syndrome usually complicates a severe VOC pain crisis involving multiple bones, particularly the pelvis and femur, with resultant bone marrow oedema, infarction and necrosis. (3) As a consequence, the contents of the marrow including cells, fat, and bony spicules, are released to the bloodstream and they get trapped in the pulmonary circulation. This leads to the development of acute pulmonary hypertension, severe lung inflammation, and hypoxaemia. (18, 19, 20) The severe lung inflammation and lung injury are believed to be initiated by free fatty acids derived from bone marrow phospholipids from the effects of secretory phospholipase A2. (19) Patients with fat emboli syndrome may manifest a more severe course of ACS with systemic complications than those without fat emboli as evidenced by more extrathoracic pain, more neurological symptoms, a lower platelet count, and higher hepatic transaminase levels. (20) ACS can occur as a part of the spectrum of disorders in the systemic fat emboli syndrome. The systemic fat emboli syndrome should be suspected in patients who develop an abrupt onset of multiple organ failure, rapid development of acute respiratory distress syndrome, sharp increases in pulmonary arterial pressures, alterations in mental status, seizures, signs of hepatic injury, significant thrombocytopenia, and in rare cases, coagulopathy. (21, 22)

The third major aetiologic factor in ACS is direct pulmonary infarction resulting from pulmonary vascular obstruction which occurs as a result of sickling and endothelial adherence of erythrocytes. However, the actual prevalence of this mechanism is unknown. Rarely, wedge-shaped pulmonary infarction is seen and this is sometimes followed by central cavitation. (5, 23)

Clinical features of acute chest syndrome

In the majority of adult patients with sickle cell anaemia, ACS develops 24 to 72 hours following the onset of severe pains in the chest, arms or legs.

ACS is however often preceded by febrile episodes in children with SCD. Generally, patients with ACS present with fever (80%), cough (74%), chest pain (57%), dyspnoea (28%), wheezing (11%), and haemoptysis (2%). (16) These features are accompanied by hypoxia, leukocytosis, and infiltrates on chest X-ray which usually progress to multilobar pulmonary involvement that tends to be difficult to distinguish from acute respiratory distress syndrome.

Investigations

ACS is related with pronounced systemic inflammation, as evidenced by a mean peak temperature of 38.9°C and a mean white cell count of 23,000 cells/μL^3. (5) Acute presentation of ACS is usually associated with a reduction in haemoglobin levels (mean drop of 0.78 g/dL from steady-state levels) and an elevation in markers of haemolysis. A low platelet count can also occur, and a platelet count of less than 200,000 cells/μL is believed to be a marker of the severity of ACS following its association with a high risk of neurologic complications and mechanical ventilation. (5) Secretory phospholipase A2 levels are raised early in the course of ACS, even prior to the occurrence of radiographic changes, and have been used as a predictor of the onset of the syndrome. (24) Pulmonary fat embolization syndrome is diagnosed by the identification of oil-red O–positive lipid accumulations within alveolar macrophages present in samples obtained either by bronchoscopy and bronchoalveolar lavage or by sputum induction. (5, 20)

Treatment of Acute Chest Syndrome

Since the risk factors and triggers for ACS are well documented, clinical surveillance plus aggressive and early therapy for this patient group can improve their prognosis. This can be achieved by close monitoring of patients with SCD in the postoperative state, those with vaso-occlusive crisis and those with a febrile illness.

General measures

Patients with Sickle cell disease admitted for painful crisis should be thought of as being in the prodromal phase of ACS. Prophylactic strategies like close monitoring of pulmonary function particularly the PO_2/FIO_2 ratio, careful hydration, optimal pain control, and incentive spirometry are important aspects in the care of these patients. There should be a low

threshold for requesting a chest radiograph and arterial blood gas analysis. Pulmonary oedema and worsening respiratory distress can result from overzealous hydration and should therefore be avoided. (25) Analgesics should be used judiciously to relieve bone pain and splinting in order to prevent lung atelectasis. Incentive spirometry should be used routinely as it has been shown to reduce chest wall splinting, with consequent atelectasis and alveolar hypoxia. (23) Although some researchers recommend the routine use of bronchodilators, it should only be given to patients when airflow obstruction is present. (5)

Oxygen therapy

Oxygen therapy should be given to correct hypoxia as failure of this may lead to multiple organ failure. (25) The aim of this should be to achieve a sustained arterial haemoglobin oxygen saturation greater than 92%. The correlation of SPO2 with arterial oxygen tension in patients with SCD may sometimes be poor; hence ABG confirmation should be done in hypoxic patients. (26, 27, 28)

Antibiotics

Broad spectrum antibiotics to provide coverage for typical and atypical respiratory pathogens should be administered. This should include a macrolide or a respiratory fluoroquinolone. (29) Consideration should also be given to the seasonal and regional risk of methicillin-resistant *Staphylococcus aureus* and influenza A or B and therapy should therefore be tailored accordingly. The use of Haemophilus influenzae vaccine and penicillin prophylaxis has reduced the incidence of bacterial infection significantly in patients with SCD and should therefore be given routinely to all patients with SCD.

Bronchoscopy

It may be necessary to consider bronchoscopy in patients who fail to respond to initial therapy. It is used for airway clearance because it aids the removal of thick and tenacious airway secretions usually found in patients with ACS in addition to the fact that it also helps in making a more accurate diagnosis of the episode. (5, 29, 30)

Blood transfusion

Simple packed red blood cell and exchange blood transfusion may be beneficial by reducing the fraction of sickle haemoglobin and also by enhancing the oxygen carrying capacity of the blood. Both simple and exchange blood transfusions have been observed to result in a similar improvement in oxygenation in patients with ACS. (5, 25, 31) Blood transfusion is indicated in individuals with severe disease, persistent or worsening hypoxaemia, multilobar involvement, neurological complications, multiple organ failure, or those with a history of cardiac disease. (5, 6, 16, 32) Simple packed red blood cell transfusion is as effective as exchange blood transfusion. (33) In order to avoid an unwanted increase in blood viscosity, simple transfusion should be reserved for patients with haemoglobin values below 10 g/dl. The aim should be to maintain haemoglobin levels at 10 to 11 g/dl. However, in those with severe or rapidly progressive illness, exchange blood transfusion is indicated. (34) In severe episodes of ACS, the response to transfusion therapy may be inadequate and support with mechanical ventilation or extracorporeal membrane oxygenation may be required. (32, 35) Chronic blood transfusion has been shown in a randomized controlled trial to be efficacious in the prevention of future episodes of ACS. (36)

Corticosteroids

In children with ACS, the need for blood transfusion and the length of hospital stay have been shown to be reduced by a short course of corticosteroids. (37) However, in patients with vaso-occlusive pain crisis, its use is associated with more rebound attacks. (38)

Nitric oxide

Use of inhaled nitric oxide (NO) therapy for patients with SCD presenting in VOC has been explored in a relatively large placebo-controlled trial. Although there were initial positive results (39, 40), there was no effect of inhaled NO therapy on pain crisis duration, narcotic use, pain scores, or the development of ACS. (10)

Hydroxyurea

In adult patients with a history of ACS, hydroxyurea should be prescribed as this has been demonstrated to be associated with a reduction in the risk

of developing ACS by about 50%. (41, 42). Hydroxyurea helps to reduce sickling by increasing the level of haemoglobin F and thereby decreasing the relative concentration of haemoglobin S in the red blood cells. (32) Hence, hydroxyurea should be considered in patients with a history of recurrent episodes of ACS.

Asthma

Asthma has been observed to be a common comorbid condition in patients with sickle cell disease. However, it is not clear whether asthma as seen in patients with SCD is purely related to genetic and environmental factors as occurs in the general population or whether it is a consequence of the background haemolytic and inflammatory state. This will have to be elucidated by further research. Asthma has however been found to be associated with increased episodes of ACS and VOC. It is also said to be associated with increased mortality in patients with SCD.

Venous Thromboembolism

Sickle cell disease patients appear to be at increased risk for venous thromboembolism. (12, 16, 43) This is based on evidence from autopsy and the natural history of the disease. This observation has been ascribed to a presumed hypercoagulable state. (44, 45, 46) Several mechanisms have been postulated to explain this hypercoagulable state including deficiency of proteins S and C, elevated levels of Factor VIII and tissue factor, fibronectin and thrombospondin elevation, platelet reactivity, and hydroxyl radical formation. (47, 48, 49, 50, 51) Large-scale epidemiological studies assessing the incidence of thromboembolism are not available in patients with SCD. Pulmonary thromboembolism may be a contributory factor to both ACS and sickle cell chronic lung disease. (46, 52)

Chronic Pulmonary Complications of Sickle Cell Disease

Chronic pulmonary complications of SCD are major contributors to early mortality because of the unavailability of specific treatment for the complications. Chronic pulmonary complications of SCD include: pulmonary hypertension, sickle cell chronic lung disease and sleep-disordered breathing. (53)

Pulmonary Hypertension

Pulmonary hypertension is increasingly recognized as a complication of sickle cell anaemia. About 40% of patients with sickle cell disease have moderate to severe pulmonary hypertension. Sickle cell patients with pulmonary hypertension have a significantly increased mortality rate compared with sickle cell patients without pulmonary hypertension. (53) The prevalence of pulmonary hypertension was suggested to be between 30% and 56% in retrospective studies. (54-58) Another recent prospective study based on echocardiograms in 154 patients with SCD, however, revealed a prevalence of severe pulmonary hypertension to be approximately 27%. (59)

Aetiopathogenesis

The aetiology of secondary pulmonary hypertension in individuals with sickle cell disease is likely multifactorial, caused by chronic hypoxaemia, *in situ* thrombosis, and parenchymal and vascular injury due to sequestration of sickle erythrocytes, fat embolization, and infection. (44, 45)

Patients suffer from chronic haemolysis which causes an increase in cell-free Hb, and leads to increased consumption and resistance to the activity of Nitric Oxide (NO), which subsequently leads to poor vasodilation. (46) The higher prevalence of pulmonary vasculopathy observed with this disorder suggests that there may be a distinct syndrome of haemolysis-associated secondary pulmonary hypertension. (60)

Chronic Thromboembolic Pulmonary Hypertension

Venous thromboembolism is a common complication of SCD and this can also lead to chronic thromboembolic pulmonary hypertension (CTEPH) in some patients. About 5% of SCD patients with chronic thromboembolic pulmonary hypertension diagnosed with right heart catheterization were said to have history of pulmonary embolism at the National Institute of Health (NIH); however, a frank diagnosis of chronic thromboembolic PH is rare. (61, 62) This diagnosis should be considered in all patients with SCD and significant PH, particularly in younger patients or those without other typical risk factors (such as severe haemolytic anaemia or renal failure).

Clinical features

The early stage of pulmonary hypertension tends to be asymptomatic. Patients with moderate to severe pulmonary hypertension experience chest pain, dyspnoea, and hypoxaemia at rest. With progression of the disease, there is risk of right heart failure and sudden death from pulmonary thromboembolism, systemic hypotension, and cardiac arrhythmia. (22)

Treatment

Appropriate therapies and strategies for prevention of pulmonary hypertension in sickle cell anaemia are unknown. Therapies such as oxygen, nitric oxide, prostacyclin, l-arginine supplementation, chronic transfusion, and hydroxyurea are indicated in the pulmonary hypertension from SCD. (22, 41, 63) Hydroxyurea as a therapy for sickle cell anaemia is given with the goal of increasing the foetal haemoglobin levels to 20–30% of total haemoglobin. Patients with sickle cell anaemia should be screened for pulmonary hypertension and an attempt should be made to identify reversible causes such as hypoxaemia, thromboembolism, and asthma. Chronic anticoagulation therapy is recommended in SCD with pulmonary hypertension unless a contraindication is present. Successful thromboembolectomy in patients with SCD has been described. (64) Cautious use of diuretics and cardiac glycosides may be helpful in relieving symptoms in patients with right heart failure. (65, 66)

Sickle Cell Chronic Lung Disease

Patients who have a history of multiple episodes of ACS are at risk for developing lung fibrosis, particularly at the lung bases. The exact incidence, prevalence, natural history, and methods of diagnosis of sickle cell chronic lung disease (SCCLD) have not been established due to the lack of detailed epidemiological studies. It is suggested that SCCLD has a prevalence of approximately 4% in patients with SCD. (67, 68) SCCLD is presumably related to recurring episodes of infarction and infection and is characterized by a decrease in radiolucency of the lungs, moderate to severe impairment of pulmonary function, and in its most severe form by evidence of pulmonary hypertension. (54, 69)

Radiographic abnormalities

Significant radiographic interstitial lung disease has been seen in patients with SCD. (68, 69) A significant percentage of SCD patients who have had at least one prior episode of ACS tend to have significant multifocal interstitial lung abnormalities on thin section computed tomography scans of the chest. (69) There is also a correlation between the severity and extent of interstitial abnormalities on computed tomography and the number of prior episodes of ACS. (69)

Pulmonary function abnormalities

Pulmonary function abnormalities in SCD are frequent and characterized by airway obstruction, restrictive lung disease, abnormal diffusion capacity, and hypoxaemia. (55, 70, 71) However, a restrictive airway abnormality is typically seen in patients with SCCLD.

Sleep Disordered Breathing

A rising body of evidence has shown that sleep-disordered breathing, particularly, obstructive sleep apnoea syndrome (OSAS) occurs at a rate in patients with SCD, and that there is significant overlap in the underlying pathophysiology of these two conditions. Through a variety of mechanisms including nocturnal hypoxaemia and increased oxidative stress, production of pro-inflammatory cytokines and endothelial dysfunction, sickle cell anaemia and sleep-disordered breathing potentiate each other's clinical effects and end-organ complications. (72). OSAS is a treatable condition with adverse health outcomes, and greater efforts are needed to screen, diagnose, and treat OSAS in this high-risk, vulnerable population. (73)

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Sickle Cell Disease and the Cardiovascular System

Akinwusi PO, Oni OO, Adebayo RA, Akintunde AA and Balogun MO

The cardiovascular manifestations of sickle cell disease (SCD) are an important feature of the disease. Anaemias including SCD are known to induce a hyperdynamic physiologic state with increase in stroke volume, heart rate and cardiac chambers dilation. The heart is largely involved in SCD, and cardiac signs and symptoms were prominent in many of the early cases of SCD described.(1-5).

Coronary artery disease and systemic hypertension are no more common in SCD than the general population. Haemolysis-induced vasculopathy has been linked to the development of pulmonary hypertension.(3) SCD has been associated with cardiomyopathy and cardiac dysfunction.(4-8)Intrinsic myocardial injury, anaemia and haemolysis-induced vasculopathy have been considered as the major pathophysiologic mechanisms in sickle cell related heart disease.(2) The magnitude of the SCD problem is increasing rapidly in Nigeria, where it is the most common symptomatic haemoglobinopathy. (11) This chapter therefore discusses the cardiovascular problems and investigational peculiarities of people with SCA.

Chronic anaemias including SCD and changes in the cardiovascular system. The World Health Organization (WHO) defined Anaemia, as haemoglobin (Hb) concentration less than 13g/dl and 12g/dl for men and women respectively.(9) Klinefelter produced the first systemic review of the cardiovascular findings in SCD. The cardiac changes seen in SCD were more marked than those in other chronic anaemias due to the long duration of the severe anaemia.(10) Chronic anaemia and SCD are known to affect the heart, and are associated with cardiac dilatation and

hypertrophy.(11-13) Anaemia not only compromises the oxygen carrying capacity but may also cause a reduction of the viscosity of blood. This compromise increases demand on the heart with an increase in cardiac output. (18)

Increase in stroke volume is the major cause of the elevated cardiac output seen in SCD with the attendant clinical findings of hyperdynamic circulation, heart murmurs and cardiomegaly.(14,15) This stroke volume increase in chronic anaemia is in contrast to acute anaemias, where an increase in heart rate is the predominant cause of increased cardiac output. Also, other causes of chronic anaemia do not cause as much of an increase in cardiac output, as sickle cell anaemia, where both stroke volume and heart rate are significantly increased as compared with controls at rest (16). A study of adolescents and adults with SCD showed a predominant increase in stroke volume with essentially similar heart rates to controls in people with SCD.(17) In other studies of adults with SCD, the resting heart rate was significantly increased as compared to Haemoglobin A (HbA) controls, though the rate was still within normal limits.(6,18) Alteration of both preload and afterload occurs in SCD.(19) Cardiac dilatation increases preload and decreased peripheral resistance reduces afterload. In severe anaemia, cardiac output and stroke volume increase because of both cardiac dilatation and decreased peripheral vascular resistance.(12,13)

Anaemia has been shown to be associated with structural changes in the right ventricle (RV), specifically dilatation and increased mass. In SCD, there seem to be some peculiarities that may not be accounted for just by the anaemia. For instance, in an SCD-Thalassaemia study, SCD was shown to be associated with larger ventricular dimensions than thalassaemia patients for similar degrees of anaemia.(20) People with thalassaemia are known to be predisposed to increased cardiac and vascular iron deposition, which leads initially to ventricular stiffening and in the late stages to dilatation. This was however controlled for, as cardiac iron was not detectable in both groups in this study. Some studies have shown that right ventricular function correlates negatively with the degree of anaemia. A study compared two groups of people with SCD, one on a chronic blood hyper transfusion protocol and another not having blood transfusion routinely.(16,21) The former group had significantly higher haemoglobin concentrations, lower LV mass and lower left ventricular filling pressures. The mean ejection fraction was also lower in the group on chronic blood transfusion, though it did not attain statistical significance.

Although SCD is a cause of chronic anaemia that often warrants frequent blood transfusion, cardiac iron overload is relatively rare in them as compared to other haemoglobinopathies and chronic anaemias.(22)This may be explained by the fact that people with SCD tend to have a lower plasma non-transferrin bound iron, raised plasma hepcidin (marker of chronic inflammation), lower growth differentiation factor-15 (indicating less ineffective erythropoiesis) and induction of haem oxygenase (by marked intravascular haemolysis).(23)

A study also showed that though there was a high prevalence of biventricular diastolic dysfunction in sickle patients with iron overload, there was no association between diastolic dysfunction and transfusional iron burden or myocardial iron deposition in people with SCD.(24)

Symptoms and Signs

Palpitation, exertional dyspnoea and fatigue on mild exertion are common complaints in SCD. These symptoms may lead to a wrong diagnosis of cardiac failure. Cyanosis is extremely uncommon, there is collapsing pulse, tachycardia, and visible precordial and apical impulse.(25)Jugular venous pressure is rarely raised in the absence of heart failure.(26)Blood pressure in the steady state is lower than normal and fails to show the age-related rise common in normal populations.(27-29)On auscultation, the first and second heart sounds are loud and frequently spilt more widely than normal, consistent with the increased haemodynamic load. A loud third heart sound and mid systolic (ejection type) murmurs are common.(30) Diastolic flow murmurs are also heard frequently.(31) In a Nigerian study of SCA patients in steady state, the presenting symptoms and signs included palpitation (4.8%), abdominal swelling (4.8%), jaundice (58.8%), displaced apex beat (63.4%), left parasternal heave (24.4%), loud pulmonary component of the second heart sound(58.5%), third heart sound (17.1%), cardiac murmurs(46.3%), hepatomegaly (68.3%), splenomegaly (17.1%), splenectomy (2.4%) and ulcers of lower extremities (2.4%).(6)

Electrocardiography in SCD

The electrocardiographic (ECG) abnormalities reported among SCD patients include prolonged P wave duration, PR interval, QRS complex duration, QRS dispersion, QTc duration and QT dispersion as compared with controls.(6,32) A prolonged PR interval correlated with raised serum triglycerides and negatively correlated with serum alanine transaminase levels.(33) Oguanobi et al. also found that 75% of the abnormality seen on ECG was left ventricular hypertrophy (LVH). This was followed in this order by left atrial hypertrophy (40%), biventricular hypertrophy (11%), ST segment elevation (10%), and increased P and QT dispersions.(34) Left ventricular hypertrophy (LVH), right ventricular hypertrophy (RVH) and left atrial enlargement (LAE) were present at a prevalence rate of 43%, 28% and 1.16% respectively in a recent study. (37) Voltage criteria for ventricular hypertrophy should be cautiously applied in SCD. This is because higher voltages may occur as a normal racial variation in black population and the lack of skin fat as well as thin chest walls in patients with SS disease may contribute to high recorded voltages.(4) The ECG changes in SCD are similar to those seen in other chronic anaemias and do not appear to be specific to sickle cell disease (SCD).(31,35) Such non-specific ECG changes include sinus arrhythmia, first degree A-V block, reversible T-wave wave inversion in the precordial leads, flattening of T-wave and abnormal septal Q-waves. (10,30,31,36,37)

Prolonged QTc as a single risk factor, has been reported as a cause of increase in death not just for adults in general, but for the sickle cell populace in particular.(38) Its other associations are elevated pulmonary artery pressures, and an increased risk of sudden cardiac death in people with SCD.(38,39) Prolonged QTc in children and young adults with SCD correlates with increased markers of haemolysis like elevated lactate dehydrogenase, aspartate transaminase, haemoglobin, and tricuspid regurgitant velocity.(39)

Sickle cell trait seems not to confer increased cardiovascular risk as regards ventricular arrhythmias, myocardial infarction or diminished left ventricular ejection fraction.(40)This is further supported by a study where no significant difference was found between army recruits with sickle cell trait and those with Haemoglobin A in terms of power, oxygen pulse, peak oxygen consumption, minute ventilation and anaerobic threshold.(41)

Radiological characteristics

SCD patients were found to have a statistically significant higher cardiothoracic ratio than controls.(42) In addition, there was radiological evidence of increased bronchovascular markings in 65.1%, widening of the pulmonary vasculature due to pulmonary venous hypertension in 4.8% and generalized coarsening of the bony trabeculae of the thorax in 51.2% of SCD patients.(42) There is often cardiomegaly with a globular configuration from an early age in SCD.(43) Cardiac enlargement was radiologically confirmed in three-quarters of SCD patients.(44,45) The increased cardiac size on x-ray reflects not only dilatation, but also hypertrophy.(25) The lungs show multiple interstitial scars which cause a generalized loss of translucency to the lung fields, this together with coarse trabeculation of the widened ribs, gives the characteristic appearance to the chest x-ray of SCD patients.(43)

Sickle cell anaemia and exercise

Cardiac function has been noticed to be normal at rest in several studies of people with SCD. The response to exercise is abnormal in SS disease.(4,6) During the exercise stress test, subjects with SCD had relatively high baseline heart rates, they attained relatively lower maximum heart rates, especially in those with ECG features of ischaemia.(46) The blood pressure responses to exercise were significantly lower than in HbA controls as well as the maximal workload exercise attained. However, those with ECG features of ischaemia also had the lowest haemoglobin concentrations, which conforms to traditional teaching that anaemia is one of the causes of ST segment changes. These findings were corroborated by McConnell et al.(47)

Electrocardiographic changes like ST segment and T wave abnormalities were more common in women than men, presumably due to the lower level of haemoglobin in the blood.(48) Hypertransfusion, which refers to transfusion of SCD patients with HbA blood to keep the haemoglobin concentration between 10 and 11g/dl, may help correct ST segment abnormalities in sickle cell anaemia patients.(49,50) Exercise performance in SCD improves significantly after isovolaemic partial exchange transfusion with normal blood and after simple transfusion.(51-53)

Cardiovascular Autonomic Dysfunction in Sickle Cell Anaemia

Cardiovascular autonomic neuropathy (CAN) refers essentially to parasympathetic and sympathetic imbalance due to damage to or accentuation of the function of one or both arms. This has been measured traditionally by non-invasive tools like Valsalva manoeuvres, variability of the heart rate, QTc dispersion, and blood pressure response to sustained hand grip and postural changes. A study showed that SCD patients with CAN had widened P waves, a prolonged PR interval and QTc dispersion.(54) The number of abnormal autonomic function tests was found to correlate with the severity of anaemia and the presence of Q-waves. They also found that certain electrocardiographic parameters correlated significantly with abnormal cardiovascular autonomic tests, namely P-wave duration and PR interval, suggesting increased parasympathetic activity in people with SCD.(54) Another study also found prolonged QTc and QT dispersion in SCD subjects with CAN in contrast to controls.(55)

People with SCD are prone to having silent cerebrovascular ischaemic events and such patients also have corresponding autonomic dysfunction. In a study using mean baseline heart rate and heart rate variability (HRV) among others to assess cardiovascular autonomic function, people with SCD were found to have significant autonomic dysfunction as compared to controls, especially parasympathetic dysfunction.(56)

Cardiac Biomarkers in SCD individuals

A classic symptom of acute coronary syndrome chest pain is among the symptom-complex that patients with SCD present with prior to their demise.(57) It is part of the common presenting symptoms in patients with acute chest syndrome, a syndrome that was second in frequency only to vasculo-occlusive crises in the co-operative study of SCD.(61) The aetiology of chest pain in people with SCD is diverse, ranging through pneumonia, pulmonary infarction, pleurisy to acute myocardial infarction.(62) Acute myocardial infarction is the leading cause of death worldwide. It is therefore not surprising that acute chest syndrome was the most common condition at the point of death in SCD patients as seen in the CSSCD study.(58)

Cardiac biomarkers have been assayed over the years to help with diagnosing myocardial necrosis. Troponins I and T have surpassed other cardiac biomarkers like creatine kinase MB fraction, aspartate transaminase and others for assessing myocardial necrosis, considering its cardiac specificity and excellent pharmacokinetic properties.(59) A study assayed for Troponin I in people with SCD presenting in crises. Out of 32 patients with crises, only 2 subjects had raised troponin levels and both of them had acute chest syndrome.(60) Another study of children with SCA showed that cardiac troponin T levels were significantly higher during vaso -occlusive crises than in stable patients. (65)

Although SCD somehow prevents large vessel coronary heart disease(61),acute myocardial infarction has however been reported.(57,61,62)This suggests that myocardial necrosis may occur in crises, likely due to microvascular occlusion, abnormal rheology of the sickled red cells, anaemia and coronary vasospasm.(57)

Brain natriuretic peptide (BNP) and N terminal-pro BNP, molecules secreted by the ventricle in response to stretch, have also been found to be increased in people with SCD and to have an important prognostic significance.(63) NT-pro BNP was found by Gladwin et al. to be predictive of increased mortality at a cut-off point of ≥160pg/ml.(64)

Systemic hypertension in sickle cell anaemia

The prevalence of systemic hypertension in the SCD populace has been found to be 8%, which is much lower compared with the general population.(65) A study by Oni et al. of 86 adults with SCA and 89 adults with HBA showed that systolic (111.4±11.1 vs 114.4±9.26; P value 0.033) and diastolic blood pressure (62.8±14.6 vs 73.5±8.3; p value <0.001) were significantly lower in the SCA group.(66) This is in agreement with studies which reported the tendency for sickle cell patients to have lower blood pressure than the controls of the same age and sex having normal haemoglobin.(67)

There is also the discussion of relative systemic hypertension (RSH) in people with SCD, as they have cardiac structural changes at much lower systolic blood pressure values, suggesting there should be a lower threshold for defining hypertension in them. Using a range of 120-139mmHg for systolic blood pressure and 70-89mmHg for diastolic pressure, relative hypertension has been found to have a prevalence of 44% in them.(65) Another study done in Ghana revealed a prevalence of

45% and 19% respectively for RSH and hypertension in adults with SCD.(68)

Left Ventricular Function at Rest and on Exercise

The chronic anaemia of SCD is associated with increased cardiac output. Stroke volume increased significantly with a relative mild increase in heart rate. The ejection fraction and fractional shortening have been found to be often preserved in people with SCD. The findings so far show that right ventricular dysfunction occurs as early as the second decade of life in people with sickle cell anaemia. While systolic dysfunction has been well noted as an integral component of cardiac failure, recent studies have paid more attention to diastolic dysfunction, a common entity placing individuals at increased risk for cardiac failure. An average of 40% of patients with cardiac failure have preserved systolic function.(69)

Left ventricular function has been noted to be normal in most patients with SCD, with only a few patients developing left ventricular diastolic dysfunction, and to a lesser extent, systolic dysfunction. This has been explained to be largely due to the reduced burden of coronary artery disease, the compensatory physiologic hyper normal ejection fraction and the relatively lower blood pressure in contrast to HbA patients. Studies in children have largely shown normal left ventricular systolic and diastolic function.(70,71)Even gated myocardial perfusion scintigraphy failed to show perfusion abnormalities in a cohort of 43 children with SCD, suggesting that the coronary artery and microangiopathic changes are rare in children with SCD.(72)

Index of myocardial performance (MPI) for both ventricles has however been found to be significantly increased in children with SCA in contrast to controls, and was found to correlate negatively with haemoglobin concentration.(21,73-75) However, a study by Ghaderian et al. revealed no difference in MPI between children with SCD and controls.(76) Reasons for this discrepancy in findings are not readily apparent but call for larger studies and possibly a meta-analysis of available studies.

Among children with SCD, those that get frequent blood transfusions have also been found to have higher MPI values, which may reflect generally worse sickle cell disease than controls.(77) Another study found in addition a relationship between MPI and pulmonary hypertension in people with SCD, with MPI values being significantly raised in the 21 people with pulmonary hypertension in contrast to those without PHT.(75)

Knight-Perry et al. however, in their study of 53 adults and 33 controls, found similar MPI values between them (p=0.43), contrary to those of Caldas and Akgul.(78) Another study by Oni et al. of 86 adults with SCD and 89 controls with HbA using MPI of the right ventricle revealed no significant difference (0.59±0.21 vs 0.61±0.16, p value :0.395) between both groups.(66) The possible explanation for the discrepancy in findings is age, with these in this latter study being much older than those in the former studies. This suggests that the ventricular function of controls also declines with increasing age. This has been confirmed in other studies, especially diastolic dysfunction.

Systolic function in SCD has been largely shown to be preserved in spite of dilated cardiac chambers. A study revealed that the ejection fraction and fractional shortening of the left ventricle were essentially the same between adults with SCD and their HbA controls.(7,79) Also, the end systolic stress-end systolic dimension ratio, a relatively load independent assessment of systolic function, did not reveal any significant difference in both groups, implying normal ventricular function in the SCD group. Another study in SCD children showed that the left ventricular ejection fraction and fractional shortening, though within normal limits, were significantly less than in age and sex matched control subjects.(70) When LV dysfunction is present, it has been seen particularly in older patients and those with associated conditions such as hypertension and renal disease.(80) A meta-analysis done in 2013 of studies done before April 2010 showed that left ventricular systolic function was normal in people with SCD and did not differ from controls.(81) However, LV function was inversely proportional to age and the cardiac index was significantly higher in people with SCA.

Covitz et al. discovered that while cardiac function was normal at rest, exercise revealed cardiac dysfunction in 18% of them.(82) In their study, cardiac dysfunction in response to exercise was reflected by reduction in ejection fraction, regional wall motion abnormalities and diastolic dysfunction as evidenced by reduced left ventricular internal diameter. In addition, van beers et al., evaluating peak oxygen uptake (V′O2), a measure of maximal exercise capacity, found decreased values in 83% of SCD subjects as compared to normal reference values.(83) Both studies showed a significant relationship between the severity of anaemia and cardiovascular function, with anaemia being the single most responsible factor for exercise limitation (38.6%) in the former study.

Diastolic dysfunction (DD) has been found to be strongly age related. 15% of people less than 50years of age have diastolic dysfunction while 50% of people older than 70 years of age have diastolic dysfunction.(84) Diastolic dysfunction was shown by Sachdev et al. to be present in 18% of the adult sickle cell population, while pulmonary hypertension and diastolic dysfunction together were found in 11% of them.(85) This shows that 7% of the patients had DD without PHT. Similar findings were noted by Qureshi et al. in their Magnetic Resonance Imaging (MRI)-based study where right ventricular dysfunction was found in subjects with SCD in the absence of PHT at rest.(86) Both studies, while supposing a link between DD and PHT, suggest that DD may antedate PHT and as such, should have alternative causative factors.

In crisis, left ventricular function has been found to be preserved by speckle tracking imaging.(76) This is because though the longitudinal shortening is impaired, the radial thickening increases to compensate and circumferential shortening is preserved or unaffected during crisis. Another study of left ventricular function in crisis revealed normal systolic time intervals during crises.(87) They also did not detect any elevation in CK-MB or electrocardiographic abnormalities suggestive of myocardial necrosis during crisis.

Structural changes

Adebayo et al. assessed the cardiac structure of subjects having SCD and found right ventricular dilatation in the SCD group, alongside dilatation of LA, LV and increased LV mass.(42) There was however no assessment of the RV function in that study.

Akgul et al. also looked at people with SCD, evaluating the right ventricular function and lung function in 48 of them (age range 11-25 years) and comparing the findings with 24 controls.(75) The people with SCD were further divided into 2 groups – those with pulmonary hypertension and those without it. Peak tricuspid annular systolic velocity(S'), a measure of right systolic function was higher (better) in those without pulmonary hypertension and controls. Diastolic dysfunction was also present only in the pulmonary hypertension group. However, both groups of sickle cell patients had restrictive lung function patterns by spirometry.

Right ventricular function has been suggested to be associated with increasing pulmonary arterial pressures. Sutton et al. in their retrospective study of 60 people with SCD found that 20% of them had TRV >2.5m/sec and dilatation of the RV with paradoxical septal wall motion, showing the association between elevated pulmonary arterial pressures and structural-functional changes of the RV.(88) However, the phase of the cardiac cycle wherein the paradoxical motion was noted was not reported. This is important to distinguish predominantly pressure overload from volume overload, though both frequently co-exist. Sachdev et al., in their study of 191 people with SCA also noticed a trend of increasing RV dimensions with increasing pulmonary arterial pressures.(85) Apart from increasing RV dimensions, right ventricular hypertrophy is expected as a normal physiological response to pulmonary hypertension. This was rightfully observed by Oguanobi et al., in their study of 62 adults with SCA which was controlled with an equal number of age- and sex-matched HbA adults.(89) Increased pulmonary arterial pressure (>30mmHg) was seen in 41.9% of them and was found to correlate positively with electrocardiographic findings of right ventricular hypertrophy. Imaging studies of SCA patients at steady state without PHT have shown dilated right heart chambers without significant right ventricular dysfunction in most cases.(17,85) However, a study in which 3 subjects had evidence of right ventricular dysfunction, showed one of them had evidence of biventricular failure while the other two had moderate to severe PHT.(90) This suggests that right ventricular function is dependent on the functional state of the left. Also, a moderate to severe increase in afterload has detrimental effects on the right ventricular function, similar to systemic hypertension and the left ventricle.(91)

Pulmonary hypertension

Pulmonary hypertension (PHT) is defined as mean pulmonary artery pressure, higher than 25mmHg, determined through right heart catheterization. However, because of its invasive nature, it is difficult to perform routinely as a screening procedure for patients. However, echocardiography, using a cut-off value of 2.5m/sec for tricuspid regurgitant jets, has been found to portend a poor prognosis.(3) Sickle cell anaemia is a well-recognized cause of PHT, having a prevalence that is greater than that of scleroderma and human immunodeficiency virus combined.(92,93) Pulmonary hypertension as an entity is associated with right ventricular hypertrophy and dysfunction. The prevalence of PHT from various studies ranges from 6 to 58% of

individuals with SCD, with the higher prevalence in patients hospitalized on account of crises.(8,90)A recent meta-analysis put the pooled prevalence at 20.7% and 24.4% for children and adults with SCD respectively.(94)

The pathophysiology of pulmonary hypertension in SCA is not well understood. There are elevated steady state levels of endothelin-1, a potent vasoconstrictor. Plasminogen activator inhibitor 1(PAI-1) and tissue factors have been reported to be elevated in SCD, leading to a pro-coagulable state. There is also reduced bioavailability of nitric oxide (NO) due to the release of arginase by lysed erythrocytes.(95) The left ventricular and atrial enlargement, with mitral annular dilatation, mitral incompetence and subsequent pulmonary venous hypertension has also been described, given a hydra-headed aetiopathogenesis of PHT in SCD. Though studies have shown increased pulmonary vascular resistance, increased mean pulmonary arterial pressure and trans pulmonary gradient (which is the pressure difference between the mean pulmonary arterial pressure and the left atrial pressure) in SCD, the degree of increase in cardiac output and relatively lower pulmonary vascular resistance (3-5 fold less) is at variance with other entities in the first class of the clinical classification of pulmonary hypertension. This partly informed the decision to re-classify SCD-associated PHT under class 5 – the class of unclear and multifactorial aetiology.(96)

Indeed, multiple mechanisms have been recognized to contribute to PHT in people with SCD. Kanadasi et al. found LV diastolic dysfunction in about 10% of adult SCD subjects who were asymptomatic for heart failure. (102) Right heart catheterization in SCD patients who had cardio-respiratory symptoms, revealed elevated pulmonary capillary wedge pressure in 80% and elevated pulmonary vascular resistance in 40% of them.(97) Pulmonary hypertension is commonly caused by left-sided heart disease and studies have shown that elevated pulmonary arterial pressures are commonly associated with elevated pulmonary capillary wedge pressures.(98,99) Other possible contributing factors include chronic haemolysis, as a positive correlation was found between pulmonary hypertension and markers of haemolysis like lactate dehydrogenase, aspartate transaminase and haematocrit by Dham et al., suggesting that pulmonary hypertension in people with SCD is multifactorial in origin.(100) Obstructive sleep apnoea, a recognized cause of pulmonary hypertension, was also found in 10.6% of children and adolescents with SCD.(101) However, after controlling for left ventricular internal diameter

and left atrial pressure, pulmonary hypertension was still noted in SCD subjects.

Another postulated pathogenetic mechanism of pulmonary hypertension in SCD is chronic haemolysis. Dosunmu et al. found a correlation between pulmonary hypertension and markers of haemolysis like lactate dehydrogenase, aspartate transaminase and haematocrit.(102) It is however worthy of note that elevated tricuspid regurgitant velocity (TRV) jets>2.5m/sec, which are often used as a surrogate for pulmonary hypertension may be a marker of more severe systemic disease, not just right ventricular dysfunction and failure. This is supported by recent findings in SCD patients with TRV >2.5m/sec, where increased haemolysis, left ventricular diastolic dysfunction, elevated serum urea nitrogen and erythropoietin levels were noted.(3) Raised TRV has been found to correlate negatively with body mass index, packed cell volume and haemoglobin concentrations by Sokunbi et al.(103) Pulmonary hypertension has also been found to be associated with the loud pulmonary component of the second heart sound (1.36-8.50; p value: 0.009) with left parasternal heave, hepatomegaly and jaundice. However, the loud pulmonary component of the second heart sound was the only significant predictor of pulmonary hypertension following regression analysis.

Pulmonary hypertension was found to be associated with dilated left atrium and ventricle, lower systolic blood pressure and increased mortality in heart failure patients. However, after controlling for left atrial pressure and left ventricular internal diameter, pulmonary hypertension was still present in subjects with SCD by Dham et al.(100) There was no correlation between NT-pro BNP and mean pulmonary arterial pressures. NT-pro BNP is a marker of degree of myocardial stretch, which has been validated in studies. The absence of a correlation between PHT and NT-pro BNP suggests that pressure overload triggers ventricular hypertrophy ab initio, not dilatation. This is further supported by the findings of Aliyu et al., in which they found no relationship between the severity of PHT and NT-pro BNP in adults with SCD.(104) The independent predictors of NT-pro BNP from their study were anaemia, HIV seropositivity and serum ferritin. Van beers et al., in their prospective study of 85 adults with SCD found that only anaemia and renal dysfunction were the important determinants of NT-proBNP.(105)Amadi et al. found that Doppler-derived PH is a frequent finding in Nigerian adults with SCD, seen in 23.9% of patients using TRV and 38% of patients using pulmonary flow Doppler.(8) It significantly affects exercise capacity negatively and has significant

relationships with some clinical parameters and echocardiographic indices of cardiac structure and function.

Pulmonary hypertension and right ventricular hypertrophy

Ahmed et al. evaluated 38 hospitalized adults with SCD retrospectively and found 3 patients with right ventricular dysfunction.(90) All of those who had right ventricular dysfunction had elevated pulmonary arterial pressure (>30mmHg). Qureshi et al. in their study of 32 children with SCD also found a pulmonary hypertension prevalence of 16% (defined as tricuspid regurgitant jets >2.5m/sec), all of whom were more than 9 years old.(86) They also noticed an elevation in the right ventricular free wall mass index with age in individuals with SCD, suggesting right ventricular hypertrophy is secondary to raised pulmonary arterial pressures.

Pulmonary hypertension and ventricular function

The impact of pulmonary hypertension on right ventricular function in people with SCD has been largely inconclusive. Akgul et al. studied 48 asymptomatic people with SCD and compared them with 24 age and sex matched apparently healthy controls.(75) They observed that pulmonary hypertension was associated with low Hb concentrations, dilated RV and diastolic dysfunction of the right ventricle in people with SCD. Diastolic function in their study was assessed using the ratio of the early to late diastolic velocities of the lateral tricuspid annulus (E′/A′), a tool that has been used infrequently in SCD studies. Aleem et al., in their prospective study also found that among the 65 adults and adolescents with SCD, pulmonary hypertension was discovered in 38% of them.(106) They also found dilatation of the right atrium, a recognized marker of RV diastolic dysfunction, in 20% of them. They however did not directly correlate diastolic dysfunction with pulmonary hypertension, making it difficult to draw conclusions.

Blanc et al., in their study of 28 children with SCD and 29 controls, used strain imaging for assessing the ventricular function of children with SCD.(107) There was a significant reduction in the right ventricular strain in the SCD group as compared to the controls. 21% of these children with SCD had elevated pulmonary arterial pressures. When they correlated PHT with the RV longitudinal strain in the SCD group, they found a significant correlation ($p = 0.024$). This may mean that there is a

correlation between right ventricular strain and PHT in children and adolescents.

However, Knight-Perry et al. in their prospective study of 53 adults with SCD and 33 controls, measured the right ventricular systolic and filling pressures.(78) Right ventricular filling pressures were significantly raised as compared to controls ($p < 0.001$), and only raised ventricular filling pressures correlated positively with the severity of the right ventricular systolic pressure, which is in keeping with Frank Starling's law. This means that increased filling pressures of the right ventricle lead to increased stretch of the right ventricular myocardium. This in turn leads to the increased force of contraction that accentuates the tricuspid regurgitation.

Pulmonary hypertension and anaemia

Studies have shown that anaemia and pulmonary hypertension have an inverse relationship, with patients having HB <8g/dl generally having higher pulmonary arterial pressures than those with higher HB concentrations.(90,108) Those with pulmonary hypertension generally had a worse prognosis.

Sickle cell cardiomyopathy

An animal study by Bakeer et al. has shown a restrictive physiology in mice with sickle cell anaemia, characterized with dilation of the left atrium and diastolic dysfunction in the presence of preserved systolic function.(109) This is in keeping with various human studies on the heart of sickle cell patients. Recognizable causes of heart failure such as hypertension and coronary artery disease are rare. After excluding all these potential causes, there remain some patients with unexplained heart failure. These observations have led to the hypothesis that a sickle cell cardiomyopathy may occur on account of occlusion or slugging within the small cardiac vessels. However, evidence supporting this is circumstantial.(110) Findings of ventricular and left atrial dilatation, diastolic dysfunction, functional valvular incompetence, and pulmonary hypertension in the presence of largely normal heart rates in people with SCD have also called for the description of a sickle cell cardiomyopathy. A restrictive cardiomyopathy which is progressive with age and first presents with left atrial enlargement has been proposed. This is the fall-out of a study by Niss et al., that found diffuse myocardial fibrosis in all of the

25 sickle cell patients studied.(111) They found that diastolic dysfunction correlated with those that had higher markers of myocardial fibrosis, lower blood haemoglobin and higher N terminal pro-BNP than the SCD subjects without diastolic dysfunction. Dilated left ventricle and left atrium, diastolic dysfunction and normal left ventricular fractional shortening were found in a meta-analysis of 68 studies with SCD.(112) This, in keeping with the increased stroke volume and hyperdynamic physiology has been found in SCD. The description has not been widely accepted as there is yet to be a consensus statement on it. However, the pathologies are apparent and the nomenclature is worth considering.

Left ventricular non-compaction(LVNC) has also been described in the SCD cohort, with the prevalence being less in children than the adult populace.(113) There is a paucity of reports on other cardiomyopathies in sickle cell anaemia.

Management of the cardiovascular disorders in sickle cell anaemia

People with sickle cell anaemia are susceptible to many cardiovascular diseases. However, they seem to get tired easily, with breathlessness on mild to moderate exertion being a common phenomenon in a majority of them (NYHA class II or III). They tend to complain more of chest pain (in addition to other body pains) and are admitted often for heart failure and cor pulmonale than most of the populace. Adegoke et al. found that Serum Triglycerides are usually higher in SCD patients than HbA controls.(33) Total cholesterol and LDL levels were significantly lower in SCD patients as compared to controls, whereas HDL levels were comparable. Diuretics, angiotensin converting enzyme inhibitors or angiotensin receptor blockers, mineralocorticoid receptor antagonists and beta blockers have been found to be useful in patients with heart failure. However, attention should be paid to the haematocrit to maintain it at optimum levels and the diuresis should be carefully undertaken in them to avoid precipitating a vaso-occlusive crisis.

Antiplatelets, statins, morphine, beta blockers and anticoagulants have all been used with a favourable response in patients with myocardial infarction. Supplemental oxygen is used for patients that have an SPO_2 <94%. Fibrinolytics are reserved for patients with STEMI, just as in HbA patients. Percutaneous coronary intervention (PCI) is preferred to fibrinolytics, if the patient presents to a PCI-capable hospital ≥12 hours

after the onset of infarction or if there are features of on-going ischaemia. Coronary artery bypass grafting is used in MI patients with triple vessel disease, left main coronary artery disease or patients with diabetes mellitus co-existing. Pulmonary hypertension is managed using phosphodiesterase inhibitors, endothelin antagonists, prostaglandin inhibitors and nitric oxide gas inhalation.(114)

As regards acute chest syndrome, management is largely supportive. Oxygen supplementation is given to patients with hypoxia. As regards pain control, non-steroidal anti-inflammatory drugs (NSAIDS) should be avoided as they can worsen the symptoms and signs. Intercostal nerve block can be given for pleuritic chest pain.(115) Patient controlled analgesia with potent opioids like morphine has been found to be preferable to continuous morphine infusion, with smaller doses of opioids required, fewer opioid related side effects and a shorter hospital stay.(116) Simple blood transfusion has not been found to be superior to exchange blood transfusion, though randomized control trials are yet to be done in this regard.

Anticoagulants have a role in improving blood flow, reducing pain and the duration of hospitalization.(117) Steroid use is controversial, having been found to attenuate the course of illness but increasing the risk of re-admission.(118) The use of bronchodilators and antibiotics is reasonable but not evidence-based.

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THE USE OF HYDROXYUREA IN THE MANAGEMENT OF SICKLE CELL DISEASE

ADEGOKE SA

Hydroxyurea is an ideal and currently the only disease-modifying therapy approved for sickle cell disease (SCD), a common chronic disorder. Apart from being prescribed as a monotherapy, single daily dose and administered orally, it is effective and offers long-term benefits in all age groups. The associated side effects, if any, are usually few, mild and short-term. Clinically, it reduces rates of painful events and hospital visits, improves anaemia and prevents both acute events and chronic organ dysfunction. Haematologically, it increases foetal and total haemoglobin, reduces leucocyte and reticulocyte counts and inhibits the adhesiveness of blood cells to themselves and vascular endothelium.

Since the curative options of stem cell transplantation and genetic therapy for SCD are not currently widely available, hydroxyurea appears to be the best available treatment option for individuals with the disease. However, despite the overwhelming evidence in support of the clinical benefits of hydroxyurea in patients with SCD, its use is still limited in many developing countries.

Sickle cell disease (SCD) is the most common hereditary haemolytic anaemia characterized by the presence of sickle haemoglobin (HbS) in addition to another abnormal haemoglobin such as haemoglobin C, D-Punjab, O-Arab, HbD-Ibadan and the thalassaemias. HbS results from a single gene mutation at the β-globin chain with eventual amino acid substitution (Glu→Val, $\beta^A \rightarrow \beta^S$). In a deoxygenated milieu, HbS undergoes polymerization and ultimately changes the shape and deformability of red blood cells. (1) In addition, HbS encourages adhesion of erythrocytes and other blood cells (leucocytes and platelets) to themselves and also to the walls of the endothelium. The disease therefore manifests clinically with chronic haemolysis and intermittent episodes of vascular occlusion and eventual organ dysfunction.

Although efforts are ongoing to develop newer agents to manage individuals with the disease, hydroxyurea, a drug that has been extensively studied, remains the only approved and effective agent. This chapter which examines the use of hydroxyurea in patients with SCD focuses on the history, pharmacology and mechanisms of actions of the drug, the current clinical evidence of its effectiveness, how it is used, challenges and prospects, especially in developing countries.

History of Hydroxurea

Since the 1980s, hydroxyurea has become an important advancement in the treatment of SCD. The drug was first synthesized in Germany by Dressler and Stein in 1869 when trying to extract derivatives of urea during laboratory experiments. (2) In 1967, about a century later, the United States Food and Drug Administration (US FDA) approved it for the treatment of solid neoplastic diseases, and then in subsequent years, for the treatment of patients with chronic myeloid leukaemia, psoriasis, melanoma, ovarian cancer and polycythaemia vera. (3-7) It was first shown to induce foetal haemoglobin (HbF) in sickle cell anaemia (SCA) in the mid-1980s, and later on, phase I and II studies were carried out in adults with SCD. (8, 9) The phase III double-blinded, placebo controlled randomized clinical trial that first demonstrated the dramatic clinical benefits of hydroxyurea for adults with very severe SCA was done about a decade later in the 1990s. (10) The United States FDA subsequently approved its use in adults with SCD in the year 1998. (11)

Pharmacology and Mechanisms of Action of Hydroxyurea

Hydroxyurea, also known as hydroxycarbamide (chemical formula $CH_4N_2O_2$) is a monohydroxyl-substituted urea antimetabolite. It selectively inhibits ribonucleoside diphosphate reductase, an enzyme that converts ribonucleoside diphosphates to deoxyribonucleoside diphosphates. Hydroxyurea therefore blocks the synthesis of deoxyribonucleic acid (DNA) by keeping cells in the G1/S phase of the cell cycle and also maintains cells in the radiation-sensitive G1 phase and interferes with DNA repair. (12)

The exact mechanism of action of HU in the management of SCD is not fully understood. However, the central effect of HU is its ability to increase HbF through the activation of soluble guanylyl cyclase and altered erythroid kinetics. (13, 14) This induction subsequently inhibits

intracellular HbS polymerization and the sickling process within the red blood cells. (13) HU also lowers the number of neutrophils and reticulocyte counts while improving their rheology; improves cellular hydration and deformability of erythrocytes hence reducing haemolysis; alters endothelial adhesion and promotes the release of nitric oxide, thus decreasing SCD-related vasculopathy. (12-15). See Table 1 and figure 1.

Table 1: Effects and mechanisms of action of hydroxyurea

	Effects	Mechanism of actions
1	Induces foetal haemoglobin production	Acts on erythroid progenitors and activate soluble guanylyl cyclase
2.	Lowers neutrophil and reticulocyte counts	Inhibits ribonucleotide reductase and causes marrow cytotoxicity
3	Improves blood rheology	Decreases adhesions of circulating neutrophils and reticulocytes
4	Prevents haemolysis	Improves erythrocyte hydration, enhances macrocytosis and reduces intracellular sickling.
5	Improves vascular response	Enhances release of nitric oxide (NO) with potential local vasodilatation, reduction of platelets aggregation and inhibition of adhesion molecules

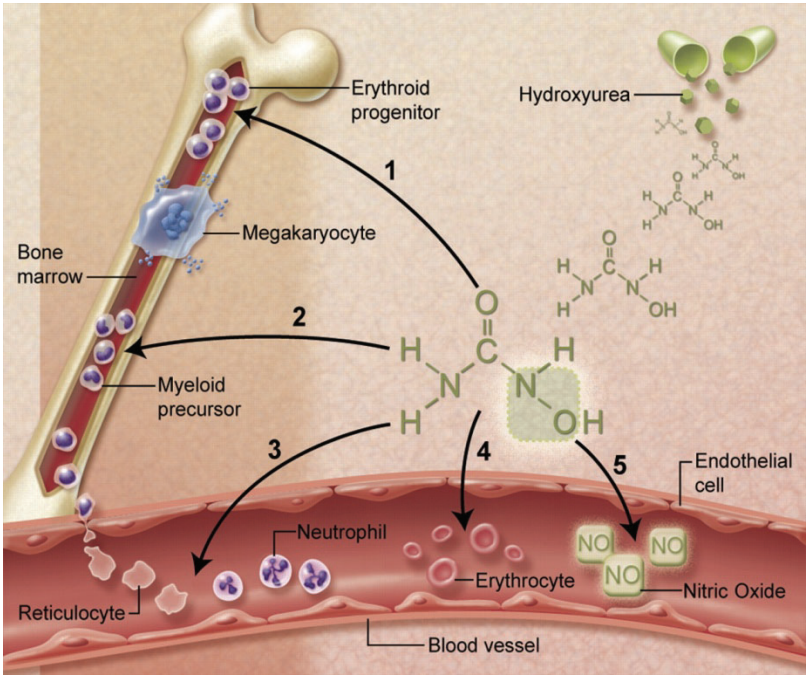

Fig 1. Multiple beneficial effects of hydroxyurea for sickle cell anaemia. (Source: Ware RE. How I use hydroxyurea to treat young patients with sickle cell anemia. Blood 2010:115;5300-5311). Illustration by Alice Y. Chen.

(1) Foetal haemoglobin induction; (2) lower neutrophil and reticulocyte counts; (3) decreased adhesiveness and improved rheology of circulating neutrophils and reticulocytes; (4) reduced haemolysis; and (5) Nitric oxide (NO) release with potential local vasodilatation and improved vascular response.

Hydroxyurea is administered orally and as a single daily dose. Absorption from the gastrointestinal tract is effective and within 1 to 4 hours after intake, the peak plasma levels will be attained. (16) The maximum plasma level may be reached between 20 and 30 minutes after administration for those who are rapid responders. The plasma half-life may take three to four hours. (12) The drug rapidly distributes and concentrates in red and white blood cells. (17) In a majority of cases, the metabolic pathways for the full conversion of the drug to active metabolites have not been comprehensively documented. However, the drug is often metabolized in

the liver or may undergo a minor catabolism in the intestine by some bacteria urease. It is excreted through the kidneys on about 80% of occasions.

Current Clinical Evidence Of Effectiveness

Strong evidence from systematic and clinical trials supports the effectiveness of HU in adults, especially in high-income countries of the world. (9, 10) Most of these reports showed that hydroxyurea is associated with improved foetal haemoglobin levels, improved haematological parameters, reduced rates of hospitalization, and reduced episodes of acute chest syndrome and decreased frequency of pain events in SCD. (18, 19) Hydroxyurea has also been found to lower the need for red blood cell transfusion, since it reduces haemolysis. One of the earliest studies on hydroxyurea known as the Multicentre Study of Hydroxyurea (MSH), was done in the United States of America and was published in 1995. (10) This randomized placebo-controlled clinical trial involved the use of hydroxyurea for adults with severe sickle cell anaemia. Outcome variables in that study included the impact of hydroxyurea on rates of vaso-occlusive crises, the number of incidences of acute chest syndrome and the number of blood transfusions required. The findings served as the eye-opener to the efficacy of hydroxyurea in adults with SCD.

In another multicentre but open-label, phase 3, non-inferiority trial, hydroxyurea was described as a substitute for chronic transfusions for high-risk children with SCD and abnormal transcranial Doppler (TCD) velocities who have received at least 1 year of transfusions. (20) A long-term cohort study in France also showed that transfusions could be stopped in patients with SCD who are switched to hydroxyurea after achieving a normal TCD velocity. (21) Studies on the impacts of hydroxyurea on mortality rates in patients with SCD showed that it can reduce mortality in up to 40% of these patients. (22-24)

Although children were not part of the initial studies on the impact of hydroxyurea in patients with SCD, hydroxyurea is now being used more frequently in children globally. Children have been reported to derive some additional benefits from hydroxyurea therapy since the drug delays the switching of foetal to adult haemoglobin, prevents or delays development of organ failure, reverses early vasculopathy, maintains optimal splenic functioning and improves linear growth. (25-27)

Guidelines for Hydroxyurea Therapy in Patients with Sickle Cell Disease

Eligibility for HU therapy (12)

Patients with the criteria below are eligible for HU therapy:

i. Confirmed laboratory diagnosis of SCD (HbSS, SC, Sβ-thalassaemia, SD), etc.
ii. Ability to attend periodic reviews and undergo laboratory tests as indicated.
iii. Negative pregnancy test for sexually active women.
iv. At least one of the following complications in the last 12 months:
    a. Three or more episodes of significant vaso-occlusive crises (i.e. a pain episode requiring a hospital visit and the use of analgesia).
    b. One recurrent acute chest syndrome (defined as acute chest pain, dyspnoea, and fever of ≥38.5°C with new pulmonary infiltrate on radiograph, with or without cough).
    c. One or more strokes or transient ischaemic attacks.
    d. Severe or recurrent priapism.
    e. Serious and persistent anaemia (Hb <6.0 g/dl on three occasions within 3 months).

Exclusion criteria

Patients who experience any of the following should not be included:

i. Hypersensitivity to hydroxyurea.
ii. Any evidence of spinal cord dysfunction.
iii. Leucocyte count less than 2,500/mm^3.
iv. Absolute neutrophil counts <2000/mm^3.
v. Total platelets <100,000/mm^3.
vi. Haemoglobin level <4.5 g/dl.
vii. Reticulocyte count <80,000/mm (where haemoglobin <9 g/dl).
viii. Pregnancy, because of the risk of teratogenicity, although there are still no adequate studies in humans.
ix. Those with Human Immunodeficiency Virus (HIV) infection.

It is advisable to exercise caution when using hydroxyurea in the following conditions, because of possible adverse effects of the drug.

i. **Breastfeeding:** It is known that the drug is excreted in milk. There is however insufficient research to determine the effect on the infant. Its use should be avoided or discontinued during breastfeeding.
ii. **Gout:** Regular monitoring of uric acid levels is advocated, especially in patients with baseline levels above the normal range. This is because hydroxyurea may increase serum uric acid levels.
iii. **Renal failure**: Although few studies have evaluated its use in patients with renal insufficiency, it is advisable to use the drug with caution in those with renal disease.
iv. **Hepatic impairment**: Since there are no data to guide the dose adjustment in this situation, caution should be exercised.
v. **Drug interactions**: There are no adequate studies on drug-drug interactions. Therefore, the concomitant use of other drugs, especially those that can also produce bone marrow depression should be carefully monitored.

Initiation of Hydroxyurea

It is mandatory to sensitize the patient or legal guardian on the nature of the drug, the need or indication for the drug, and the clinical benefits, potential risks and related side effects of the drug. They should give written informed consent which should be countersigned by the physician.

In addition, the following tests should be carried out before initiating hydroxyurea

i. Complete blood count: haematocrit/haemoglobin, leucocyte count (total and differential), platelet count, reticulocyte count. This is because of the bone marrow cytotoxicity.
ii. Haemoglobin electrophoresis to estimate and monitor HbF, S, and A_2/A fractions.
iii. Renal function tests, especially urea/creatinine/uric acid/sodium/potassium. The drug is excreted via the kidneys primarily, hence the renal status must be known before commencing it.
iv. Liver function tests: Lactate dehydrogenase (LDH)/aspartate aminotransferase (AST), Alanine aminotransferase (ALT), and Alkaline Phosphatase (AP). Its metabolism like most other drugs takes place in the liver, therefore liver function tests are mandatory before starting the therapy.
v. Serology: HIV, Hepatitis B and C screening.

vi. Coagulation studies: Prothrombin time (PT), partial thrombopastin time (PTTk), thrombin time (TT), and International Normalized Ratio (INR).
vii. B-Human Chorionic Gonadotropin (HCG) for females of childbearing age to exclude pregnancy.

Monitoring of Patients on Hydroxyurea

Hydroxyurea (HU) is available in hard gel capsules containing 100 mg and 500 mg. The initial dose is 15 mg/kg/day, as a single daily dose, and it should be increased by 5 mg/kg/day every 8-12 weeks until reaching the maximum tolerable dose (MTD). The MTD is defined as the highest dose capable of promoting the most prominent improvement of the clinical and laboratory course without the occurrence of haematological, hepatic or renal toxicity. (12) The maximum dose does not usually exceed 35 mg/kg/day.

Every 4 weeks, a complete blood count and reticulocyte count should be done. Similarly, renal and liver function tests should be done every 3 months, while the levels of HbF should be monitored every 6 months.

Duration of treatment

Hydroxyurea treatment should be maintained indefinitely according to the laboratory response and clinical course of the patient, except during pregnancy and lactation periods.

Causes of Treatment Failure with Hydroxyurea

About 25% of patients on hydroxyurea do not show any remarkable clinical or haematological improvement. (12) It is advised that in such cases, hydroxyurea treatment should be discontinued. Poor or non-response may be due to poor adherence to treatment, use of a fake drug, inadequate dosage or dose adjustment, or may be due to certain genetic factors which may interfere with the response to hydroxyurea. In developing countries, treatment failure with hydroxyurea arises from a combination of factors.

Challenges with the Use of Hydroxyurea in the Management of Sickle Cell Disease

In developing countries, there are several challenges facing physicians and patients on the use of HU. These include:

1. Drug availability: The drug is not widely available in many parts of developing countries.
2. Cost: When available, it may be unaffordable or its use unsustainable due to cost.
3. Presence of fake drugs in many developing countries.
4. Drug Interactions: There are no adequate studies on drug interactions. Therefore, the concomitant use of other drugs with hydroxyurea should be closely monitored.
5. Concern about side effects such as
   i. Carcinogenesis: Development of cancers. In a report, six patients who were taking HU developed leukaemia, but the evidence did not support causality. (28)
   ii. Teratogenicity.
   iii. Neurological effects: lethargy, headache, dizziness, disorientation and hallucinations.
   iv. Gastrointestinal discomfort: stomatitis, anorexia, nausea, vomiting, diarrhoea and constipation.
   v. Dermatological effects: maculopapular rash, facial and peripheral erythema, skin ulceration or worsening of existing ulcer and changes such as dermatomyositis.
   vi. Renal: increase in serum urea, uric acid and creatinine.
   vii. Hepatic: elevation of aminotransferases.
   viii. Hypersplenism in children.
   ix. Reproductive: oligospermia, azoospermia.
   x. Other reported side effects include fever, chills, malaise, asthenia.

Protocol for Initiation of Hydroxyurea Therapy in Patients with Sickle Cell Disease

Laboratory tests (recommended before starting therapy)

1. Complete Blood Count (CBC): haematocrits, WBC total and differentials, reticulocyte count, platelet count and RBCC. Other haematological tests include red blood cell indices such as MCV and MCH
2. Comprehensive metabolic profile, including kidney and liver

function tests
3. Pregnancy test for women
4. Quantitative measurement of HbF, if available (e.g., haemoglobin quantitation by high-performance liquid chromatography).

Initiating and monitoring therapy

1. Baseline elevation of HbF should not affect the decision to initiate therapy
2. Males and females of reproductive age should be counselled about the need for contraception while taking hydroxyurea
3. Starting dosage for adults: 15 mg per kg per day (round up to the nearest 500 mg); 5 to 10 mg per kg per day in patients with chronic kidney disease
4. Starting dosage for infants and children: Usually 15 mg per kg but may be up to 20 mg per kg per day
5. Monitor CBC with WBC differential and reticulocyte count at least every 4 weeks when adjusting dosage
6. Aim for a target absolute neutrophil count ≥2,000 per μL (2.0×10^9 per L); younger patients with lower baseline counts may safely tolerate absolute neutrophil counts as low as 1,200 per μL (1.2×10^9 per L)
7. Maintain platelet count ≥80,000 per μL (80.0×10^9 per L)
8. If neutropenia or thrombocytopenia occurs:
   i. Maintain hydroxyurea dosing
   ii. Monitor CBC with WBC differential weekly
   iii. When blood counts have recovered, reinstitute hydroxyurea at a dosage of 5 mg per kg per day lower than the dosage given before onset of cytopenia.

If dose escalation is warranted based on clinical and laboratory findings:

1. Increase by 5 mg per kg per day every 8 weeks
2. Give until mild myelosuppression is achieved (absolute neutrophil count 2,000 to 4,000 per μL [2.0×10^9 to 4.0×10^9 per L]), up to a maximum of 35 mg per kg per day
3. Once a stable dosage is established, laboratory monitoring should include CBC with WBC differential,
   reticulocyte count, and platelet count every 2 to 3 months.

Other important information to managing physicians

1. Patients should be reminded that the effectiveness of hydroxyurea depends on their adherence to daily dosing, and should be

counselled not to double dose if a dose is missed
2. A clinical response to treatment may take 3 to 6 months; therefore, a 6-month trial at the maximum tolerated dose is required before considering discontinuation because of lack of adherence or nonresponse
3. Monitor RBC, MCV, and HbF levels for evidence of consistent or progressive response
4. A lack of increase in MCV or HbF is not an indication to discontinue therapy
5. Long-term hydroxyurea therapy is indicated in patients who have a clinical response
6. Therapy should be continued during hospitalizations or illness.

Hydroxyurea and Malaria Infection

Interactions between hydroxyurea and malaria have been a subject of interesting debate especially in sub-Saharan Africa where SCD and malaria are two leading diseases contributing to morbidities and mortality. A randomized controlled study in Africa concluded that HU did not increase the incidence or severity of malarial events when compared with a placebo. (29) Postulations have however been made that hydroxyurea may indeed reduce the rates and/or severity of malaria infection. Some of these hypotheses include:

i. Induction of HbF – HbF is known to inhibit *Plasmodium falciparum* growth and is responsible for malaria protection in young infants. (30)
ii. Generation of nitric oxide – NO has been linked to malaria protection. (31, 32)
iii. Hydroxyurea may reduce the levels of soluble ICAM-1, hence reducing the adhesion of malaria parasite to vascular endothelium and consequently reducing the risk of severe malaria, especially cerebral malaria. (33) However, some other in vitro studies reported an increase or no significant change in the levels of these molecules in SCA. (34, 35).
iv. Direct antiparasitic activity at high concentrations. (36)
v. Improvement in splenic function. (36)

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Gastrointestinal and Hepatic Manifestation of Sickle Cell Anaemia

David A. Ofusori and
Benedict A. Falana

Sickle cell anaemia can affect any organ and system of the body including the gastrointestinal tract. Painful vaso-occlusive crisis in patients living with SCD is often associated with abdominal pain which may result in some abdominal complications. Some of the major GIT and hepatic manifestations in SCD patients include but are not limited to: Abdominal Vaso-Occlusive Crisis, Cholelithiasis with or without cholecystitis, Choledocholithiasis with or without cholangitis, Acute splenic sequestration crisis, Splenic infarction, Splenic abscess, Acute pancreatitis, Peptic ulcer disease, Acute appendicitis, Hepatic infarction, excessive iron stores, viral hepatitis, hepatomegaly, Hepatic abscess, biliary sludge, Ischaemic colitis, Hepatic sequestration crisis, and Mesenteric lymphadenitis. (1, 2) Other Miscellaneous liver disorders may include: hepatic infarction, focal nodular hyperplasia, pyogenic liver abscess, and autoimmune hepatitis. Colonic involvement is the least affected of the gastrointestinal manifestations and usually present in the form of ischaemic colitis. (3) Hepatic complications are common in patients with SCD due to the sickling process and the treatment associated with it. (4-6) Also, due to multiple transfusions received by patients with SCD, they are often at risk of developing pigmented gallstones, iron overload and viral hepatitis. All these add to the hepatic manifestations in SCD patients. (5) Sometimes sickle cell hepatopathy refers to some causes of liver dysfunction in patients with SCD. Sickle cell hepatopathy occurs more frequently in homozygous sickle cell anaemia patients than in patients with HbSC disease or HbSß-thalassaemia. Although the incidence of liver disease in patients with SCD has not been well established, it is known that liver disease in patients with SCD occurs due to multiple blood transfusions, which is associated with excessive iron stores and infection (hepatitis B and C). (5)

Elevated bilirubin concentrations are common in patients with SCD due to chronic haemolysis. There could be twice the normal (<6 mg/dL) levels of total bilirubin concentrations during sickling crises. (7) The serum aspartate aminotransferase (AST) level is elevated due to haemolysis and it correlates with the lactic dehydrogenase levels while serum alanine aminotransferase (ALT) levels always suggest hepatocyte injury. (8)

Abdominal Vaso-Occlusive Crisis

This may occur in patients with sickle cell anaemia as part of a generalized vaso-occlusive crisis or in isolation. This manifestation is difficult to distinguish from other causes of acute abdominal crisis. (9) Approximately 10% of admitted patients with sickle cell anaemia are presented with acute abdominal pain. Investigation has shown that abdominal vaso-occlusive crisis is often attributed to micro-vessel occlusion involving postcapillary venules; in most cases, infarcts of the mesentery and abdominal viscera are particularly involved resulting in severe abdominal pain. (1)

Figures 1 and 2 show the bowel of a child with abdominal vaso-occlusive crisis

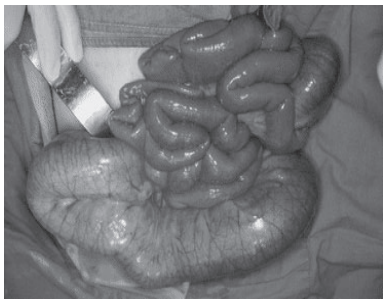


Figure 1: Intraoperative photograph of a child with abdominal vaso-occlusive crisis. Note the congestion and ileus of the affected bowel which is slightly dilated (8)

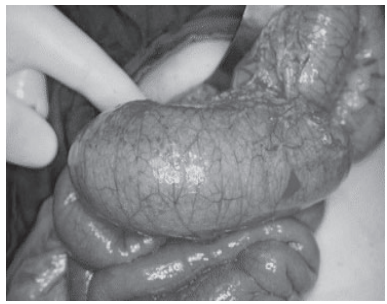


Figure 2: Intraoperative photograph of a child with abdominal vaso-occlusive crisis. Note the dilated small intestine and also small areas of haemorrhage in the bowel wall (8)

Karim et al. (10) and Dhiman et al. (11) noted that some of the gastrointestinal abnormalities that accompanied abdominal vaso-occlusive crisis in patients living with SCD include segmental or diffuse bowel wall thickening as shown in Figure 3. In some cases, due to super-infection of the ischaemic bowel, intra-abdominal abscess formation may occur resulting in colonic perforation; if this condition persists, death is inevitable. (12, 13)

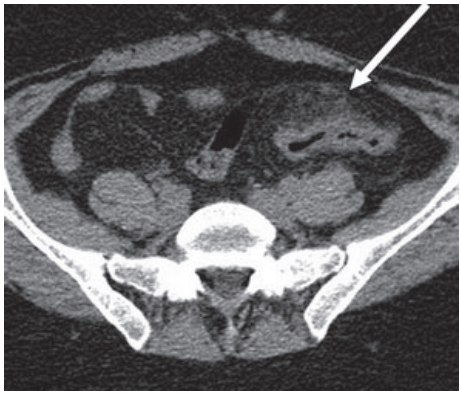


Figure 3: Unenhanced axial abdominopelvic CT image of a 39-year-old woman with abscess formation. The arrow shows the thickening of the sigmoid colon, with surrounding inflammatory changes (9)

In patients with abdominal vaso-occlusive crisis, it is necessary in most cases to admit for close observation and frequent evaluation, intravenous hydration, administration of analgesics once the diagnosis of acute surgical conditions was ruled out and transfusion of Packed RBC blood when there is an associated anaemia (Hb <9 g/dl). (8) In most cases abdominal vaso-occlusive crisis attacks resolve spontaneously.

Colitis (Inflammatory bowel disease):

Colonic involvement is not common in SCD patients and when present, it usually comes in the form of ischaemic colitis. It occurs at some point during vaso-occlusive crisis. (1) Because of the similarities with other surgical emergencies, if not properly diagnosed it may result in avoidable surgery. Alqoaer et al. suggested that for proper categorization, ischaemic and infectious colitis should be included in the diagnosis of colitis in SCA patients. (3) According to Terry et al. in their study: “Ulcerative colitis in

sickle cell disease", all of the four patients who presented with chronic colitis and diarrhoea ended up having ulcerative colitis. (14) It should be noted that ischaemic colitis even though rare because of the rich collateral blood supply to the colon (8), may present with serious complications.

A Black Saudi female with SCD was reported by Alqoaer et al. (3) as having chronic diarrhoea with watery bowel motions mixed with blood.

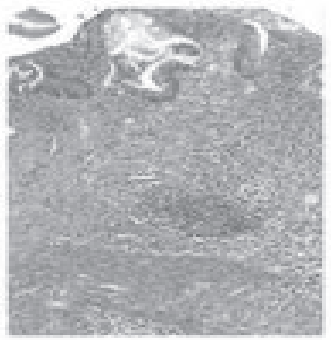


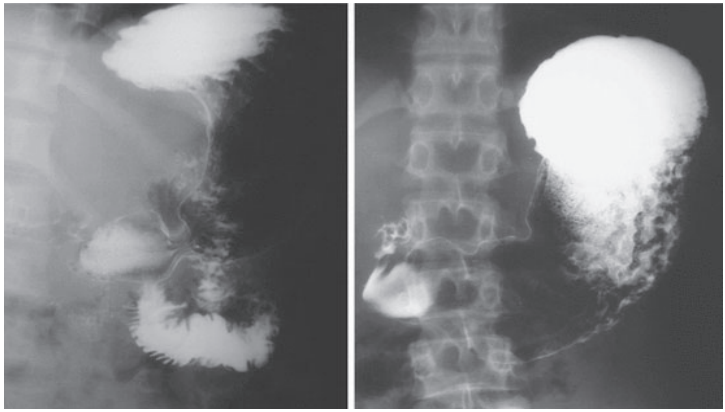
Figure 4: Showing the inflamed colonic biopsy with disorganized glands (1)

Histopathological analysis of this patient revealed inflamed colonic biopsy (Fig. 4). The treatment ranges from intravenous fluid hydration and resuscitation to surgical intervention.

Peptic ulcer disease

About 33.33% of patients with SCD have been reported to have peptic ulcer. (8) Out of 35% of SCD patients reported by Al-Salem in 2016, 27% have duodenal ulcer while 8% have gastric ulcer. The increment in the occurrence of peptic ulcer in patients with SCD may be due to ischaemia and mucosa hypoxaemia. (15) In some cases, it may result in gastroduodenal perforation. The pathogenesis of peptic ulcer in patients with SCD has been traced to mucosa ischaemia due to repeated "sickling" rather than an increase in acid secretion. This is because the basal and peak gastric acid output in patients with SCD has been found to be normal when compared with patients without SCD. The place of *helicobacterpylori* in the pathogenesis of peptic ulcer in patients with SCD is not clear; but study has shown that the decrease in mucosa resistance due to repeated ischaemia in patients with SCD may be the cause of peptic ulcer in

patients with SCD. Peptic ulcer occurrence in patients with SCD using barium meal is presented in Figure 5.



Acute Pancreatitis

Acute pancreatitis is not one of the common causes of abdominal pain in patients with SCD. It may develop idiopathically with no apparent cause (8) and sometimes occur either by biliary obstruction or microvessel occlusion causing ischaemic injury to the pancreas. (16) Acute pancreatitis must be considered when patients with SCD complain of abdominal pain. In some cases, it might develop acute chest syndrome. (8) Hasan et al. reported a rare case of vaso-occlusive crisis in a 37-year-old patient with SCD which led to pancreatitis. They maintained that in hypoxic patients, treatment may be conservative but exchange transfusion may perhaps be the therapy of choice. (17)

Acute splenic sequestration

Splenic sequestration occurs when sickled cells obstruct the blood vessels preventing the free flow of blood from the spleen. This makes the spleen to be enlarged, palpable and sometimes painful. Acute splenic sequestration (ASS) is life-threatening and occurs early in life in patients with SCD. As a result of parental education and appropriate management, the mortality rate has greatly reduced. (18) ASS is commoner in infants between 2 months and 48 months. It can also occur in older children with SCD with the feature of an enlarged spleen or in some cases, a spleen with the capacity of enlargement. Some of the basic symptoms of ASS include

but are not limited to: big spleen, abdominal pain, paleness, weakness, increased heart beat and irritability. If the blood count (RBC) is extremely low, blood transfusion is normally recommended as the first line of treatment. ASS often resolves spontaneously in the case of minor ASS characterized by slight episodes with a moderately enlarged spleen. If there are repeated episodes of ASS, it may be expedient to perform splenectomy. It should be noted that the frequency of occurrence of ASS can be more than once in patients with SCD.

Cholelithiasis

Cholelithiasis is also referred to as gallstones within the gallbladder. When the gallstones are present in the common bile duct it is called Choledocholithiasis. In some instances, gallstones may lead to inflammation of the gallbladder which is referred to as cholecystitis. Cholelithiasis is one of the abdominal complications commonly associated with SCD patients. A study conducted in the United Kingdom suggests a significant incidence rate of cholelithiasis in patients with homozygous HbSS when compared with HbSC and HbS-beta thalassaemia patients. In Jamaica and Africa, the incidence rate of cholelithiasis was put at 13% and 28.9% respectively in SCD patients. (7) Out of a hundred and seven patients with SCD at the Fundação Hemominas in Uberaba and the Hospital das Clínicas of Universidade Federal do Triângulo Mineiro, 25.2% have an incidence of gallstones. Coats et al. (19) conducted a study on 344 patients with SCD with a record of ultrasound scan of the biliary tree. This showed that 134 had cholecystitis. Of the 134 patients, 119 are HbSS, 12 are HbSC, 2 are HbSB+ and 1 is HbSB0.

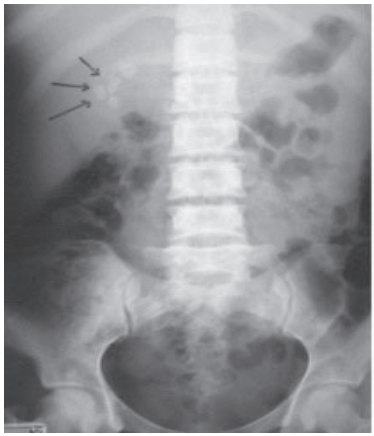


Figure 6: Plain abdominal X-ray showing gallstones (8)

Excessive iron stores

Excessive iron stores in patients with SCD are dependent on the number of blood transfusions received. Transfusion is beneficial to SCD patients as it helps to reduce recurrent stroke and acute chest syndrome. (20, 21) A significant reduction in pain crises was also noted in patients that received prophylactic transfusions. (22) Despite the beneficial effects of blood transfusion in patients with SCD, multiple transfusions have been reported to increase iron deposition within the Kupffer cells and reticuloendothelial cells. There is a dearth of information on the association between the steady state of ferritin in the plasma and hepatic iron stores. A study conducted however, showed poor correlation between hepatic iron stores and the plasma ferritin level. (23) Oral chelation has been proved to be effective in the management of excessive iron stores in patients with SCD. (24, 25)

Hepatic sequestration crisis

The most common types of sequestration involve the pulmonary vessels and spleen in patients with SCD. However, hepatic sequestration can also occur. (26) When it occurs, hepatomegaly, pain within the right upper quadrant and a fall in the haematocrit levels are inevitable. Just like in splenic sequestration, the treatment of Hepatic sequestration involves urgent attention aimed at restoring the red cell mass and blood volume.

This should be coupled with the process of reversing the sickling process. (25, 27)

Viral hepatitis

It is advisable for patients living with SCD to be vaccinated against hepatitis A and B because patients with SCD are at risk of developing liver disease when they have acute infection. Although in countries like the United States, there is a low prevalence rate; a thorough study showed that in other countries with a high prevalence rate of liver diseases such as hepatitis B, patients living with SCD have a higher percentage when compared to general patients. (28-30) Antibodies against hepatitis C virus were detected in some SCD patients (25); the degree of susceptibility is dependent on the frequency of blood transfusion. (25) The aetiology of progression of hepatitis C to cirrhosis in patients with SCD is still shrouded in mystery.

Acute appendicitis

Acute appendicitis is not common in patients with SCD (31). Al-Salem et al. showed that, out of all appendicectomies conducted, 0.43% (9) were SCD patients (32). The study further showed that of these, nine patients with SCD presented with acute appendicitis, and six of the appendixes were perforated and characterized with haemorrhagic congestion and transmural inflammatory cell infiltrates as shown in Figure 7.

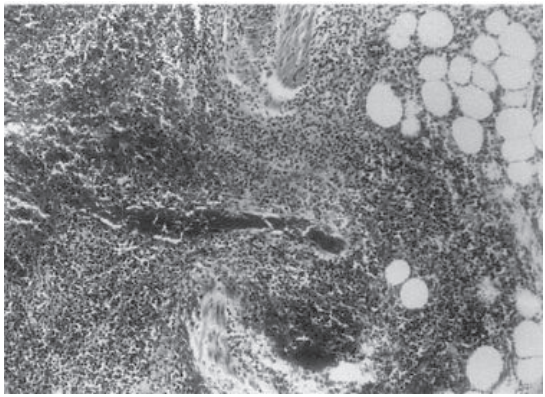


Figure 7: Photomicrograph showing perforation of the appendiceal wall with (H&E, 100) (32)

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MUSCULO-SKELETAL SYSTEM IN SICKLE CELL DISEASE

DARE BJ

Sickling effects caused by polymerization of deoxygenated HβS in the arterial and capillary blood vessels, and red cells stretched into a defective shape, together with the vaso-occlusive crisis effects form the major complications in sickle cell disease, underlining the pathological conditions affecting the bones and the surrounding tissue (musculoskeletal system). Among the clinical manifestations affecting the bones and the soft tissues in sickle cell disease; bone marrow necrosis, infarction, osteomyelitis, and avascular necrosis have been the most frequent complications. This chapter step-wisely examines in detail the manifestation of each of these conditions including; dactylitis, orbital compression syndrome, aseptic necrosis, osteopenia and osteoporosis, growth retardation and skeletal immaturity among others.

Sickle cell disease exerts both acute vaso-occlusive crises, and chronic progressive avascular necrosis in the bones and the surrounding soft tissue. These conditions are worsened by the imprecision in the diagnosis, both in laboratory analysis and in radiological imaging. Sickle cell disease is a molecular disease that involves a single gene disorder, abnormal haemoglobin S (single mutation in the β-globin gene) substitutes a single amino acid in a normal polypeptide chain, changing the sixth amino acid from glutamic to valine. (1) This is one of the most common severe monogenic disorders (haematology disorders), haemoglobin S substitutes a single amino acid in a normal beta polypeptide chain, and is inherited by an autosomal codominant. (2, 3) Sickle cell disease includes sickle-cell anaemia; a condition referred specifically to as homozygosity for the βS allele (haemoglobin HβSβS), haemoglobin SC disease (HβSC disease) a coinheritance of the βS and βC alleles and HbS/β-thalassaemia occurs when βS is inherited with a β-thalassaemia allele. (2) Vaso-occlusive crisis (VOC), acute splenic arrest, and haemolytic anaemia characterize the

clinical signs and symptoms of Sickle cell disease. Vaso-occlusion exerts sharp and localized pain in the chest region and also causes avascular necrosis (AVN) of skeletal bones in both young and old living with sickle cell disease (4). Nigeria has the largest population of people with sickle cell disorder, with about 150,000 births annually; the prevalence of sickle cell trait is about 25% while the homozygous state is found in about 3% of the population. (5)

Bone Vasculature

Bone is a matrix filled tissue with haematopoietic cells (marrow) in the core and highly vascularized; blood vessels are found in all regions of the skeletal system except at the growth plate and articular cartilage. (1, 6, 7, 8) The arterial blood branches extensively to form capillary networks, that drain into a single vein along the core area of the diaphysis (the bone shaft containing marrow). Bone capillary can be grouped into TWO (2) subtypes H and L, these form a single network. Type H capillaries are located in the avascular growth plate region of the metaphysis, organized into columns of vessels, interconnected at the distal end, close to the growth plate region of the metaphysis. Type H vessels including endosteal Type H capillaries are found peripheral and proximal to a compact area of bone, and are densely packed, interconnected close to the growth plate. The type L vessel is a sinusoidal form of capillary, a dense and highly branched vascular network in the core area of the bone, formed in a marrow cavity of the diaphysis. Type L capillaries, within the haematopoietic cells are connected to the central vein. Type L sinusoidal capillaries interconnect to Type H vessels in the metaphysis and endosteum and there is no direct artery supply into Type L sinusoidal capillaries. (9, 10)

Long arteries to the bones and muscles bring arterial supply to the Type H capillaries, blood flow from Type H vessels enters the Type L sinusoidal network at the interface between the metaphysis and diaphysis, and from the Type L sinusoidal network blood is drained into the large central vein at the core of the long bone. The metaphysis is well oxygenated as a result of direct blood supply; however, the diaphysis is hypoxic owing to the indirect arterial blood supply and the comparable large haematopoietic cell populations. Processes of haematopoiesis are regulated by the action of mural cells and leptin cell receptor; these are perivascular cells that surround the Type L sinusoidal vessels and secrete molecular signals such as stem cell factor (SCF, or KITL), CXCL12 and angiopoietin. Bone

contains several distinct perivascular cells (of mesenchymal origin) that regulate haematopoiesis, osteogenesis and vascular homeostasis.

Endothelial cells lining the inner layers of blood vessels are covered or enveloped on the abluminal surface/peripheral surface by perivascular (mural) cells. Mural cells express protein profiles with different morphological appearance as seen in pericyte mural cells that line the subendothelial basement membrane and establish cell-cell contact with capillary endothelial cells, and vascular smooth muscle cells, that line the larger arteries and veins, with no contact with endothelial cells.

Vaso-occlusive crisis (VOC)

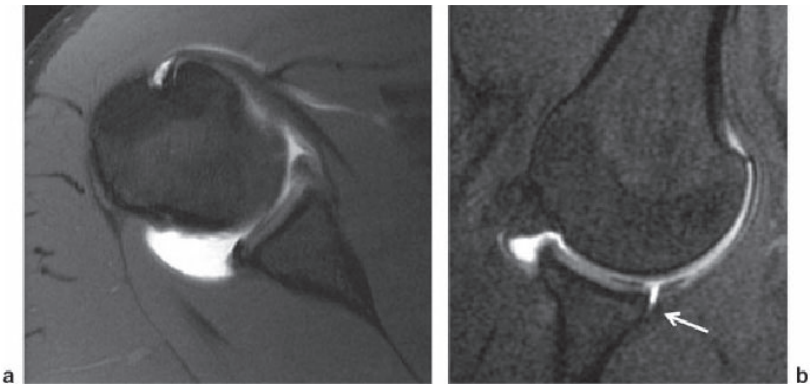
Sickle cell diseases cause an accelerated atherosclerotic process in bone vasculature. (11) Fibroblast growth factors (FGFs) regulate blood vessel growth and bone formation, and lack of FGFs reduce trabecular bone volume, mineral apposition and bone formation rates. (8) Therefore, VOC is the capillary obstruction caused by adhesion of the nondeformable sickle red blood cells (HβS-RBC) to the capillary endothelial. Vaso-occlusion can be classified as acute when it involves peripheral vaso-occlusive crisis such as stroke; and chest pain and chronic conditions when it involves renal failure and avascular necrosis of long and tubular bones. In low oxygen tension, hypoxic conditions, haemoglobin S ($\alpha 2\beta 2\ 6^{Glu \rightarrow Val}$) polymerizes into a network that distorts the erythrocytes, forming a rigid sickle shape that obstructs blood flow and causes premature red cell destruction. Vaso-occlusion causes protean joint or bone abnormalities such as dactylitis, and osteonecrosis, while in capillary occlusion by the HβS-RBC, anoxia, osteocyte death, and bone necrosis occur. However, high foetal haemoglobin levels prevent the sickling of HβS-RBC and AVN, causing the collection of erythrocytes and leucocytes in the microcirculation, and subsequent vascular obstruction and tissue ischaemia. (2, 6, 11, 12, 13, 14, 15, 16, 17)

Vaso-occlusive crises begin during late infancy and reoccur severally throughout life in sickle cell disease patients. Vaso-occlusive crises initiate microvascular occlusion caused by marrow hyper-cellularity that impairs blood flow and regional hypoxia, and consequently activate adhesion of leucocytes, platelets and endothelial cells with HβS-RBC. The vaso-occlusive crisis process is common in the bone marrow, resulting in bone marrow infarction affecting the medullary cavity or epiphyses in the long bone. The usual clinical manifestation is intense localized pain in the bone,

accompanied by rebound tenderness, swelling and erythema over the site of infarction; fever and leukocytosis could be observed. Vaso-occlusive crises of the marrow infarction of epiphyses, result in joint effusions similar to the clinical manifestation in the diagnosis of septic arthritis. (4, 14)

Avascular Necrosis of Bones

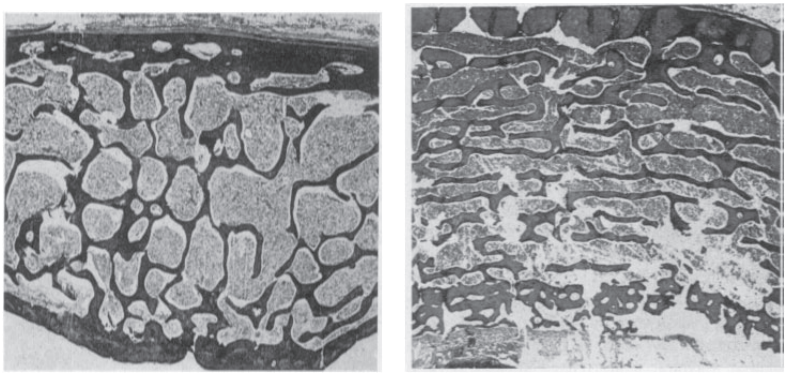
Avascular necrosis is the cell death that results from the compromise of the blood supply to the particular region of the body. Avascular necrosis of bones produces local pain, limping, limited mobility of the affected joint, and muscular atrophy. Avascular necrosis of the femoral head is rare in sickle cell anaemia patients usually below the age of 10 years but produces severe symptoms in adults (about 10-30%). (4) The head of the femur is most commonly affected with Perthes-like lesions (Perthes lesion occurs when the scapular periosteum remains intact but is stripped medially and the anterior labrum is avulsed from the glenoid but remains partially attached to the scapula by the intact periosteum) in both HbSS and HbSC, and they are rarely noticed in HbAS. Avascular necrosis of bones causes subchondral sclerosis of the head of the femur, which developed into Perthes-like necrosis and consequent damage to the femoral head.



Avascular necrosis results in degenerative changes of osteoarthritis between the ages of 5 and 10 years, trauma to the head of the humerus, lower thoracic vertebrae (T10-12), and osteochondritis of the tibial tuberosity (Osgood-Schlatter disease). (4,14)

Diploe Lamellation

This is the formation of the trabecular pattern within the diploe in the skull, perpendicularly to the curvature of the cranial vault and producing a characteristic hair-on-end appearance called intra-diploic curvilinear lamellation or stripes. (15, 16)



Histology section of the skull with the detailed appearance of the diploe in both normal (A) and in sickle cell diseases (B diploic lamellation appearance) (15)

Bony bridges connect the long bony trabeculae and convert them into quadrangles. These quadrangular islands of hypercellular marrow accommodate fragments of bone and varying numbers of sickle erythrocytes with minimal osteoclastic activity within the lacunae, these define the clinical manifestations of diploe lamellation commonly observed in thalassaemia and sickle cell disease. Moreover, extensive infarction with fibrosis and hypercellularity of the marrow in the trabeculae of diploic bone remain diagnostic indices in the identification of diploe lamellation in sickle cell disease. (15, 17)

Bone Marrow and Bone Infarction

Bone marrow necrosis involves myeloid tissue and stromal necrosis without affecting the cortical region of the bone, however, in bone infarction, avascular necrosis of the bone affecting only the cortical elements, differentiates bone infarction from the bone marrow necrosis in sickle cell disease. Bone marrow ischaemia, infarction and necrosis in the

region of bone supplied by an end artery (where circulation is terminal and blood vessel anastomosis is poor) have been linked to intravascular sickling that results from the blood vessel obstruction and consequent hypoxia observed in sickle cell disease. (18) However, it is important to know that proliferation of vascular endothelium in the marrow has equally been linked to stasis and hypoxia and these two processes activate various intracellular signalling pathways that regulate target gene expression through transcriptional hypoxia inducible factor. (8)

Bone marrow hyperplasia occurs as a consequence of the haemolytic anaemia that results in the thinning of the cortex of bones. (18) For example, the core area of the vertebrae has a poor vascular supply relative to the marginal area, therefore, the central region of the vertebrae is subjected to stasis and sickling effects that result in bone growth impairment and flattening of the vertebrae core region.

Bone marrow infarction occurs relative to bone infarction; this is because hypoxia and endothelial alteration that occur in marrow infarction, compromise the nutrient arteries supplying the bone. This bone marrow hyperplasia (caused by haemolytic anaemia) results in loosening bone cortex, endothelial changes such as intravascular stasis, hypoxia, and necrosis or infarction of the long and tubular bones found in the hands and feet, the heads of the femur, humerus, and fibula among children and adults with sickle cell anaemia.

Among other clinical manifestations associated with HβS patients with bone marrow hyperplasia are tower skull and gnathopathy and fat emboli in the cerebral and chest vasculature (acute chest syndrome). (1, 12, 19, 20) Infarcts of the long bone, sternum, skull, facial bones (facial bone infarction of the orbital, mandibular, sphenoidal, supraorbital, and frontal bones), and acute chest syndrome that results from hypoventilation and thoracic back pain, thoracic bony infarcts and pulmonary infiltrates are common diagnostic signs and symptoms in young and old HβS patients.

Dactylitis

This is inflammation of the finger or toe. Dactylitis affects the bones of the hands and toes including the soft tissue of the digits as seen in syphilitic dactylitis. Sickle cell dactylitis occurs when only the bone is involved; tuberculous dactylitis and sarcoid dactylitis occur when the bone and the soft tissues are involved; and when only the soft tissues are involved it produces a clinical manifestation of distal dactylitis and spondyloarthritis

dactylitis. Dactylitis occurs in various forms: non-inflammatory (sickle cell dactylitis), inflammatory infectious (tuberculous dactylitis, syphilitic dactylitis, and blistering distal dactylitis), and inflammatory non-infectious (sarcoid dactylitis and spondyloarthritis dactylitis). (1, 19) Dactylitis (hand-foot syndrome) is the initial manifestation of sickle cell disease in infants (less than 6 months of age), however, the syndrome reduces/attenuates from the age of 4, this is because the haematopoietic tissue (stem cells) in the long bone of the hands and feet is replaced by fatty tissue and the potential for marrow infarction ceases as the child grows older.

Dactylitis is recognized by painful swelling of the hands and feet followed by fever (increased warmth and redness). Periosteal swelling, increased leukocyte count, extreme tenderness, warmth, redness and a high temperature distinguish osteomyelitis from dactylitis. Localized bone marrow infarction of the carpal, tarsal bones and phalanges consequently results from sickle cell dactylitis and continuous asymptomatic bone marrow infarction. It is worthy of note that, after two (2) years of age, the bone marrow is replaced by common fibrous tissue, thus, the symptoms of dactylitis cease in sickle cell patients.

Dactylitis is a bioindicator for severe complications of sickle cell diseases and severe anaemia and leukocytosis. Dactylitis can be a predictor of homozygous sickle cell disease, sickle-cell haemoglobin C disease and sickle cell beta thalassaemia disease. Early symptoms of dactylitis include soft tissue swelling, followed by periostitis of the surroundings and osteosclerosis in the core area of the long bone leading to necrosis of the central part of the epiphysis and premature fusion and shortened phalanges and metacarpals.

Aseptic Necrosis

Aseptic necrosis occurs at the articular surfaces and heads of long bones, this is different from the bone infarction that involved the perivascular surface, marrow and bone cortex. Aseptic necrosis is identified by chronic pain around the articular regions of the joint. Bone articular surfaces of the long bones have a limited vascular supply of blood without enough compensating anastomoses and collateral blood supply. Blockage of small vessels as a result of sickling, could lead to ischaemia, necrosis, coxa plana and collapse of the femoral head, narrowing of the articular space, aseptic necrosis of the acetabulum, and protrusion of the femoral head

through the acetabulum as well as the humeri head and other long bones. Reduced movement and pain around the hip, shoulder and in other forms of joints are common symptoms in aseptic necrosis among sickle cell disease patients.

Orbital Compression Syndrome

One of the rarely occurring complications among adults living with sickle cell disease is caused by vaso-occlusive event in the vasculature of the orbital bones. It is common in young patients, characterized by painless oedemic swelling of the upper eyelid and exophthalmia eye ball with normal eyesight, periorbital cellulitis, pains in the thigh and back, accompanied by acute chest syndrome, and necrosis of the hip as seen in osteomyelitis. Inflammation of the eye muscles (eye muscle paresis) with oedematous swelling and perineural oedema (orbits are small and swelling is rapidly visible) are the complications and associated syndromes that follow the compression of blood vessels and the optical nerve of the orbital bone. (12, 20)

Avascular Necrosis Involving Short (Small) Bones

Ischaemic necrosis in the small bones of the wrists and hindfoot has been observed in sickle cell anaemia, but it is less commonly observed compared with the level of prevalence of osteonecrosis in the long tubular bones. Osteonecrosis occurs in the talus, calcaneus, and lunate (avascular necrosis of the lunate called Kienbock's disease is rare). Ischaemic necrosis in the small bones is caused by sickling of the red blood cells in the small bones, obstructing the intraosseous vascular supply resulting in osteonecrosis. (20, 21)

Hands in Sickle Cell Anaemia

Distal phalangeal sclerosis and osteosclerosis occur in adult with sickle cell anaemia, this sclerosis is similar to the clinical manifestation in sarcoidosis, systemic lupus erythematosus, scleroderma, rheumatoid arthritis, psoriatic arthritis, osteoarthritis, gout, periarteritis nodosa, dermatomyositis, myelofibrosis, osteopetrosis, chronic active hepatitis, trauma, and in aged women above 40 years of age. (12, 22, 23, 24, 25) It affects both child and adolescent sickle cell patients before 20 years of age independent of gender. Distal sclerosis of the phalanges that affects the endosteal or periosteal bone is called **cortical sclerosis**, while, **spongiosa**

sclerosis occurs in the spongiosa or medullary bone, and necrosis of the cortical and medullary bone can occur together which is the most common type of sclerosis in sickle cell diseases.

Osteomyelitis

Acute osteomyelitis is an acute bacterial infection that follows pyrexial illness, affecting children between 1 and 10 years of age. This condition is prevalent in sickle-cell disease affecting the long bone; the upper end of the femur, the shafts of the tibia, radius and ulna, and the humerus. Common clinical features include pain, swelling, inflammation and inability to use the affected limb, as well as pyrexia and leukocytosis. Hypo-splenism and infarcted or necrotic bone have been implicated in the bone-muscle infections, affecting the sickle cell disease patients. (18, 23-25)

Among other bacterial infections in sickle cell disease that cause bone inflammation, **Salmonella** (non-typical serotypes) is the most common cause of osteomyelitis and can be found in various forms (Salmonella typhimurium, Salmonella enteritidis, Salmonella choleraesuis and Salmonella paratyphi B). Staphylococcus aureus and Gram-negative enteric bacilli have been implicated as well, producing intravascular sickling of the bowel with consequent ischaemic infarction of the bowel patchy. Associated anomalies that accompany the osteomyelitis in sickle cell disease include tuberculosis and systemic spread of Mycobacterium ulcerans from a Buruli skin ulcer. (25-27) Osteomyelitis in sickle cell disease results in severe bone damage and associated systemic infections, and consequently, causes inflammatory response eliciting fever symptoms. Osteomyelitis among individuals living with sickle cell disease occurs with Septic arthritis**,** and can be easily identified through imaging techniques.

As observed on radioisotope bone scanning, osteomyelitis in sickle cell disease produces a characteristic non-invasive periostitis, osteopenia and periosteal elevation in acute osteomyelitis while, MRI shows reactive marrow oedema and hyperaemia of the surrounding soft tissue. Nevertheless, in sickle cell disease clinical assessment blood cultures from bone marrow remain a valid diagnostic means of osteomyelitis

Septic arthritis

Septic arthritis in sickle cell disease is caused by Salmonella bacterial infection as observed in osteomyelitis above. It is usually an associated syndrome in vaso-occlusive crisis and causes irreversible joint damage.

Osteopenia and osteoporosis

In sickle cell disease, marrow hyperplasia causes mineral density reduction in bone, mostly occurring in vertebral osteoporosis. Vertebral osteoporosis consequently produces vertebral trabeculae and a fish-mouth like biconcave deformity of the vertebrae caused by compression by the adjacent intervertebral discs, and vertebral collapse from vertebral infarction.

Rib Infarction

Vaso-occlusion of the ribs results when the blood supply to the rib bone is embarrassed, leading to rib infarction and acute chest syndrome, ultimately resulting in pleuritis, splinting and inflammation, hypoventilation, regional hypoxia in the lungs, a diminished supply of oxygen and nitric oxide potentiates vasoconstriction and sickling effects in the bones of the ribs (14, 28). This series of events can lead to massive bone infarction and fat embolism syndrome. Infarcted ribs are characterized with disrupted blood supply and consequent destruction of the osteoblasts. Rib infarction is mostly associated with surrounding soft tissue inflammation, including pleuritis and splinting in areas of regional hypoxia as noted above.

Leg Ulcers

Leg ulcers are caused by stasis and thrombosis in the vascular supply to the lower third of the leg above the medial malleolus as a result of trauma, infection, anaemia, and compromise in the blood supply to the lower third of the leg. Excision of the affected cells, split skin graft and human epidermal autograft have proven effective treatment protocols. (19, 29, 30)

Growth Retardation and Skeletal Immaturity

Growth retardation is caused by hyperplasia and ischaemia of the bone marrow in the long tubular bones particularly in vertebral bones. This equally involves premature and early closure of the epiphysis part of the bones with consequent impairment or asymmetrical growth of the long bones of the upper and lower limbs and subsequent retardation in bone growth and in angular deformities of the long bone. Ischaemia of the central portion of the vertebral growth plate has been associated with retardation in vertebral growth, leading to the formation of H type tower vertebrae due to a depression in the vertebral end plates. Deficiency in the amount of available vitamins such as A, B6 and D has been linked to morbidity and growth retardation in children with sickle cell disease. (22, 31, 32)

Osteoporosis

Increased haemopoietic activity during bone resorption in sickle cell diseases initiates erythroid hyperplasia that leads to a reduction in bone marrow density, osteoporosis, and thinning of the cortex. These clinical manifestations together with the weakening of the vertebral bones precede vertebral collapse. Osteoporosis and Vertebral Collapse are achieved as a result of deterioration in the central part of the vertebral bones, but the peripheral vertebral end-plates are maintained. This deterioration of the intervening disc on the adjoining vertebral end plate is as a result of the vaso-occlusion and consequent necrosis to the long branches of the vertebral nutrient artery of the endplates and thus vertebral collapse readily sets in following weakening from thrombosis or infarction.

Arthritis

Inflammatory and non-inflammatory responses have been linked with arthritis in sickle cell disease such as seen in bone infarcts, hyperuricaemia, gout, and osteomyelitis. Arthritis potentially leads to the destruction of joint components (synovitis, periarticular osteopenia and joint space narrowing) and bone erosion. Polyarticular arthritis has been noted to be specific for sickle cell disease and is usually symmetrical, affecting the joints and lower extremities.

Connective tissue diseases

The occurrence of connective tissue diseases, including rheumatoid arthritis and systemic lupus erythematosus has been rarely reported in sickle cell disease. However, individuals with sickle cell disease have a greater risk of developing autoimmune diseases. (22, 32)

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SICKLE CELL AND THE KIDNEYS

OKUNOLA O, OYEBISI O
AND ALEBIOSU CO

The kidneys are two paired bean shaped organs located in the posterior abdominal wall, each measuring 12 cm x 6 cm x 3 cm and weighing an average 150 grams each. It has an outer cortex and an inner medulla and receives 25% of the total cardiac output.

It is involved in functions such as maintaining the internal fluid environment of the body, excretion of waste products of metabolism, active involvement in calcium and phosphorus balance, control of blood pressure and production of red blood cells.

The kidney is a highly vascular organ with low partial oxygen saturation in the renal medullary interstitium. The basic pathophysiology revolves around decreased medullary flow, ischaemia, micro infarcts and papillary necrosis.18% of mortality in sickle cell disease is attributed to end-organ involvement, mainly renal in origin. In the tropics, kidney disease is a common complication of sickle cell disease and contributes significantly to mortality(1). Age, duration of the disease and frequency of crises and hospitalization are major predictors of kidney disease.

Kidney involvement in sickle cell disease could manifest as

1. Haematuria.
2. Renal papillary necrosis
3. Tubular dysfunction
   - Renal concentrating defects/ Hyposthenuria
   - Proximal tubular defects
   - Distal tubular defects, and
   - Acidification and potassium excretion defects.
4. Glomerular disease.
5. Chronic kidney disease/ ESRD.
6. Medullary carcinoma.

7. Hypertension and the kidneys.
8. Acute kidney injury.
9. Genitourinary manifestations.

Haematuria

This is commonly seen in patients with sickle cell anaemia and sickle cell trait, and less commonly seen in haemoglobin SC. It may be gross or microscopic, painless or painful, and usually involves the left kidney in about 80% of cases, bilateral in 10-20%.

The left is mainly affected due to the resultant increased venous pressure from the greater length of the left renal vein. It may also be due to the ‘‘nut cracker’’ phenomenon, in which there is compression of the left renal vein between the aorta and the superior mesenteric artery, leading to renal venous hypertension and formation of ureteral and renal pelvic venous varicosities. The elevated left renal venous pressure could predispose to low oxygen tension in the medulla thus increasing the likelihood of vaso-occlusion in the left kidney (1,2).

Common causes include amongst others, glomerulopathy, renal papillary necrosis and renal medullary carcinoma.

The haematuria is produced by increased acidity, anoxia and hypertonicity of the medulla. This causes sickling of the medullary erythrocytes with resultant sludging of the blood in the inner medulla causing ischaemia and extravasation of blood cells into the tubular lumen. The sickling in the vasa recta also causes microinfarction.

Investigations

1. Kidney ultrasound scan
2. Urine cytology
3. Coagulation tests to rule out the concomitant appearance of von Willebrand disease in sickle cell trait
4. Computerized tomography
5. Renal arteriography
6. Cystoscopy to identify the source of the bleeding
7. Immunology for lupus nephritis
   - Auto antibodies

- Double stranded DNA antibodies
- Complement levels

8. Renal biopsy if there is associated proteinuria and the above are negative.

Treatment

- Often self-limiting and remits spontaneously after bed rest.
- Recurs in 50% of cases.
- If severe and prolonged, multiple blood transfusion.
- Forced diuresis with hypotonic infusion fluids (4L/1.73m^2/day) to reduce clot formation.
- Alkalization of the urine to reduce medullary sickling 8-12g of sodium bicarbonate.
- Amino-caproic acid (anti fibrinolytic agent) 4-12g/day in four divided doses to dislodge clots and obstruction in the urinary collecting systems.
- If haematuria is chronic and relapsing, exchange blood transfusion is indicated.
- Very rarely, nephrectomy for life threatening hemorrhage because of the tendency to bleed in the contralateral kidney.

Renal Papillary Necrosis

This is seen in both sickle cell anaemia and sickle cell trait as a result of sickling and ischaemia in the renal medulla. It is more frequent in HBSC disease than in other sickle cell syndromes. It has an incidence of 30-40% (2).

It is often painless and asymptomatic and sometimes may manifest as microscopic haematuria or renal colic.

It results from localized medullary ischaemia and necrosis of the medullary tip as a result of obliteration of the medullary vessels from sickling. The renal papillae are dependent upon the vasa recta for their blood supply and are thus susceptible to ischaemic insults due to localized sickling. Chronic analgesic consumption could also be contributory.

Investigations

Abdominal ultrasound scan shows increased echogenicity of the inner medullary pyramids, later the 'garland' lesion showing a pattern of medullary calcifications(4,5,6).

Helical CT urography (more sensitive than the above).

Direct ureterorenoscopy.

Treatment

- Same as for haematuria
- Hydration
- Pain control
- Antibiotics (as indicated).

Tubular dysfunction

The hallmark is *hyposthenuria* (defined as the inability to concentrate urine under conditions of water deprivation). Most patients are unable to reach urine osmolality of 400 mosm/kg by adolescence. It is seen more in SCA than SCT and manifests as childhood enuresis and nocturia. It is often reversible with exchange blood transfusion until the age of 15 years. At this time, the concentration defect is fixed and associated with fibrosis and obliteration of the medullary vasa recta with papillary shortening.

It is caused by sickling in the vasa recta promoted by contact with the relatively hypertonic inner medulla, disrupting normal function of the counter current multiplier system, making maximal concentrating impossible. It is also caused by local endothelin-1 production which has strong natriuretic and diuretic properties. Also it is caused by the intra renal secretion of prostaglandins which dilate the vessels of the inner medulla, the region of the kidney responsible for urine concentration. Patients with SCA in the tropics should therefore drink 2-3 litres of water daily to prevent dehydration that could precipitate sickle cell pain crises.

Proximal defects; As a result of the reactive increase in sodium and water reabsorption, there is an increased absorption of phosphates and β2 microglobulin and also increased secretion of creatinine and uric acids (7). Creatinine based equations can affect GFR estimation hence a cystatin C based equation is more reliable.

Distal tubule defects; there is reduced excretion of potassium and hydrogen ions and an incomplete renal tubular acidosis type IV, there is consequent impaired acidification.

Acidification defects; they often have a normal acid-base balance. However metabolic acidosis occurs when there are precipitating factors such as infections or diarrhoea that results from gastrointestinal bicarbonate loss. It is also an incomplete form of distal RTA as a result of an inability to lower the urinary PH to less than 5.3. There is a resultant decrease in titratable acidity and ammonium excretion. Some patients also have hyperkalaemic distal RTA, as a result of an inability to generate the tubular trans-epithelial electric gradient that permits normal potassium or proton excretion(8).

Glomerular disease

The hallmark for this is proteinuria. It occurs in 27% of patients in the first decade and 68% of older patients. In the latter it is present in 30% of patients at follow up and increases with age (9). As the diseases progresses, there is impairment of perm selectivity with increased glomerular hyperfiltration coefficient, worsening hyperfiltration and further proteinuria. There is an increase in glomerular pore size in SCA patients with proteinuria, indicative of impaired membrane perm selectivity (10,11).

Dipstick-positive proteinuria occurs in 25% to 30% of adult SCA patients and 14% have proteinuria of 2+ and above (2).

Nephrotic syndrome is found in approximately 40% of patients with SCN. Further progression gives rise to ischaemia and fibrosis with obliteration of glomeruli and progressive renal insufficiency.

The general histological picture on biopsy is hypertrophied glomeruli with distended capillaries due to the sickled blood cells and hemosiderin deposits in tubular cells (2).

There are four types of glomerulopathies seen in sickle cell disease and these are;

1. Focal and segmental glomerulosclerosis; there is hypertrophy of the unaffected glomeruli, segmental sclerotic lesions that are more prominent in juxtamedullary nephrons and in the peri hilar region,

global nephrosclerosis. There is also obliteration of the capillary lumens and glomerular collapse accompanied by severe medullary fibrosis. No immune deposits on electron microscopy are seen. Some sclerotic areas on IF show minor deposits of immunoglobulin M (IgM), C1q and C3(2,12).

2. Membranoproliferative glomerulonephritis; this was the glomerulonephropathy first described. Immunofluorescence shows immune deposits in the capillary wall with immunoglobulin A, M, C3, CIq and interstitial fibrosis(12).
3. Glomerulopathy specific to SCD.
4. Thrombotic microangiopathy (TMA).

Treatment includes immunosuppressive agents such as azathioprine, cyclosporin and mycophenolate mofetil (MMF). Angiotensin converting enzyme inhibitors or angiotensin receptor blockers are also given to reduce proteinuria(13).

Genetic associations in Proteinuria

i. Albuminuria occurs in patients who express specific single nucleotide polymorphism in the *MYH9* and *APOLI* genes, and is associated with increased risk of CKD in African Americans (14).
ii. Microdeletions in the genes that encode the α-globin (a form of the α-thalassaemia trait) lead to a lower prevalence of microalbuminuria among patients with SCA(15).
iii. Glomerular filtration rate in sickle cell anaemia is also influenced by genetic polymorphism of bone morphogenetic protein receptor 1B (16).

Chronic kidney disease

Sickle cell disease should always be considered at risk for chronic kidney disease. Once a year measurement of the urinary albumin to creatinine ratio is done (2).

Positive albuminuria UACR > 30mg/g

Positive proteinuria UACR > 300mg/g, then blood levels of cystatin C or GFR

A kidney biopsy should be considered in cases of nephrotic syndrome or rapidly progressing kidney disease.

Management is along the usual line of management of the various stages of CKD, which generally include amongst others blood pressure control, treatment of dyslipidaemias, management of mineral bone disorders and also careful control of fluids and electrolytes.

Haemodialysis is offered as indicated and survival is the same as for those in the general population (7).

Risk factors for ESRD in sickle cell disease include; HbSS, S gene-cluster haplotype, proteinuria, anaemia and hypertension (2).

Renal transplantation is the preferred form of renal replacement therapy as the quality of life is improved. There is better long term patient survival in transplantation than those on maintenance dialysis (17).

A high level of panel reactive antibodies due to repeated prior blood transfusions may significantly prolong the transplant waiting time (2).

Also, one-year allograft survival is similar to that of the general transplantation population. At 3 years, there is reduced allograft survival (48%) compared with the general transplantation population (17).

Patient survival is also reduced at 59% compared with the general population of 81%.

In general, the median survival for patients with ESRD is 4 years despite RRT. This poor outcome is influenced by concomitant end organ damage and refractory anaemia.

There is an increased incidence of post transplantation crises due to post transplantation haemopoiesis which increases plasma viscosity. The use of hydroxyurea to increase haemoglobin F production may help in reducing the frequency of sickling crises. Venesection is advised if Hb is greater than 10g/dl.

Acute kidney injury in sickle cell disease

Acute kidney injury (AKI) refers to an abrupt but often reversible decline in the glomerular filtration rate (GFR) occurring over a period of minutes to days with the retention of blood urea nitrogen and serum creatinine. It may occur in the setting of pre-existing normal renal function or without pre-existing renal disease. Depending on duration and severity, it is accompanied by azotaemia and (though not invariably), oliguria. Acute

non oliguric renal failure is present in 4-10% of patients hospitalized with SCD(18).

Causes include;

1. Pre-renal failure; intravascular volume depletion.
2. Acute tubular necrosis; secondary to rhabdomyolysis, sepsis, drug nephrotoxicity, renal vein thrombosis.
3. Post renal causes include urinary tract obstruction secondary to blood clots, sequelae of papillary necrosis.

Renal medullary carcinomas

This rare but highly aggressive tumor is found in young black patients with the sickle cell trait. It is commonly seen in males. Then the reported age at diagnosis ranges from the second to the fifth decade (19,20).

Patients present with gross haematuria, flank pains, abdominal mass and weight loss.

Chromosomal abnormalities in the tumor tissue have been localized to chromosome 11, and less often to chromosome 3.

CT shows a centrally located infiltrative lesion arising from the medulla, invading the renal sinus with peripheral caliectasis (21,22).

Prognosis is not favourable. Neither radiotherapy nor chemotherapy have been found useful.

Hypertension in sickle cell disease

This is often uncommon in SCA. Blood pressure values are, on average 5 to 15mmHg lower in SS patients than in those of matched age and gender.

Hypotheses put forward include;

1. Sodium and water wasting due to the medullary deficit,
2. Systemic vasodilatation compensating for microcirculatory flow disturbance,
3. Reduced vascular reactivity, and
4. Increased production of prostaglandins and nitric oxide.

There is a risk of adverse cardiovascular outcome, if the supposedly “normotension” is not adequately treated. Blood pressure values higher

than 130/8mmHg are considered abnormal in SCA and should be treated promptly (23,24,25).

Diuretics should be avoided as initial antihypertensive agents, as they may cause volume depletion and precipitate sickle cell crises.

Priapism and erectile dysfunction

Priapism is a common acute complication of sickle cell disease in men. It could simply be defined as penile erection in the absence of sexual stimulation. It is also regarded as prolonged, painful erection which results in tissue ischaemia and a reduced or absent return of erectile function. Priapism is considered a medical emergency because if it is not promptly treated it could lead to permanent damage and erectile dysfunction(26). The reported prevalence of priapism in sickle cell disease ranges from 2 to 35% and it is as high as 44.9% among Nigerian males with sickle cell disease (24). The typical cases occur around the 2nd and 3rd decades of life (16).

According to the American Urological Association Guidelines on the Management of Priapism, priapism can be subdivided into three categories: ischaemic, stuttering, and nonischaemic. Ischaemic priapism (veno-occlusive, low flow) is a persistent erection marked by rigidity of the corpora cavernosa and little or no cavernous arterial inflow. In ischemic priapism, there are time-dependent changes in the corporal metabolic environment with progressive hypoxia, hypercarbia, and acidosis that typically generate penile pain. Penile sinusoids are regions prone to red blood cell sickling in SCD men because of blood stasis and slow flow rates, and ischemic priapism is thought to result from prolonged blockage of venous outflow by the vaso-occlusive process. Clinically, there is congestion and tenderness in the corpora cavernosa, sparing the glans and corpus spongiosum, usually with a prolonged course of over 3 hours, and frequently resulting in fibrosis and erectile dysfunction. Stuttering priapism (acute, intermittent, recurrent ischemic priapism) is characterized by a pattern of recurrence, but an increasing frequency or duration of stuttering episodes may herald a major ischaemic priapism. Nonischaemic priapism (arterial, high flow) is a persistent erection caused by unregulated cavernous arterial inflow. Typically, the corpora are tumescent but not rigid, the penis is not painful and it is most frequently associated with trauma(27,28). Ischaemic priapism is often seen in sickle

cell disease and is considered an emergency. It is characterized by an abnormally rigid erection not involving the glans penis.

The goal of treatment is to preserve erectile function and prevent recurrences. As such, there is the need for early presentation at the hospital if home remedies are unsuccessful within 2 hours of onset. At the onset, patients should be counselled to drink extra fluid, use home-based simple or compound analgesia, and attempt to void. Other self-help strategies such as warm baths and gentle exercises like jogging may be helpful. If the priapism persists more than 2 hours, hospital care is required. This includes intravenous hydration and opioid analgesia. If the priapism persists more than 3 hours, aspiration and irrigation of the corpora with dilute phenylephrine, epinephrine, or etilefrine are indicated. Frequently, aspiration of blood from the cavernosal bodies is performed with a 23-gauge sterile needle, followed by irrigation with a 1 : 1,000,000 dilution of epinephrine in saline, after adequate counselling, conscious sedation, and local anaesthesia(27). If detumescence is achieved lasting more than one hour, the patient may be discharged home on oral analgesic, pseudoephedrine, and clinical follow-up. Penile aspiration and irrigation may be repeated up to 3 or 4 episodes if detumescence is not achieved early.

EBT is indicated in recalcitrant cases. Surgical shunt procedures such as the proximal shunt of Quackel or the distal shunt of Winter may be tried, if conservative measures remain unsuccessful. However, surgical penile shunts may also be unsuccessful and may induce impotence (28,29,30). Often, priapism will resolve with one or a combination of medical interventions.

In preventing priapism, male sickle cell patients ought to be adequately informed and counselled about priapism from adolescence. Patients with frequent episodes (≥2 per month, ≥4 per year) should receive priapism prophylaxis with oral pseudoephedrine 30 mg daily if they are less than 10 years of age and 60 mg per day if they are older than 10 years.

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OTORHINOLARYNGOLOGIC-HEAD AND NECK MANIFESTATIONS OF SICKLE CELL DISEASE

OLAOSUN AO

Sickle cell disease (SCD) is the name given to a group of common inherited conditions that affect the red blood cells. It is a haemoglobinopathy and thought to be the most common inherited blood disorder. The majority of cases occur in sub-Saharan Africa, but it is also common in India, the Arabian Peninsula and among people of African origin living in other parts of the world. Since the underlying pathology is related to abnormal blood cells with the effects potentially affecting blood vessels all over the body, SCD has multi-systemic manifestations. It can affect virtually all organ systems and lead to end-organ damages. Expectedly, there are Otolaryngologic-Head and Neck complications. These have been reported in the ears, paranasal sinuses, upper airway, soft tissues and bones of the face and skull base, and in the lymph nodes of the neck. These complications are often severe and life-threatening, and sequelae have major impacts on the quality of life of patients. In the past, these manifestations did not receive much attention because the focus was more on the life-threatening complications. However, with improved management and longevity in patients with SCD, these complications are now encountered more frequently, receive more attention. and have more severe presentations than in the past.

Otorhinolaryngologic–Head and Neck Manifestations of Sickle Cell Disease

Sickle cell disease (SCD) is the name given to a group of common inherited conditions that affect the red blood cells. It is thought to be the most common inherited blood disorder, affecting over 400,000 babies annually. (1) About 4.4 million people have sickle cell disease, while an additional 43 million have the sickle cell trait. (2, 3) The greatest burden (about 80%) of sickle cell disease cases occurs in sub-Saharan Africa but

the disease is also common in parts of India, the Arabian Peninsula and among people of African origin living in other parts of the world. (4, 5)

SCD is a haemoglobinopathy. The basic abnormality is a substitution of valine for glutamic acid in the β-globin chain (at the sixth codon on the short arm of chromosome 11), leading to an abnormal haemoglobin structure (HbS). (6, 7, 8, 9) Individuals who have one HbS chain with another abnormal β-globin chain – usually another sickle cell chain (resulting in homozygous HbSS disease or Sickle cell anaemia), a haemoglobin C chain (HbSC) or a thalassaemia chain (HbS-thal) (1, 2) – are said to have SCD. (7, 8, 9) The most serious type is sickle cell Anaemia (HbSS disease). Rarer forms include Haemoglobin SD disease (with a haemoglobin D chain), haemoglobin SE disease (with a haemoglobin E chain) and Haemoglobin SO disease (with a haemoglobin O chain). (7, 8, 9) Haemoglobin SD disease and haemoglobin SE disease are sometimes not classified under SCD as they usually only lead to mild Anaemia.

Since the underlying pathology is related to abnormal blood cells with the effects potentially affecting blood vessels all over the body, SCD has multi-systemic manifestations. It can affect virtually all organ systems and lead to end-organ damages. (9, 10) Expectedly, there are Otolaryngologic-Head and Neck complications. These have been reported in the ears, paranasal sinuses, upper airway, soft tissues and bones of the face and skull base and the lymph nodes of the neck. In the past, these manifestations did not receive much attention because the focus was more on the life-threatening complications. However, with improved management and longevity in patients with SCD, these complications are now encountered more frequently, receive more attention and have more severe presentations than in the past. (11) The Otorhinolaryngologic-Head and Neck Manifestations of Sickle Cell Disease that have been reported in the literature are shown in Table 1.

Table 1: Otorhinolaryngologic Manifestations of Sickle Cell Disease in the Literature

Ears	• Sensorineural Hearing Loss • Conductive Hearing loss • Vertigo and other Vestibular Symptoms • Tinnitus • Labyrinthine Haemorrhage • Labyrinthitis Ossificans • Middle Ear Extramedullary Haematopoiesis • Higher burden of Otologic disease
Nose and Sinuses	• Nasal Obstruction • Epistaxis • Priapism of Nasal Turbinate • Nasal/Paranasal Sinus/Nasopharyngeal Extramedullary Haematopoiesis
Airway	• Adeno-tonsillar hypertrophy • Upper Airway Obstruction • Sleep Disordered Breathing • Obstructive Sleep Apnoea
Facial soft tissue	• Facial soft tissue swelling • Infections – cellulitis, abscess
Bony	• Maxillofacial and Skull base bone infarction • Osteomyelitis • Subperiosteal haemorrhage and abscess • Bone marrow hyperplasia • Osteoporosis • Iron deposition
Neck	• Cervical lymphadenopathy • Lymphoma
Immunologic	• Head and Neck Infections

Otologic Manifestations of Sickle Cell Disease

Most otologic manifestations are due to vascular complications of SCD in the inner ears. As is usual with inner ear disorders, the manifestations include Sensorineural Hearing Loss, vestibular symptoms and tinnitus.

These manifestations can occur separately or as different combinations of the various symptoms. (12)

Sensorineural Hearing Loss

The most clearly documented otologic manifestation of SCD is Sensorineural Hearing Loss. It can occur in both children and adults although the incidence appears to be higher in adults. Studies report a prevalence ranging from 3.8% to 21.4% of children with SCD (compared with 0% to 6.2% in controls) and in 46% to 66% of adults with SCD (compared with 7.5% to 47% in controls). (9, 13-18)

Sensorineural Hearing Loss could be unilateral or bilateral, mild or severe, transient or permanent and its onset could be sudden or progressive. (11) It could also be sensory or neural. It is thought that hearing loss in patients with HbSS appears to be neural and of earlier onset, while that in HbSC disease, appears to be sensory (cochlear) and of later onset. (15) Some studies have also suggested that damage in the auditory system can affect retro-cochlear structures, causing functional deficits without deterioration of auditory sensitivity. (19)

It is important to recognize Sensorineural Hearing Loss early and especially when onset is sudden. Accordingly, it is important to note that the onset of sudden Sensorineural Hearing Loss in SCD patients may be with or without pain and may or may not be associated with acute vaso-occlusive crises. As is customary with sudden Sensorineural Hearing Loss, early intervention with steroids is recommended, and complete recovery has been reported in the literature. (20)

Vestibular Symptoms

Patients with SCD also commonly present with vestibular symptoms. These may occur as frequently as, or even more commonly than Sensorineural Hearing Loss as suggested by a study of SCD patients presenting with ear symptoms in which more patients presented with vestibular symptoms than with Sensorineural Hearing Loss. (12) The vestibular symptoms reported have been described using various terms including dizziness and vertigo. (12)

Tinnitus

Tinnitus is also common among SCD patients. It often occurs along with Sensorineural Hearing Loss and/or vertigo but can occur in isolation. (12)

Pathophysiology of inner ear manifestations

Inner ear manifestations in SCD patients are thought to be due to recurrent vaso-occlusion of the labyrinthine blood vessels although the precise nature of labyrinthine blood flow and the factors that affect it are not well known. (9, 13-18, 21-24) It is hypothesized that alterations in labyrinthine blood flow in SCD patients initiate progressive local hypoxia which culminates in cellular damage leading to deafness and/or vestibular symptoms. (11) Proposed specific mechanisms of the pathophysiology include Labyrinthine Haemorrhage and Labyrinthitis Ossificans. (9, 10, 12-18, 21)

Features of both Labyrinthine Haemorrhage and Labyrinthitis Ossificans have been demonstrated by temporal bone imaging in association with Sensorineural Hearing Loss and appear to be associated with specific anatomic structures of the inner ear: labyrinthitis ossificans is always identified in the lateral semi-circular canal and labyrinthine haemorrhage in the basal turn of the cochlea and vestibule. (12) Despite these findings, the exact relationship between temporal bone radiological findings and clinical presentation in SCD patients has also not been clearly defined as there are also situations where there are no temporal bone radiologic features of Labyrinthine Haemorrhage, Labyrinthitis Ossificans or other radiologic findings in SCD patients presenting with inner ear manifestations. (10, 12)

Labyrinthine Haemorrhage

Labyrinthine Haemorrhage is widely thought to result from altered capillary haemodynamics or from reperfusion injury. (9, 10) It seems to occur most commonly in patients with HbSC disease and it has been noted that the few cases of Labyrinthine Haemorrhage in patients with SCD that have been reported in the literature were from patients with HbSC disease. (10, 12) Consequently, it is also postulated that blood viscosity-related factors may be important in Labyrinthine Haemorrhage because these factors are thought to be related to proliferative retinopathy which is also more prevalent in HbSC disease. (12, 25) Labyrinthine haemorrhage is

also thought to be usually associated with sudden onset of Sensorineural Hearing Loss and vestibular syndromes. (10, 12)

Labyrinthitis Ossificans

Labyrinthitis Ossificans is the end-stage of labyrinthitis and associated mostly with Sensorineural Hearing Loss. It is characterized pathologically by proliferation of fibroblasts and finally osteoblasts. (12) It is theorized that Labyrinthitis Ossificans occurs secondary to Labyrinthine Haemorrhage, a result of a reparative response triggered off by haemorrhage into the labyrinth which progresses from fibrosis to sclerosis and ultimately ossification. (25) A firm association between the two has however not been fully demonstrated. More so, unlike Labyrinthine Haemorrhage, Labyrinthitis Ossificans seems to be more prevalent among patients with sickle cell anaemia, and this is thought to be because they tend to have more vaso-occlusive episodes and therefore a higher probability of developing vascular complications thus linking Labyrinthitis Ossificans to vaso-occlusion. (12) Further confounding the picture, some studies have suggested that unlike other complications of SCD, deafness and other otological complications are more common in HbSC disease and other variants than in HbSS disease. (11)

Other causes of Sensorineural Hearing Loss in SCD patients

Sensorineural Hearing Loss in SCD patients has also been reported from other causes apart from middle ear pathology. It has also been reported following bacterial meningitis and in association with acoustic neuroma. (11) A famous case of SCD in association with Sensorineural Hearing Loss and acoustic neuroma is that of singer Tionne “T-Boz” Watkins, who was successfully treated surgically after some hesitation and fear of complications. The case was referred to in a book by her surgeon, Dr Keith Black. (26, 27)

Higher burden of otologic disease

While the inner ear manifestations are the most clearly documented, it has been reported that there is a higher overall burden of ear disease in patients with SCD. A higher prevalence of wax-related pathologies, Otitis Media with Effusion, Suppurative Otitis Media and Otosclerosis has been found in the SCD compared with the non SCD population and it has been

suggested that there is a need for special Otorhinolaryngological care for SCD patients, especially children. (28)

Rare Causes of hearing Loss in SCD

Extramedullary Haematopoiesis has been described in SCD and may lead to conductive hearing loss. (29) Extramedullary Haematopoiesis is discussed in more detail later.

Management of Otologic Symptoms

Patients with SCD who complain of ear symptoms should have a prompt and thorough work-up. This work-up should include computed tomography and MRI if there are inner ear symptoms. As earlier noted, Sudden Sensorineural Hearing Loss should be promptly treated with steroids as an adjunct to other management. Regular audiologic assessment and counselling of SCD patients are recommended, and rehabilitation with hearing aids will often be needed. (13) Acute incapacitating vestibular symptoms can be symptomatically treated with short courses of labyrinthine sedatives as an adjunct to other treatment and vestibular rehabilitation may be necessary if imbalance persists.

Rhinologic Manifestations of Sickle Cell Disease

The nose and paranasal sinuses are highly vascularized and SCD complications can manifest in them. Complications that have been reported in the literature include extramedullary haematopoiesis and priapism of nasal turbinates. (9) Clinically, these nasal complications will usually manifest with epistaxis and/or nasal congestion or obstruction.

Extramedullary haematopoiesis

Although extremely rare, extramedullary haematopoiesis has been reported in the nasal cavity, nasopharynx, maxillary and sphenoid sinuses as well as in the ethmoidal air cells. The maxillary sinus is thought to be the most commonly involved sinus. (9, 30, 31, 32) Extramedullary haematopoiesis is a compensatory response to an increased need for blood production which leads to bone marrow hyperplasia and medullary tissue prolapse. (31) It occurs in SCD and other chronic anaemic conditions such as thalassaemia and myeloproliferative disorders. (30, 31) In the head and

neck region, it has also been found in the middle ear, thyroid gland, cervical lymph nodes, and lacrimal fossa. (29, 30, 31, 32)

In the nose, paranasal sinuses and nasopharynx, extramedullary haematopoiesis may present with epistaxis and nasal/airway obstruction. (31, 32, 33) It is however often asymptomatic and may be an incidental finding while investigating for other conditions. (9, 30, 31) On CT and MRI imaging, extramedullary haematopoiesis is displayed as a soft-tissue mass which demonstrates attenuation or signal intensity and homogeneous enhancement similar to that of red marrow and more intense than that of normal bone. (34, 35, 36)

Treatment of Nasal/Paranasal/Nasopharyngeal Extramedullary Haematopoiesis

There are no definitive therapeutic recommendations in the literature for the treatment of nasal/paranasal sinus/nasopharyngeal extramedullary haematopoiesis. (30) Endoscopic excision, which also allows for histological confirmation of the diagnosis has been reported to be successful. (37)

Priapism of the turbinates

Priapism of the nasal turbinates is another rhinologic manifestation of SCD. (38) Priapism is a term that is traditionally used for a condition in which there is a painful or painless, purposeless and persistent state of penile erection following or occurring in the absence of sexual stimulus. (39) This condition is well-known, though one of the less well characterized complications of sickle cell disease. It derives its name from the Greek God of fertility, Priapus, protector of livestock, and gardens, who is depicted in Greek mythology as being endowed with an enormous phallus. (39, 40)

In the nose, when the turbinate manifests a persistent state of enlargement with a pathophysiology similar to that of priapism of the phallus, the term priapism of the turbinate is used. It is suggested in the literature that there is a relationship between the nose and the sex organs. (39, 41, 42) The blood supply to the turbinates has also been described as pseudoerectile, similar to that of the penis, and the cavernous structure of the conchae is comparable to the erectile tissue of the penis and clitoris. (39, 41, 42) Also, excision of the conchae in young animals has been found to result in

hypoplasia of the sex organs and degenerative changes in the nasal mucosa, reversible by oestrogen injections, have been observed following castration. (42)

The mechanisms underlying sickle-cell induced nasal turbinate priapism have not been as well studied as those for priapism in the penis and clitoris but due to the supposed relationship the mechanisms are thought to be similar.[39] Classically, the primary mechanism is thought to be obstruction of venous drainage resulting in viscous, hypoxic blood, interstitial oedema and eventual fibrosis of the erectile tissues of the turbinates. This ultimately results in a persistent turbinate hypertrophy. (43) The resulting nasal obstruction usually fails to respond to even vigorous therapy to reduce the size of the turbinate and to relieve nasal congestion. As obstruction is usually unremitting, a partial turbinectomy may be necessary for the relief of nasal obstruction. (41, 44)

Airway Manifestations of Sickle Cell Disease

Hypertrophy of the tonsils and adenoids is common among children with SCD and may lead to Obstructive Sleep Apnoea and Upper Airway Obstruction. (45) Children with SCD have a higher incidence of Obstructive Sleep Apnoea associated with snoring, sleep disturbances and Upper Airway Obstruction than matched non-sickle cell controls. (46, 47) One study reports a prevalence figure of 43% for Obstructive Sleep Apnoea in SCD children compared to 18% of sibling controls and another reported a prevalence of 36% of children with SCD. (46, 47) These complications can cause significant airway narrowing promoting hypoxaemia and in a vicious cycle increasing the risk of sickling and attendant complications.

Several pathophysiological mechanisms have been proposed for the increased prevalence of adeno-tonsillar hypertrophy among SCD patients. The most widely accepted is that hypertrophy of lymphoid tissues of Waldeyer's ring occurs alongside other compensatory lymphoid hyperplasia. Such hyperplasia occurs in SCD secondary to functional hyposplenia and defects in the complement pathway that affect immune surveillance. It has also been proposed that reactive hyperplasia of these pharyngeal lymphoid tissue collections occurs secondary to repeated upper airway infections in SCD patients. (48)

Reduced tone in the pharyngeal musculature during sleep worsens airway patency in the presence of adenotonsillar hypertrophy and leads to various

degrees of Upper Airway Obstruction. Partial airway obstruction from enlarged adenoids and tonsils leads to snoring and sleep-disordered breathing. The resulting spectrum of sleep-disordered breathing ranges from simple snoring to Obstructive Sleep Apnoea. Obstructive Sleep Apnoea is characterized by repetitive episodes of shallow or paused breathing during sleep, despite the effort to breathe, and is usually associated with a reduction in blood oxygen saturation. These episodes of apnoea typically last 20 to 40 seconds. (49) Other manifestations in patients with Obstructive Sleep Apnoea are snoring, daytime somnolence, mouth breathing, abnormal behaviour, learning difficulties, early morning headaches, sudden startled or gasping awakening, sweating, nightmares, night terrors and nocturnal enuresis. (50)

Untreated Upper Airway Obstruction and Obstructive Sleep Apnoea can lead to a myriad of systemic and cardiopulmonary complications. Failure to thrive, pulmonary hypertension, cor pulmonale, polycythaemia, systemic hypertension, congestive heart failure, vagal bradycardia strokes and sudden death are complications that have been reported in patients with SCD. (46, 50, 51, 52) In the SCD patient, there is more severe nocturnal desaturation and hypercapnia compared to Upper Airway Obstruction uncomplicated by SCD. (50, 53) There is also more marked hypoxaemia with a heightened risk of vaso-occlusive crises and repeated or chronic hypoxia increases the risk of complications associated with Upper Airway Obstruction and Obstructive Sleep Apnoea in SCD patients. (50, 53)

As with all suspected cases of Obstructive Sleep Apnoea, careful history, clinical evaluation and lab studies including polysomnography are required to assess these as it has been found that more than half of patients with snoring and other sleep associated symptoms do not actually have Obstructive Sleep Apnoea. (55, 56) If confirmed, Upper Airway Obstruction and Obstructive Sleep Apnoea in SCD patients are indications for Tonsillectomy and/or adenoidectomy due to the higher risk of vaso-occlusive crises from hypoxaemia and of high risk of other complications including cerebrovascular accidents. (57) Tonsillectomy and/or adenoidectomy is undertaken in these patients with great care bearing in mind the perioperative risks related to hypoxaemia, dehydration and hypothermia. However, with a better understanding of these risks and the protocol-based comprehensive team-oriented management of pre-operative transfusion, hydration, antibiotics, anaesthesia and post-operative care, the risk of perioperative complications following

Tonsillectomy and/or Adenoidectomy in SCD children has decreased. (50, 57, 58, 59)

Improvements in sleep study parameters and symptoms, including better sleep habits and quality, decreased snoring, decreased day time somnolence, better school attendance and academic performance and reduced risks of complications have been demonstrated following Tonsillectomy and Adenoidectomy in SCD patients. (50, 54)

Facial Soft Tissue

Facial soft tissue swellings have been reported in patients with SCD. (60, 61) The differential diagnosis includes facial cellulitis and abscess. (60, 61) Idiopathic facial swellings have also been reported in the literature and these are thought to be due to vaso-occlusion. (60) Thorough assessment to rule out underlying dental affectation or bony involvement is important, and investigations should include a full blood count, acute inflammatory markers and appropriate radiological investigations (such as orthopantomography for swellings around the cheeks and jaw). Treatment remains multidisciplinary and according to general principles of SCD management because the swellings may occur as part of an SCD crisis and may herald it. If a patient is not a known SCD patient, thorough assessment and a high index of suspicion are needed for an accurate diagnosis of the underlying SCD. A red flag is raised if physical findings and blood results are out of consonance with a painful facial swelling.

Bony Complications

Maxillofacial and Skull base

Bone involvement is known to be the most common clinical manifestation of SCD. (36, 62, 63) Although rare in the bones of the face and skull base because of the small amount of marrow space in these bones, bony complications have been reported in the region. The most common sites affected are the orbital wall, mandible and skull base in that order of frequency.[64] Manifestations can be acute or chronic. Acute manifestations include orbital wall infarction, vaso-occlusive crisis and osteomyelitis, while the chronic manifestations are marrow hyperplasia, osteoporosis and iron deposition within the marrow.

Acute Manifestations

Orbital wall infarction

Orbital wall infarction can result from vaso-occlusion. It is typically associated with haematomas, which may be orbital (subperiosteal) or intracranial (epidural). (65-68) Clinically, it presents with acute, rapidly progressive periorbital pain and swelling, with or without features of an orbital compression syndrome, symptoms of which include proptosis, reduced ocular mobility, corneal hypesthesia, and optic nerve dysfunction. (66, 68) Treatment is conservative if there are no neurologic symptoms or signs, but urgent needle aspiration or surgical drainage is necessary for large haematomas or if there is optic nerve dysfunction. (68)

Vaso-occlusive crisis and Osteomyelitis

Vaso-occlusive crisis is reported to be about 50 times more common than osteomyelitis among children with SCD. (36, 69) It presents as pain from ischaemia of the medullary cavity and subsequent infarction. (36, 69) As infarcted or necrotic bone is a good environment for bacterial growth, osteomyelitis can follow bone infarction. The most common organisms implicated are Salmonella organisms (especially the atypical serotypes Salmonella typhimurium, Salmonella enteritidis, Salmonella choleraesuis, and Salmonella paratyphi B), followed by Staphylococcus aureus and gram-negative enteric bacilli. (63, 70) The most common site affected in the face is the mandible, because of its relatively poor blood supply. (71, 72)

The presenting features for these two acute entities overlap as do the conditions themselves and it may be difficult to differentiate one from the other as they may both present with fever, pain, and swelling. However, prolonged fever and pain, as well as bone pain and swelling at a single site are thought to be indicative of osteomyelitis. (73) Imaging findings are also similar and MRI imaging (T2-weighted fat-saturated MR imaging and contrast-enhanced fat-saturated T1-weighted MR imaging) may be necessary to differentiate between the two. (74, 75)

Chronic Manifestations

In SCD chronic bone conditions such as marrow hyperplasia, osteoporosis and iron deposition within the marrow are common. (36, 63, 69, 76)

Marrow hyperplasia occurs as a result of increased red blood cell destruction and chronic anaemia.[9] There is an expansion of red marrow with the subsequent thinning and crowding of trabeculae, and osteoporosis. (9) Deposition of iron in the bone marrow occurs as a result of iron overload from repeated transfusions that are often necessary in SCD patients. (9, 69, 76) In the head and neck, iron deposition can also be found in the salivary glands. (9)

The Neck

Lymph Node Enlargement

Lymph node enlargement is common among SCD patients and often bilateral. Lymphadenopathy secondary to infection is the most common cause as SCD patients are at increased risk for infection. While this is so, it is important to exclude other causes of lymph node enlargement as patients with SCD have been reported to develop haematologic malignancies such as lymphoma, multiple myelomas, and hairy cell leukaemia, although the relationship of these with SCD is not clear. (77, 78)

Immunologic Complications

There is a high incidence of bacterial infections in sickle cell disease, particularly in sickle cell anaemia. This also manifests in the head and neck as an increased incidence of head and neck infections. Although the pathological basis for susceptibility to infections is complex, defective splenic function is the most important factor. Other factors include abnormalities of opsonization, alternate complement pathways, antibody production, leucocyte function, and cell-mediated immunity. Pneumococcal immunization and prophylactic penicillin are indicated in the prevention of pneumococcal infections. (79)

Conclusions

In conclusion, Otolaryngologic-Head and Neck complications are not uncommon in patients with SCD. With improved management and longevity, the incidence of these complications of SCD have become more apparent and previously milder complications have more severe presentations. (11) Considering the seriousness of these complications, the impact of sequelae on the patient's quality of life and the huge difference

that early diagnosis makes in the eventual outcome, it is important for clinicians to be familiar with the manifestations in order to facilitate early diagnosis and prompt adequate treatment.

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Pregnancy and Labour in Sickle Cell Disease

Farinloye EO and Abiodun OM

Sickle cell disease is an autosomal recessive genetic disorder which may manifest itself either in its heterozygous or homozygous form in the patient. About 8.5% of African Americans are heterozygous for the sickle cell gene (sickle cell trait), while Nigeria has a carrier rate of about 40%. A pregnant SCD patient is exposed partly to complications due to her SCD status such as acute chest syndrome, bone pain crises, urinary tract infections among others and partly due to her pregnancy state such as preeclampsia-eclampsia, intrauterine growth restriction or foetal death. The management of these patients is best done under a multidisciplinary setting with available manpower for blood screening and transfusion. The obstetric care of these patients must include *Preconception Care, Antenatal Care, Intrapartum Care* and *Postpartum Care*. Prenatal care focuses on evaluating the patient in readiness for pregnancy. Antenatal care evaluates the risk of development of SCD in the foetus with the aid of prenatal diagnostic tests including Chorionic Villus Sampling at around 12 weeks, Amniocentesis at 16 weeks and foetal blood sampling after 20 weeks. In their intrapartum and postpartum care, measures are put in place to avoid undue stress and other medical complications. Effective contraception is also very important.

Sickle cell disease (SCD) is a genetic condition characterized by the presence of deformed or sickle-shaped haemoglobin generally denoted as HbS. (1) Sickle cell disease is an autosomal recessive genetic disorder. About 8.5% of African Americans are heterozygous for the sickle cell gene (sickle cell trait), and they do not become anaemic or exhibit any other related clinical symptoms. On the other hand, less than 1% of African American babies are homozygous for the disease with the attendant morbidity and mortality. (2) Nigeria, a developing country in West Africa has a sickle gene carrier rate of roughly 40%, and yearly, about 150,000 children are born with sickle cell disease. (3) Due to the fact that SCD is a blood pathology, it can manifest itself in any organ or

system in the human body including the reproductive organs and the system generally. Pregnancy in an SCD woman is a high-risk pregnancy. This is so due to the superimposition of the risk of pregnancy on the risk of sickle cell disease in the same woman.

The maternal and foetal obstetric complications of SCD include anaemia, hypertensive disorders of pregnancy such as preeclampsia-eclampsia, intrauterine growth restriction (IUGR), painful crises and premature delivery among others. (4-8)

These patients are also prone to developing acute chest syndrome, bone pain crises, urinary tract infections and in extreme cases, maternal or foetal death.(9-10)In the advanced countries of the world, SCD pregnancies are closely monitored throughout pregnancy with the resultant favourable maternal and foetal outcomes. (11-14) But this is not the case in countries like Nigeria, having many challenges. (6)As a result of the risks associated with pregnancy in an SCD patient, the management of these patients has to be multidisciplinary in approach in centres with facilities for blood screening and transfusion.

Due to the chronic nature of the disease, the principle is to stay ahead of complications that may arise. The obstetric care of these patients will include *Preconception Care, Antenatal Care, Intrapartum Care* and*Postpartum Care*. The patients are also encouraged to attend haematology and medical clinics in and outside of pregnancy.

Preconception Care

Determining the haemoglobin genotypes of the prospective mother and her partner by carrying out haemoglobin electrophoresis is one of the most significant things to do in the preconception care of a sickle cell disease patient. (15) If the results of investigations show the partner to also have sickle cell disease or carry the trait, the implications as regards the baby either being a carrier of the trait or developing the disease must be explained to the patient.

Prenatal care in an SCD patient also focuses on evaluating the patient in readiness for the added stress of pregnancy. The risks (maternal and foetal) that she faces should be explained to her. Possible complications, when they are likely to occur, what precipitates them and how to avoid some of them must be explained to the patient. It is important for her to make informed choices. Many of these patients with proper counselling may

decide to defer pregnancy at this stage in which case appropriate contraceptive options must be explained to them. If she however wishes to carry a pregnancy now, then she would need all the necessary support from her spouse and place of work or engagement as may be applicable to her.

Crucial information for SCD patients looking forward to getting pregnant includes the following: (16)

(a) The possibility of her baby inheriting the trait or disease depending on her spouse's genotype;

(b) The possibility of growth restriction, increasing the chances of operative deliveries;

(c) Effects of cold, dehydration and other stressful situations;

(d) Aggravated anaemia and painful crises; and

(e) Increased risk of bacterial infections including urinary tract infection (UTI).

These patients must be screened for the presence of other chronic diseases that may complicate the pregnancy. Blood pressure measurement and urinalysis for protein are essential to detect women with hypertension and proteinuria. Renal and liver function tests should be conducted to rule out pre-pregnancy nephropathy and abnormal hepatic functioning. (17)

In view of the increased incidence of pulmonary hypertension in SCD patients, echocardiography will be important. A tricuspid regurgitant jet velocity greater than 2.5 m/second is a pointer to an impending pulmonary hypertension. (18-19) This would make a review by a cardiologist very crucial. Magnetic Resonance Imaging (MRI) is needed in patients who have had multiple blood transfusions in the past to detect iron overloading which may necessitate iron chelation. Retinal screening for proliferative retinopathy, a condition that is often present in SCD patients which may cause blindness is also important and appropriate corrective measures must be instituted where such an abnormality is found.

Penicillin prophylactic treatment is of value in patients with SCD because they are hyposplenic and susceptible to bacterial infections from agents such as Haemophilus influenzae, Neisseria meningitides, and

Streptococcus pneumonia. (20) Hepatitis B and influenza vaccinations are to be encouraged. (17)

The drug management of SCD patients in and outside of pregnancy is very important. Folic acid, 5mg daily should be commenced and must continue in pregnancy to prevent neural tube defect and to alleviate folate deficiency due to the haemolytic anaemia in them. (21-22)

Hydroxycarbamide (Hydroxyurea), which has been found to reduce the severity of acute pain crises and acute chest syndrome must be stopped about 3 months before the commencement of the pregnancy because of its teratogenic effects as shown in animal studies. (23) In the same vein, Angiotensin Converting Enzymes Inhibitor must be stopped before conception if the patient was taking it because of its possible teratogenic effects on the foetus.

Antenatal Care

Many times, apart from their routine medical or haematology clinic visits, these patients present in pregnancy for the first time for antenatal booking, having missed the counselling and evaluations that the preconception care offers. At other times, they are rushed in by husbands and relatives in crisis and needing urgent help. As time would permit, all the evaluations prescribed for preconception care must be carried out when seen at this time. Where facilities are available, the following prenatal diagnostic tests are advised: Chorionic Villus Sampling (CVS) at around 12 weeks, Amniocentesis at 16 weeks and foetal blood sampling after 20 weeks, the latter is however associated with a risk of foetal loss (about 2%). The aim of these tests is to obtain foetal cells for genetic evaluation. Research has made it possible to obtain free circulating foetal cells in the maternal circulation which can be analysed to get information about the foetal genetic make-up. (24)

The possibility of terminating a pregnancy affected by SCD should be discussed with the patient after reviewing the results of the prenatal diagnostic tests. (25)This may be the case in some countries e.g. Cuba, China, South Africa, India, and others where the termination of pregnancies affected by foetal abnormalities is allowed. (26)However the woman reserves the right to continue with the pregnancy if she so desires.

In the event that the woman chooses to continue with the pregnancy, initial ultrasound scanning is done at around 12-13 weeks and this is followed by

scanning for foetal abnormalities at 20 weeks while from 30 weeks regular scanning should be embarked upon for amniotic fluid volumes and foetal growth. (27)

Urinalysis and urine culture should be done monthly and appropriate treatment given as the case may be. All necessary pregnancy immunizations must be given. Research has recently shown that iron deficiency is not an issue in these patients, iron administration would only be needed in cases of iron deficiencies. (28)

Women who are prone to preeclampsia should take low dose (75mg) aspirin daily, from 12 weeks. (29) Usage of graduated compression stockings is advised for women at risk of venous thromboembolism.

Acute stroke and acute anaemia are not uncommon in SCD patients during pregnancy and these conditions would need exchange blood transfusion. (17) For SCD patientsin pregnancy, there is no need for thrombolysis.(17)

Other medical situations like malaria must be treated with drugs that are safe for the specific periods in pregnancy.

Intrapartum Care

On account of the high risk associated with SCD pregnancies, these patients should deliver in standard, well-staffed and equipped hospitals. The aim should be to achieve vaginal delivery as much as possible between 38 and 40 weeks, reverting to Caesarean section only for obstetric indications. (30) Labour in these patients should be monitored with a partograph in order to detect prolonged labour early and institute an appropriate intervention. The factors that precipitate crises such as dehydration and cold should be avoided. Adequate pain management is very essential. An intravenous line should be secured for rehydration and possible blood transfusion. Blood must be taken and saved for grouping and cross-matching. Good oxygenation is also provided. Pregnant SCD patients are known to be at an increased risk of having stillbirths, placental abruption and other obstetric problems; intrapartum electronic foetal monitoring is therefore very important to help detect any anomaly early and expedite delivery by Caesarean section if indicated. (31-32) General anaesthesia should be avoided as much as possible, rather opting for regional anaesthesia for Caesarean section. (33)

Postpartum Care

Hydration and oxygenation should be maintained a few hours after delivery. NSAIDs are administered for pain relief and they are safe during breastfeeding. Low dose molecular weight heparin should be given for 1 week in vaginal delivery and 7 weeks following Caesarean section as a measure towards thromboprophylaxis. Progestogens are safe contraceptives in SCD patients. Intramuscular depo-medroxyprogesteroneacetate (DMPA) has an added advantage of reducing pains. (34)

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SPECIAL GYNAECOLOGY IN SICKLE CELL DISEASE

ADELEKE NA AND ADEYERA O

Sickle cell disease SCD is the commonest single gene disorder globally. SCD including Thalassaemia affects about 5% of the world population (1, 2) and occurs in Africa, Asia, Caribbean, Europe, North and South Americas. In sub-Saharan Africa two-thirds of the global 300,000 babies with sickle are born each year. Africa thus has the highest concentration and heaviest disease burden. (2).

In those who suffer from SCD there is chronic anaemia, relative tissues/organ hypoxia and under nutrition of varying severity affecting the entire organ systems including the reproductive system. (3, 4, 5) The disease impacted on the functional integrity of the reproductive organs of both males and females, such that certain clinical differences occurred compared to the normal population.

Puberty development in adolescents with sickle cell disease

Adolescence is a period of transition from childhood to adulthood characterized with physical and psychological development. (1) Puberty is a multiple transition phase taking place during the adolescent period, making it a very crucial period in the lives of the young ones. Biologically, it is that stage where the development of secondary sexual characteristics begins and it ends when anatomical and physiological maturation is achieved with the individual being capable of sexual reproduction. (6, 7) The period is critical for both males and females, and even more challenging for those with SCD. Decreased growth velocity has been observed in SCD and this is independently associated with haemoglobin concentration. (8) Both boys and girls with SCD suffer growth and other developmental delay. (9, 10)

Beyond these, adolescents with SCD have peculiarities with puberty and sexual development. The process of attaining puberty is slower for adolescents with SCD when compared to their counterparts who have a normal haemoglobin genotype. The physical growth pattern is also different for adolescents with SCD. Metabolism, haematology, and endocrinology have been implicated in the delayed growth and puberty development of adolescents with SCD. (8) The smaller body weight coupled with the increased metabolic demands of physical and sexual maturation is challenged in people living with SCD . Anaemia, aside from its effect on growth rate, in worse cases puts pressure on the heart and circulatory system in order to meet the energy demands. (9) For adolescent females, the abnormal endocrine function is that of hypogonadism which is primary or secondary in origin, this causes the ovarian steroid hormones: estradiol and progesterone, to be produced in low quantities leading to delayed puberty and primary amenorrhoea. (10) Menarche could be delayed for 2 to 3 years for adolescents with SCD. (11) This could be associated with profound anxiety, psychological disorders and depression if not properly managed. (12)

The menstrual cycle and acute pain crises among females with SCD

There are many reports on the patterns and association of menses with acute pain crisis in sickle cell disease, while many reports confirmed that menstrual patterns are similar to those of women in the general population. (13) Others reported shorter, heavier blood loss and the association of menses with acute pain crises. (14). While the discomfort of menses may precipitate acute pain crises in SCD, primary dysmenorrhoea is considered a physiological phenomenum that must be separated from acute pain crises in SCD as it occurs in both non-SCD and the Sickler. This requires a prospective study of the prevalence of dysmenorrhoea among non-SCD women and women living with SCD on one hand and the prevalence of acute pain crises among both the female and male SCD population. It is only then that the true effects of menses on acute pain crisis in SCD can be demonstrated. However, a wide range of factors may influence pain episodes ranging from biological, gender, psychological and possibly social and cultural factors. Anaemia as a characteristic of SCD could get worse and life-threatening due to heavy menstrual bleeding, and this must be considered by the health-care providers managing women with SCD.

Vaso-occlusive pain, also known as acute bone pain crisis is a common occurrence and an indication for hospitalization among individuals with SCD. The crisis is experienced by both males and females with SCD. (14, 15, 16, 17)

Pain crisis has a cyclical pattern with the menstrual cycle which may be suggestive of the influence of gonadal hormones. Though the specific mechanism of the gonadal hormone's interaction in the causation of vaso-occlusive pain is not exactly known, the effect of oestrogen hormones on the blood level concentration of Nitrous oxide NO, a powerful anti-oxidant and vasodilator, has been implicated. (18)

The frequency of vaso-occlusive episodes increases during pregnancy and puerperium, while the incidence of painful crises decreases after menopause. These observations further gave credence to the possible role of the fluctuation in the level of oestrogen and progesterone hormones in the pathogenesis of vaso-occlusive pain. (13, 14, 15). This gave rise to the application of hormonal therapy in the management of associated painful crises of menses. (8) The use of combined oral pills, COCP therapy or depot medroxyprogesterone acetate DMPA to modulate menstruation was shown to reduce the frequency and severity of painful crises among women. (13, 19)

Fertility in people living with Sickle Cell disease

Life expectancy, the disease disability free period and quality of life of people living with SCD have improved significantly as the direct results of better understanding of the pathology and the improved holistic (medical and social support) care of this hereditary group of diseases. Consequently, the fertility and fecundity of people with SCD became an emerging issue in the management of the disease.

The heterozygous state does seem not to have a significant negative impact on the fertility potential in both males and females when compared to the general population. However, a female carrier may experience increased prevalence of urinary tract infection (UTI) during pregnancy and probably anaemia.

The situation in the homozygous state (SCA) is different, there is consensus that fertility is reduced in males with SCA and this has been studied extensively. (13, 20) The reduced fecundity is a result of the effects of the disease and some of the treatment methods. Aside from

delayed sexual maturation, males with SCA have low testosterone, the dominant male hormone indicative of hypogonadism, and variable values of gonadotrophic hormones (follicular stimulating hormone FSH and luteinizing hormone LH), suggesting that some of the hypogonadism has a central origin. (21) Sub-optimal masculine features include sparse hair in the armpits and pubic area as well as small testicular volume.

Among other causes of male infertility in SCA are sperm abnormalities characterized by low semen density, morphology and motility anomalies, others are erectile dysfunction ED as a result of priapism and low libido. (13)

Various treatment modalities are in use which include testosterone and human gonadotrophin for hypogonadism, clomiphene and similar medicines for sperm abnormalities and penile implant for ED. These have achieved some levels of successes.

Repeated blood transfusion BT, hydroxyurea HU and haematopoietic Stem Cell Transplantation (HSCT) are all effective treatment modalities of the disease. Paradoxically all of them have been implicated in impaired fertility in both male and female patients. This major drawback is being overcome by various therapeutic adjustments, and these include reduced rate/frequency of blood transfusion, adoption of a minimum effective dose of HU as well as immune cell modulation and fertility preservation techniques prior to HSCT 9. (22, 23)

Female fertility in SCD has been poorly researched compared to male fertility. Most of the available information is from works carried out two to three decades ago with methodology constraints, as there are not many current prospective works. (13) Some reports documented reduced fertility and others reported no effect.

However, female SCA patients like their male counterparts suffer delayed sexual maturation. They also experience hypogonadism, premature ovarian failure, hypothyroidism and other endocrinopathies, all of which have negative impacts on fertility. (23)

Voluntary contraception and informed use of contraceptives in female SCD must not be confused with infertility. Most obstetricians will recommend that women living with SCA limit births to two and not more than three.

The role of negative social factors such as subtle discrimination, difficulty in maintaining a quality hetero-sexual relationship and negative psychology in people living with SCD in infertility needs further investigation.

Sexuality and contraception in sickle cell disease

There are limited studies on the sexual behaviours of people living with SCD especially women. (24, 25)

Males and females with SCD have health challenges, may experience subtle societal discrimination and difficulty in maintaining a lasting hetero-sexual relationship. Pregnancy, delivery and child parenting are associated with increased maternal morbidity and mortality in SCD. How these factors influence the reproductive choices of people living with SCD is poorly understood especially in sub-Saharan Africa where the majority of people with SCD live.

In the United Kingdom, a study showed an unintended pregnancy rate of 53% and lower contraceptive use among the SCD population compared to the general women population, in Ibadan Nigeria Okunlola MA, Olutayo AA, Okonkwo NS, and Akingbola TS. While in Jamaica, Knight-Madden J and Barton-Gooden A documented low contraceptives among the SCD female population. (26, 27, 28) In the same vein a Survey of Contraceptive Use among women living with SCD in Baltimore USA reported an unmet need for contraception. (29)

There are three main critical issues of concern amongst others about SCD clients and contraception. These include the safety of oestrogen containing commodities and increased risk of venous thromboembolism (VTE), progestogens and irregular vaginal bleeding and the complex relationship between steroid hormones, acute pain crises and menses in sickle cell disease. (30, 31) SCD places a woman in category 2 with respect to most contraceptive methods. (32, 33) There are concerns with the use of combined hormonal contraceptive in patients with SCD. The potential thrombotic complications as a result of oestrogen and the risk of increased pain are concerns with the use of the combined hormonal contraceptive. (14, 32)

Many studies showed that the number one choice of contraceptive for women with SCD is the progestin-only contraceptives, as the likelihood of thrombotic complications and painful events are reduced with this form of contraceptive. However, unpredictable vaginal bleeding as a side effect of progesterone-only contraceptives is a constraint. (14, 32, 33)

Non-pharmacological contraceptives have unique values in SCD clients and should be offered when appropriate. These include bilateral tubal ligation BTL for women and vasectomy for men. Barrier methods which may be combined with fertility awareness methods have special relevance in SCD. Whichever method is adopted it must be based on proper counselling, motivation, professional guidance and follow up services. On a balance of scale, using contraception is safer, healthier and more beneficial to SCD than unwanted pregnancy and induced abortion.

Living with a hereditary disorder such as sickle cell disease constitutes a life-long challenge to the afflicted as the disease impacts negatively on physical growth, the attainment of puberty, fertility potential and general health status and is a limiter of longevity.

Knowledge of the aetio-pathogenesis of haemoglobinopathies has advanced, and so has that of prevention. However, therapeutic measures to combat multiple health issues including psycho-social morbidity are far from satisfactory especially in the developing world, sub-Saharan African in particular. Therefore, there is yet a need for further research into novel treatment methods in the holistic care and management of people living with the disease, that is often described as mortal inheritance.

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MENTAL HEALTH CHALLENGES IN SICKLE CELL DISEASE

IBIGBAMI OI AND OPAKUNLE T

This chapter reviews mental health challenges in sickle cell disease. It gives an overview of what these health challenges are and the implications of mental health challenges in chronic medical conditions, with a focus on sickle cell disease patients. There has been a review of specific mental disorders including, depression, anxiety disorders, schizophrenia, psychoactive substance use, somatization, obsessive-compulsive disorders and eating disorders. The prevalence and clinical presentations of these disorders were also discussed. The chapter ends by discussing whether the sickle cell disease trait confers any additional risk of mental health challenges on individuals who have the illness. Mental health challenges are more common among SCD patients than the general population but they are similar in prevalence to those found among individuals with other chronic medical conditions. The presentations are not different from those found in other conditions with co-morbidity of mental disorders. Early detection and provision of adequate psychosocial support will go a long way to reduce the prevalence of mental health challenges in SCD patients by preventing breakdowns and enhancing prompt recovery for better prognosis.

Mental Health Challenges in Sickle Cell Disease

The saying "No Health without Mental Health" summarizes the importance of mental health and wellness in every individual. More importantly, individuals who are living with chronic medical conditions have been shown consistently to be prone to having more mental health challenges when compared to those who have no such illnesses.(1) According to the World Health Organization, being healthy is not just the absence of disease but living in "a state of complete physical, mental and social wellbeing". Furthermore, being mentally healthy connotes that the individual is able to maintain stability in three domains

which include emotional, psychological and social wellbeing. In addition to these, there is the expectation that the individual must be able to function optimally towards attaining "a dynamic state of internal equilibrium which enables individuals to use their abilities in harmony with universal values of society. Basic cognitive and social skills; ability to recognize, express and modulate one's own emotions, as well as empathize with others; flexibility and ability to cope with adverse life events and function in social roles; and harmonious relationship between body and mind represent important components of mental health which contribute, to varying degrees, to the state of internal equilibrium".(2)

Individuals who are mentally healthy are expected to be able to live satisfactorily in the midst of others with a subjective experience of wellness and the potential of being able to attain set goals and achieve a productive life experience devoid of limitations in their day to day pursuits. These expatiate the concept of "impairment in functioning" which seems to be the hallmark of mental disorders. In adults, functioning is described in the domains of personal care, family life, occupation and broader social context; while in childhood, the focus is towards the attainment of optimal psychological development, having a good sense of identity and self-worth, maintaining family and peer relationships and overall the ability of the young person to be productive and learn. Bearing these in mind, it becomes difficult to see individuals with chronic medical conditions who will be free from mental health challenges. Specifically, SCD is a disease that begins to manifest very early in childhood with its clinical presentations occurring intermittently as the child becomes an adolescent and the adolescent matures into adulthood. The negative psychosocial impact of SCD, as well as other chronic diseases like asthma and juvenile arthritis, has been shown to begin in early childhood with its impact extending to siblings and other family members of the sufferer. (3, 4) This has necessitated the recommendation of a multidisciplinary approach including both medical and psychological interventions in the management of this disease. (5) Mental health challenges that have been reported in SCD patients include depressive disorders, anxiety disorders, schizophrenia, substance use disorders and in children and adolescents; disruptive behaviours.(6-12)

Depression

Depression is a disorder that is characterized by the presence of low mood, loss of interest in pleasurable activities and decreased energy. Biological

symptoms of depression include poor sleep, loss of appetite and libido. These symptoms (with their related clinically significant impairment in functioning) could be a reaction to the stigma and frustration that accompany the disease or a primary functional mood disorder.(13) Studies have reported prevalence rates of depression in sickle cell disease to be between 21% and 50%.(14, 15)It is well documented that the prevalence of depressive disorders in SCD patients is higher than that found among physically healthy persons in the general population or populations of people attending outpatient clinics for acute ailments but similar to that found among populations of persons living with other chronic medical conditions.(16) Increased frequency of hospitalizations and episodes of painful crisis are major factors that worsen depressive symptoms (17-19) while ample social support could mitigate the effect of depressive symptoms on the psyche of the individual who is living with SCD. Dysthymia is another mood disturbance distinguished by seemingly low-grade depressive symptoms. The symptoms are chronic (over two years), recurrent and not severe enough to be described as a major depressive episode. (20)

Anxiety and related disorders

Anxiety disorders are a group of neurotic disorders distinguished predominantly by the presence of anxiety which can be free floating (generalized anxiety disorder) or episodic in relation to specific objects or situations (phobic anxiety disorders), occurring with clinically significant impairment in function. Anxiety disorders are less prevalent than depression among SCD patients as about 29% to 32% of SCD patients have been shown to have anxiety disorders.(21, 22) A specific type of phobic anxiety disorder that has been described among SCD patients is kinesiophobia; the fear of movement. (22) According to Pells and others(2007), SCD patients have been shown to exhibit concerns about moving around because of the fear of pain associated with their movements and their perception of movement being a contributory factor to their painful crisis.(22) This kinesiophobia has been shown to be positively correlated with other psychopathologies like depression, anxiety, and obsessive-compulsive disorders. SCD patients with kinesiophobia are also more likely to report more frequent episodes of painful crisis. Post-traumatic stress disorder has also been reported among SCD patients.(23, 24) It presents with recurrent, intrusive thoughts, images, perceptions, dreams and (or) nightmares. Vaso-occlusive crisis is believed to be a potential trigger for this disorder.

Schizophrenia

Stress associated with a vaso-occlusive crisis can be severe enough to trigger a psychotic experience. Psychotic features include hallucinations and delusions with significant disturbances of behaviour or disorganization. There have been case reports of recurrent psychosis during episodes of crisis.(8, 25)

Psychoactive substance use

Mental and behavioural disorders due to psychoactive substance use include drug intoxication, dependence syndrome, withdrawal syndrome, and harmful use. Intoxication is a transient syndrome of behavioural disturbance as a result of the recent use of a psychoactive substance. The symptoms tend to subside when the level of that substance in the blood drops. Dependence syndrome is a clinical syndrome of persistent, compulsive use of a psychoactive substance in spite of the negative consequences of that substance on the user. There is an associated craving for the substance, the neglect of all alternative sources of pleasure and a progressive increase in the quantity of the substance used and the time and resources spent on the use of that substance. Opioids, cannabis, and alcohol are some of the psychoactive substances abused by individuals with SCD. Opioids are the mainstay of treatment of the excruciating pain seen in individuals with SCD. Hence, those whose pain was treated with opioids learn what opioids and which dose are best to relieve their pain. (11) Consequently, there are wide reports that SCD patients are assumed to be associated with opioids abuse and addiction. (26-28) Also recently, there has been popular interest in using cannabis as an analgesic for various types of pain among which is SCD pain. (29) More than a third of SCD patients used cannabis in the previous 12 months to relieve symptoms of SCD in a study reported in the United Kingdom. (30) However, cannabis use is not limited to pain relief alone, but these patients also use it for relaxation and self-medication of symptoms of depression and anxiety(31). In addition, the tendency of alcohol abuse is high among SCD patients because it also helps to relieve pain and decreases the frequency of unscheduled clinic visits and healthcare utilization. (32) SCD patients also use benzodiazepines, cocaine, and phencyclidine. (31)

Somatization

Somatization is a documented finding in patients with SCD. These are multiple recurrent frequently changing physical symptoms. (33) It has been described as the pathological attention to a range of bodily symptoms and conditions regardless of their cause and often to the exclusion of other life priorities.(34) SCD patients who focus too much on their health have been found to have features of somatization which is predictive of a range of negative psychological experiences including depression, anxiety, and hostility.(34)

Obsessive-compulsive disorders(OCD)

OCD, trichotillomania and Tourette syndrome have all been shown to be interrelated disorders.(35) They are all disorders with negative reinforcement with an associated premonitory urge and temporary relief after the action is completed. OCD is a disorder characterized by persistent obsessions and ruminations which can be followed by the compulsive or ritualistic act which brings temporary relief until the cycle begins again.

Eating disorders in SCD

SCD patients have been documented to have eating disorders. Pica is an eating disorder characterized by persistent eating of non-nutritive substances for a period of at least one month. From case reports(36) to cross-sectional studies(37), studies have shown that the prevalence of pica is higher among SCD patients when compared to the general population and other individuals with chronic illnesses. Factors responsible for pica in SCD are believed to be nutritional deficiencies which include zinc and (or) iron deficiencies.(38-40)

Does the sickle cell trait confer any added risk of mental health challenges?

The coexistence of SCD and mental illness in the same person can be in three categories. Mental illness could occur in an individual SCD patient who has a family history of mental health challenges. This is because nearly all types of mental disorders have a genetic component to their aetiological factors.(41) Hereditary contributions to mental illness generally are believed to be poly-genetic in most cases. The presence of these genetic factors might not lead to illness if there are no environmental

factors to trigger the illness. According to the stress-diathesis model for the aetiology of mental disorders, there needs to be an interaction between genetic or biological factors and environmental stress for mental illness to occur.(42) Individuals who have high levels of resilience are less vulnerable to mental illness while persons with low resilience will be more vulnerable to having a mental illness. Hence, the other category of aetiological factor comprises environmental factors/triggers of mental illness. In SCD patients, the intense pain and discomfort associated with a vaso-occlusive crisis are a major trigger factor for psychological disturbances. (43) Other environmental factors include the psychological reaction to frequent crises and limitations in the fulfillment of personal goals (44), negative public perception and attitudes towards individuals who have SCD (45), family attitudes, family functioning and overall resources available for the family.(4, 46) The third category of relationship between mental illness and SCD is that a psychological disturbance or emotional stress could actually trigger a vaso-occlusive crisis in an SCD patient.(47) Mental and behavioural disorders due to psychoactive substance use that results from chronic use of painkillers or abuse of other psychoactive substances like alcohol and hallucinogens towards altering consciousness in order to reduce the effect of the illness or its related symptoms on the psyche of the SCD patient could also be regarded as an environmental factor. In all these, there appears to be no direct link between the genetic basis for SCD and any mental disorder. The trait itself does not directly confer any added risk for mental illness beside the fact that it is a chronic illness with associated implications on psychosocial wellbeing and overall quality of life.

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DIAGNOSIS OF SICKLE CELL DISEASE

OLUFEMI-AWORINDE KJ AND AKINWUSI OP

The diagnosis of Sickle cell disease can be divided in several ways based on

1. Timing – early or late diagnosis,
2. Timing – prenatal or postnatal, and
3. Nature – Screening or Confirmatory.

1. Timing Early or late

Diagnosis of sickle cell disease can be early or late. Early diagnosis can be immediately after birth before symptoms and complications set in e.g. neonatal screening or when the normal change for switching from foetal haemoglobin to adult haemoglobin synthesis occurs around 3-6 months of age.

Late diagnosis is when a patient is symptomatic of one or more of the numerous crises and the diagnosis is suspected and thus investigated. It can also be when a patient presents with symptoms of the complications of the disease without prior diagnosis and the patient is now investigated.

2. Timing – Prenatal or postnatal

Prenatal diagnosis can be done especially when both parents are known sickle cell carriers. This is done using foetal blood, amniotic cells or chorionic villi. Prenatal diagnosis can also now be divided into pre-conception or pre-implantation.

Postnatal is when a patient is born without symptoms (newborn screening) or with symptoms or complications before the patient is investigated.

3. Nature – Screening or Confirmatory

A screening test is done to detect the presence of HbS in a patient or a group of asymptomatic individuals' blood. It is not a specific test because it is positive for HbAS individuals, who are just carriers of the disorder.

Confirmatory tests are those tests useful for the diagnosis of sickle cell disorder. These are tests which are specific for quantitative and/or qualitative diagnosis of the disorder.

Other supportive tests are also done to monitor the patient because Sickle cell disease is a pan systemic disorder which affects almost all the organs in the body at one time or another in the course of the disorder. These are tests done to confirm the functionality of organs or structures in the body or to detect abnormal functions.

These tests are discussed in more detail in this chapter.

Screening test

Haemoglobin S can be checked for in the blood of newborns, children and adults. It can be done using either the sickling test (this is based on polymerization of the deoxygenated HbS) or direct identification of HbS based on the biochemical properties of the haemoglobin protein.

The sickle solubility test is the most popular sickling test and it is based on the reduction of HbS using sodium hydrosulphite. (1) A turbid solution results on adding sodium hydrosulphite to the blood as a result of precipitation of the erythrocytes. This is seen on visual inspection or by the use of automated readers. (2) In developing countries, the less expensive and readily available sodium metabisulphite is usually used instead of sodium hydrosulphite, despite the fact that a peripheral blood smear needs to be done. (3) This is because sodium hydrosulphite is expensive and is also not readily available.

Prenatal Diagnosis

It can be done through the analysis of foetal DNA obtained from foetal blood, amniotic cells or trophoblastic cells. Foetal tissue can be collected using chorionic villus sampling, amniocentesis, cordocentesis or foetoscopy. It can be done as early as the first trimester (depending on the

method used) There is risk of abortion, foetal malformation amidst other complications. (4, 5, 6, 7, 8)

Analysis of foetal cells in the maternal circulation is being offered as an alternative to methods of foetal tissue collection. It reduces the risk of abortion and foetal malformation. (9, 10, 11, 12)

Pre-conception and Pre-implantation genetic diagnosis

Pre-implantation genetic diagnosis is used in diagnosing sickle cell before implantation via the nested polymerase chain reaction PCR of the early blastocyst. This helps to reduce the incidence of induced abortion in affected couples. Pre-conception diagnosis on the other hand is carried out on the DNA of the first polar body obtained from the oocytes taken from ovarian stimulation. PCR is also used in this analysis. Unaffected oocytes are then fertilized. (12, 13, 14, 15)

Postnatal Confirmatory test for sickle cell disease

Diagnosis of SCD in postnatal life is divided into: newborn screening and symptomatic diagnosis.

Newborn screening

This is introduced to all neonates that are at risk of SCD. Being at risk, means children whose parents are heterozygous for the disease. This will ensure proper diagnostic testing, adequate health education of the care givers and thorough health care which will lead to less morbidity and mortality associated with SCD in the early years of life. (16, 17, 18)

Symptomatic diagnosis

This is a confirmatory test done when a patient presents with symptoms and signs suggestive of SCD.

For both the prenatal and postnatal diagnosis of SCD, the following tests are used to confirm the presence or absence of the disorder when used alone or in combination.

1. Haemoglobin electrophoresis in alkaline or acidic medium,
2. High performance liquid chromatography (HPLC), and

3. Iso electric focussing (IEF).

Haemoglobin electrophoresis

This can be done using either alkaline or acidic media. At alkaline pH, the negatively charged haemoglobin migrates to the positively charged anode during electrophoresis. This leads to its separation from haemoglobin A. Certain haemoglobins like HbS, D and G migrate together at this pH, hence the acidic medium. At acidic pH, the above-mentioned haemoglobins migrate differently. Thus, both acidic and alkaline media are needed to determine the patient's haemoglobin.

High performance liquid chromatograpy

This is a chromatographic method used to identify, quantify or purify the individual components of a mixture. When used to separate the components of the haemoglobin, it gives the percentages of individual concentration. It depends on the exchange of charged groups on an exchange medium with charged groups on the haemoglobin molecule.

Isoelectric focussing (IEF)

IEF utilizes a matrix containing carrier ampholytes of low molecular weight and varying isoelectric points. The involved molecules migrate to their respective isoelectric points when a current is applied, resulting in a pH gradient. Haemoglobin molecules migrate through the gel until they reach the point at which their individual isoelectric point is equal to the corresponding pH on the gel and the migration ceases.

Other investigations

1. **Complete blood count**
   This cannot be used to diagnose SCD but it can be suggestive.

   There is usually leucocytosis which is due to repeated infections and also on the effect of anaemia on erythropoiesis. Neutrophilia is also a common feature with thrombocytosis. (19) There is also reticulocytosis because of the chronic haemolysis associated with the disease.

Peripheral blood film will show polychromatic cells, macrocytes, target cells, sickle cell, leucocytosis, thrombocytosis and Howell-Jolly bodies.

2. **Renal function test**

   This is needed because the disease process in SCD is associated with varied tubular and glomerular disorders as a complication. (20) Therefore, baseline renal function test is mandatory at diagnosis and subsequently yearly to know when a complication is setting in for prompt intervention.

3. **Liver function test (LFT)**

   Abnormality of the liver in sickle cell anaemia is established even in steady state especially in children. (21) This abnormality tends to decrease with advancing age of the patients. Therefore, LFTs are needed at diagnosis and yearly to know if abnormalities are improving or deteriorating with advancing age.

4. **Radiological investigation,** most importantly chest X-ray and abdominopelvic USS. Baseline chest x-ray is mandatory in all SCD cases. It serves as a reference when there is acute chest syndrome, chest infections, cardiac abnormalities and pulmonary hypertension. Abdominal USS is also mandatory as a baseline to interpret RFT and LFT when abnormalities of the kidney and liver set in respectively. (21)

   ECG. Various abnormalities are well documented in homozygous SCD which include a significant increase in mean heart rate, P-wave duration, P-wave dispersion, PR interval, QRS duration, QRS dispersion, QTc interval and QTc dispersion. (22) Therefore, baseline ECG is a must-do investigation at diagnosis, to be repeated yearly in order to notice the early onset of any of the above-mentioned problems for early intervention appropriately.

Conclusion

SCD is a pan systemic disorder and after making the diagnosis, various investigations are also needed regularly to monitor the patient in order to achieve near normal life expectancy.

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MANAGEMENT OF SICKLE CELL DISEASE

ASEKUN-OLARINMOYE, EO,
FARAMADE, IO AND
ASEKUN-OLARINMOYE, TF

The World Health Organization (WHO) has indicated the need to improve disease prevention, awareness and early detection in Africa. Proper management of sickle cell anaemia (SCA) begins with establishing the correct diagnosis early in life during the newborn period. The identification of affected infants by neonatal screening programs allows for early initiation of prophylactic penicillin and pneumococcal immunizations, which help prevent overwhelming sepsis. Family education also promotes early recognition of disease-released complications which allows prompt and appropriate medical evaluation and therapeutic intervention. Periodic evaluation by trained specialists provides comprehensive care with the identification of other parenchymal organ damage as patients become teens and adults.

Treatment approaches that previously highlighted acute vaso-occlusive events are now evolving to the concept of preventive therapy while blood transfusions and early consideration of hydroxyurea treatment represent a new treatment paradigm for the management of anaemia associated with sickle cell disease.

Treatment Approaches

There are five treatment approaches for SCD that are basically tailored to the clinical phenotype of a patient, namely: supportive, preventative, abortive, curative and symptomatic approaches. (a) The supportive approach is the most common, aimed at the management of the patient and such an approach includes a balanced diet, hydration, and folic acid supplementation. (b) A preventative approach is taken to preclude the occurrence of disease complications such as pneumonia and influenza vaccination, hydroxyurea for the induction of foetal haemoglobin (HbF)

and blood transfusions to avert primary and secondary stroke episodes. (c) Nitric oxide (NO) is the only accepted agent for the abortive approach with a strong tendency to terminate episodes of chronic pain in some SCD patients. (d) The curative approach is the ultimate goal for all genetic disorders, intended to correct the disease-causing mutation and prevent all complications. Currently, transplantation of haematopoietic stem cells (HSCs) is the only accepted curative treatment for SCD. However, most recently, in a first, a Sickle Cell patient (Victoria Gray, a 34-year old mother of four) received CRISPR Gene Therapy on July 29, 2019 at Sarah Cannon Research Institute in Nashville, Tennessee. In the clinical research, the aberrant cells in the bone marrow were removed and the genetic error they carried was repaired using the CRISPR editing tools. CRISPR does not only make cuts in the genome to reduce gene expression, if a repair template is introduced at the same time, the gene can be altered in a very specific way (as encoded by the repair template). (4) Follow-up still need to be conducted on the patients in this study to make sure that the changes made to the bone marrow cells result in the production of normal red blood cells, to learn how the procedure has improved the health of the patient, whether there are any side effects and how long the hypothetical benefits will last. Another report is of a man in Alabama, USA who became sickle cell free through a new gene therapy clinical trial. Lynndrick Holmes underwent gene therapy at NIH in Washington, D.C. According to NIH, the treatment involved taking stem cell from the patient's bone marrow fixing the gene that causes the cells to sickle and reinserting that gene using the H-I-V virus; minus the components of the virus that cause infection after undergoing chemotherapy to prepare patient for the introduction of the new cells. (5) The three current major strategies for effective treatment of SCD are a blood transfusion, hydroxyurea (HU) and HSC transplantation. (e) Symptomatic approaches include blood transfusions, analgesia, and antibiotics because their function is to alleviate specific SCD symptoms.

Early Identification and Screening

SCD ideally should be identified at birth as part of routine newborn screening or at any subsequent contact that the child has with a health facility. Depending on the national policy, early identification can be done by the universal screening of all newborns, targeted screening of babies born to carrier mothers, and screening of pregnant women. Blood samples from a heel prick can be tested using iso-electric-focusing or high-performance liquid chromatography. The diagnosis of SCD is often

accompanied by medical, ethical and cultural issues and may differ from one country to another, therefore, counselling and health education services should be made available also.

Provision of Affordable Medicines for SCD Management and Pain Relief

The use of quality generic medicines as a component of the national essential medicine list should be promoted. Sub-regional economic entities can help in the manufacture and purchase of these medications. Since many SCD patients tend to revert to traditional medicine practices, traditional pharmacopeias should be fostered after proper testing, validation, and standardization. Traditional health practitioners should be involved in SCD management and referral whenever possible as seen in the context of Ghana. (7)

Blood Transfusion

The essence of blood transfusions is to improve the oxygen-carrying capacity and oxygen-delivery efficiency of blood to the tissues and decrease the blood concentration of sickle cells so as to improve perfusion of tissue microvasculature. Transfusions are typically used to ameliorate chronic anaemia and pain episodes and are highly effective in patients with sporadic episodes of severe anaemia by preventing organ damage. Although transfusions can be applied as a preventative, abortive or curative approach for the treatment of certain complications, they have some drawbacks. (7,8) This is one of the challenges surrounding transfusions. Complications include transfusion-induced haemolytic reaction or autoimmune hyperhaemolysis and blood volume and iron overload, graft versus host disease (GVHD) after alloimmunization. Despite its effectiveness, blood transfusion alone is not a sufficient treatment for SCD nor is it curative thus hydroxyurea is a drug of choice in the treatment of SCD. (8-14)

Drug Treatment

Several cytotoxic agents such as hydroxyurea and 5-azacytidine enhance the levels of foetal haemoglobin developing erythroid cells. Hydroxyurea is an oral, cytotoxic, anti-metabolic and neoplastic drug for principal haematological disorders.In an effort to enhance foetal haemoglobin production hydroxyurea has been administered to patients with sickle cell

disease. It works bystimulating foetal haemoglobin production; increases the red cell mean corpuscular volume, and decreases the number of dense cells and irreversible sickled cells in the body, thereby reducing morbidity and mortality in SCD patients. The first clinical application of HU was in 1984 and since then it has been supported by numerous clinical trials demonstrating clinical efficacy and an increase in survival rates and life expectancy, protection against cerebrovascular disease, long-term drug safety, and capacity to prevent organ damage, reduce morbidity and mortality in school-age children, toddlers, and infants. (12-17)

Treatment with hydroxyurea has been found to cause a significant reduction in the median annual rate of painful crises in patients with SCD. (18,19) HU is still not included within national guidelines for use in children below the age of 5 in some African countries such as Kenya where the disease burden is highest, and a recent report suggests that less than 5% of SCD patients in Cameroon ever used HU while the possible benefit of HbF in reducing the frequency of crisis in SCD in Ghana is not clear. (20-22) The most notable evidence for the clinical efficacy of HU came from the Multi-center Study of Hydroxyurea (MSH) clinical trial which showed decreases in the frequency of painful episodes, acute chest syndrome, hospitalization, and transfusions. HU receive approval from the European Medicines Agency (EMeA) as a treatment for both adults and children with SCD. (12,13,20-25)

Very recently, a newer drug Adakveo, also known as Crizanlizumab was approved in the United States for the management of SCD. It is the first ever available targeted therapy, as a monthly infusion which halves occurrences of episodes of sickle cell pain and also prevents sticking of red blood cells to the blood vessel walls thereby reducing the frequency of painful vaso-occlusive crises. Studies have shown that the drug is likely to work better the longer patient receives it. It is suitable for patients from sixteen years and older. It has also been found that it reduces the median hospitalization days in a year by 42%. Patients on existing sickle cell disease therapies may be switched to adakveo or this newer drug be added to the previous ones since these drugs work through different mechanisms. Adakveo side effects include influenza and high fever. (26-28)

Haematopoietic Stem Cell Transplantation (HSC)

Currently, allogeneic HSC transplantation is the most successful curative treatment for SCD. (29,30) Transplantations can either be autologous or allogeneic. Autologous HSC transplantation is used depending on how bad the presenting symptoms are, as this approach averts immune rejection. After a comprehensive screening, the patient receives immunosuppressive and myeloablative treatment. Although the myeloablative treatment has been linked with secondary toxicity-related sequelae like infertility graft versus host disease (GVHD), immunosuppressants such as cyclosporine and methotrexate have been used to prevent GVHD. (31)

Primary Prevention including Genetic Counselling and Testing

Prevention entails setting up genetic counselling and testing interventions in high prevalence countries to reduce partnering between carriers. Genetic counselling and health promotion activities can result in a substantial decrease in the prevalence of newborns with the disease. Widespread community involvement and support are essential.

Strengthening Laboratory and Diagnostic Capacity and Supplies with Nationwide Coverage

Tools for the diagnosis of SCD should be made available according to their complexity throughout all the health system levels beginning at the primary care level. A system for maintenance and uninterrupted provision of supplies should be made available. Diagnostic and imaging facilities should be made available for early detection of complications.

Initiate and Enhance Sickle Cell Disease Surveillance

Community-based activities including surveillance and supervision, monitoring at all levels of operation, and periodic evaluation at the national level should be undertaken to reduce the burden of SCD. The information generated should serve as an evidence-based decision tool in policymaking and the daily routine decision-making process of the management of the program.

Research Promotion

It is important to describe the history of SCD, its clinical evolution, and association with malaria and other diseases. In line with the Algiers Declaration (32), the need to promote innovative research in SCD directed towards basic knowledge and its transformation into new tools such as medicines, vaccines, and diagnostic tools is crucial as well as to identify knowledge gaps and evaluate strategies. It is necessary to promote research in both conventional and traditional medicine to produce evidence of safety, efficacy, and quality.

Supportive Activities for Special Groups–Children Under Five Years, Adolescents, and Pregnant Women

National governments should reinforce national SCD supportive activities for children under five years old, adolescents and pregnant women who are the most susceptible and vulnerable group which should benefit from financial packages for case management. The supportive measures include early diagnosis and treatment of complications; special transfusion regimens; surgery; immunization; prophylactic antibiotics, folic acid and antimalarials; and special programs for prenatal care, psychosocial and professional support to patients, and adaptive educational interventions. (32)

Comprehensive Health Care Management for SCD Patients of all Ages

Comprehensive health care management consists of parent and patient education; adequate nutrition; adequate hydration; use of prophylactic antibiotics and antimalarials; folic acid supplementation; use of specific vaccines; continuous medical follow-up; and early detection and management of complications. (6) These measures will reduce morbidity, prevent complications and improve quality of life. In line with the Ouagadougou Declaration (6,18), Comprehensive Health Care Management (CHCM) should also be integrated into health systems using the PHC approach to meet the needs of both rural and urban dwellers, including prevention of complications and patient referral to higher care centres when necessary. Family and community-based care should be integrated into the national program. Implementation of CHCM requires trained personnel, adequate facilities, and interventions adaptable to the local needs of communities.(7,31,33)

Management of Painful Crisis

Acute painful sickle cell episode is a condition that occurs in people with sickle cell disease. In these people, red blood cells behave differently under a variety of conditions which include; dehydration, low oxygen levels and elevated temperature. (1,34) Changes in any of these conditions may cause red blood cells to block the small blood vessels, restricting blood flow. This damages the tissue, which causes pain. The occurrence of acute painful sickle cell episodes is unpredictable and without definite precipitating factors, however, the frequency of occurrence may vary widely from between less than one episode a year to severe pain at least once a week. The pain also varies in both severity and duration. (1,34)

The majority of painful episodes are handled at home, with people usually seeking hospital care only if the pain is uncontrolled or they have no access to analgesia. The primary goal in the management of an acute painful sickle cell episode is to achieve effective pain control both promptly and safely. The management of acute painful sickle cell episodes for people presenting at the hospital is variable throughout the UK and is a frequent source of complaints. (33)

Sickle Cell Management in Nigeria

The major cause of mortality in childhood is overwhelming bacterial infections especially due to encapsulated organisms, principally pneumococcus. (35) This is secondary to a variety of immune defects of which the most important is splenic dysfunction. (35)Acute chest syndrome, stroke and multiple organ failure are other not uncommon causes of death. (36) In older patients, chronic organ failure, especially renal failure, becomes quite important. Some other distressing, but not necessarily fatal, complications include chronic leg ulcers and avascular bone necrosis typically affecting the femoral heads. (35,36)

In 2014, the Federal Government of Nigeria launched national guidelines for the control and management of SCD (NGCMSCD). These comprise major recommendations for the care of persons living with SCD in Nigeria and consist of nine chapters, each dealing with specific aspects of SCD. Furthermore, the long-standing handbook for parents of patients with SCD in the USA was adapted in the formulation of the parent handbook for SCD in Nigeria. (34)

Care and treatment of SCD patients require expertise and commitment, as well as a wide array of therapeutic and prophylactic measures including adequate analgesia, anticoagulation as indicated, transfusion of requisite blood components when necessary, haemopoietic stem cell transplantation, oxygen therapy when needed, routine prophylactic medications (antimalarial, multivitamin supplements, low dose aspirin, and antioxidants), hydroxyurea therapy, adequate hydration, and immunization against infectious pathogens especially in early childhood. (35,36) Moreover, care of SCD patients requires a multi-specialist team including haematologists, orthopedic surgeons, plastic surgeons, urologists, nephrologists, specialist nurses, counsellors, and medical social workers.

Carrier detection and genetic counselling have been recommended by the World Health Organization for the control of SCD. (32) In Nigeria, efforts at public enlightenment on sickle cell disease and its prevention as well as carrier detection with genetic counselling have not made sufficiently far-reaching improvements in its control. There is still a palpable dearth of public knowledge about the disease. Also, the option of selective abortion following prenatal diagnosis has been unacceptable to a significant proportion of persons. At the primary prevention level, there are currently no functional nationwide neonatal screening policies or programs for early detection and optimal treatment. Though it is expected that a country like Nigeria with a very high prevalence of sickle cell trait should have a nationwide program at all levels of care for the control and care of sickle cell disease, available evidence suggests that effective control of SCD in Nigeria is still largely infantile.(37-40)

Ghana Context

Treatment and Management of SCD

SCD can affect multiple special organs and systems of the body. Best practice indicates that SCD is ideally managed at specialized units through a multidisciplinary approach involving teams of specialists including doctors, nurses, social workers, health educators and genetic counsellors facilitating in-patient, outpatient and follow-up care. (41)These services are delivered in comprehensive SCD centres in the USA and UK. No such centres currently exist in notable sub-Saharan countries like Nigeria and Ghana. (41,42)

Following diagnosis, the goal of SCD management is to maintain patient health and prevent or manage complications. Management of SCD is broadly divided into five areas: supportive, symptomatic, preventive, abortive and curative. Many authorities categorize SCD management into health maintenance, general management, and management of specific problems. Health maintenance management includes patient-focused education, continuous health care, preventive treatment, counselling, and special health assessment. The procedures involved differ between children and adults. Child health maintenance involves parental education of physical assessment skills such as splenic palpation, administration of prophylaxis including penicillin and folic acid, strategies to avoid crises, and how to navigate the medical system. The education covers fever and pain recognition and home management. Parents are also counselled on nutrition including avoidance of iron supplements, correction of nutritional deficiencies, and use of fluoride in water to prevent dental decay. In addition, the counselling involves academic, vocational, recreational and air travel precautions. The SCD child also requires continuous healthcare at the well-baby clinic for growth monitoring, immunization (especially pneumococcal vaccination), and counselling in preventive measures.

In the special physical laboratory other investigations are conducted on children while parents are informed of typical SCD features including jaundice, protruded abdomen, anaemia, cardiac systole flow murmur, maxillary hypertrophy with an overbite, delayed physical growth, development, short stature, and delayed reproductive health development. Baseline laboratory values should be obtained for future comparison and routine investigations will be conducted on organs that can be damaged from SCD, especially the lungs and the brain.

Health maintenance in adult patients addresses the medical and psychosocial issues of SCD and the interactions with age-related co-comorbidities such as hypertension and cancer. Patient education involves identifying and addressing knowledge deficits, identifying emergency signs and symptoms and managing pain at home. Continuous care includes occupational and physical therapy such as behaviour modification, neurological interventions, and counselling on nutrition and lifestyle including alcohol and tobacco use. Counselling also includes folic acid supplementation, avoiding precipitating factors, contraception, pre-conceptual genetic counselling, choosing safe occupations, legal protection against discrimination and other work-related policies, dental and psychosocial care. Patients may also require vaccinations for infections such as tetanus, hepatitis, and influenza. A special evaluation

includes an annual haematological assessment, pulmonary function test, and ophthalmic examination.(42-45)

Treatment of complications

The treatment of SCD related illnesses and complications is based on the presenting symptoms though SCD management is largely supportive despite the possibility of a cure through allogeneic haematopoietic stem cell transplantation. The treatment of SCD problems is classified as either general or specific. The general classification involves interventions that modify the pathology of the disease to improve the clinical outcomes. The most established of these interventions, with wide international consensus, are hydroxyurea therapy and red cell transfusion. (43-47)

Acute complications require immediate evaluation and treatment to reduce or prevent morbidity and mortality and preserve organ function. Pain relief, hydration, management of sepsis and blood transfusion are the key strategies for acute management. Pharmacological measures used to manage acute pain are analgesics, mainly opioids, NSAIDs and adjuvants such as sedatives and anxiolytics. Non-pharmacological measures may include spirometry, oxygen administration, massages, muscle relaxation therapies, self-hypnosis, baths, and distraction strategies. Blood transfusion may be given for debilitating pain.(7)

Chronic complications can affect any organ and chronic pain is the commonest. The treatment aim is to minimize pain, increase coping, improve social and physical functioning, improve quality of life and prevent organ damage. In addition to the use of analgesia, other interventions including occupational and physical therapies, behaviour modification and neurocognitive therapies are utilized in managing chronic complications.(44-46)

Prevention of Complications and Improvement of Health Outcomes

Sickle cell disease has a deleterious effect on immune system functions, and thus children who have the condition are greatly predisposed to life-threatening infections, especially with Streptococcus pneumoniae and Haemophilus influenza. However, many of the infections are preventable. The strong protective effect of penicillin prophylaxis has been demonstrated by several studies. According to a clinical guideline for the

management of SCD, children with Hb SS or sickle Sβ0-thalassaemia should receive regular penicillin prophylaxis from as early as 2 months through to 5 years, and parents should have the option to continue prophylaxis for patients aged more than 5 years; for patients with Hb SC, penicillin prophylaxis has been stated to be probably wise. (35)

In addition to antibiotic prophylaxis, children with SCD need to be up to date with routinely recommended vaccines, including pneumococcal and H. influenzae type b (Hib) vaccines. Children with SCD should receive both the 13-valent pneumococcal-conjugated vaccine (PCV13) starting at age 2–6 months and the 23-valent polysaccharide vaccine from the age of 2 years.(48) Public health efforts, when appropriate, are needed for the promotion of adherence among children prescribed regular penicillin prophylaxis and the receipt of all recommended pneumococcal and other vaccines.

The management of SCD also involves psychosocial interventions including cognitive behavioural therapy (CBT), self-regulated therapies, behaviour strategies, social support interventions, education, and medical self-management. (7) CBT has received the most empirical support in the literature but the successful delivery of CBT relies on qualified expert mental health professionals.(49) While these interventions are integrated into comprehensive care and management in countries with high financial resources like the US and the UK, there is a paucity of these interventions in countries with low financial resources including Ghana and Nigeria. (49,50) Such low-income countries therefore need to consider locally suitable alternative interventions to assist patients and families to address the psychosocial issues of SCD, and this must include self-management.

Currently, only two phytomedicines (Ciklavit, Niprisan) have been scientifically shown to reduce severe painful crises but these medicines have a limited impact in preventing complications. Researchers, however, have recommended Ciklavit use with caution. (51-54) Ghana has an opportunity to scientifically explore the role of traditional medicine in SCD care due to the efforts by the MOH to formalize traditional medicine in the health system and the existence of the Centre for Scientific Research into Plant Medicine. (55)

Patients and families' responsibility in health maintenance includes physical assessment such as splenic palpation and temperature, understanding and keeping the results of physical findings and laboratory values, and engaging in medication administration. It also involves

avoiding triggers of disease exacerbation such as exhaustion, dehydration, and extremes of temperature. Among children, parental responsibility involves taking the child to well-baby clinics, administering prophylactic penicillin, adhering to immunization and informing school teachers and the child's school friends about the child's condition. Among adolescents and adults, patients' responsibilities involve safe sexual behaviours, use of contraception, awareness of pregnancy risks and choosing occupations compatible with SCD.

Patients and families' roles in the management of complications are to monitor signs and symptoms, report dangerous signs and symptoms or deviations such as fever, chest pains, difficulty in breathing, atypical pain and severe pain. Furthermore, patients' responsibilities include following medical instructions, keeping clinical appointments and undertaking requested investigations. Patients and families' roles further include learning the common signs and symptoms specific to their condition and the recommended actions when such signs and symptoms are recognized.

Regarding specific complications, the National Heart Lung & Blood Institute indicates that patients experiencing avascular necrosis of the femoral head should reduce weight. (42) Patients on blood transfusion therapy should be aware of iron overload and the need to use iron chelators. Furthermore, pregnant women on hydroxyl urea are required to be aware of the need to withdraw from the medicines during pregnancy as it is cytotoxic. Patients' responsibility in pain management involves pain assessment, use of pain diaries, home treatment and reporting pain that is unsuccessfully managed. Patients using opioids are required to monitor the side effects and take stool softeners. Patients treated with ulnar boots for leg ulcers are taught to change their dressing and ensure complete bed rest with limb elevation. Male patients who experience priapism should avoid a full bladder and prolonged sexual activity. As SCD patients, especially those with HbSC and HbSβ^+ thalassaemia, are prone to eye complications, patients are advised to have an annual ophthalmic evaluation and report eye traumas or an acute change of vision to an ophthalmologist.

USA Context

Options for interventions

Analyses of trends in mortality in SCD in the USA have shown dramatic reductions in childhood deaths with a dramatic reduction within the age group 0–3 years, which is most likely the result of identification of newborns with SCD by newborn screening (NBS) and prevention of infection. Four options for SCD interventions are identified. (56)

Options for management of sickle cell disease

Option one: After diagnosis, the use of a combination of the best possible patient care with the use of prophylactic penicillin, together with retrospective genetic counselling.

Option two: the best possible patient care, in combination with a neonatal screening program and the use of penicillin for all homozygous babies, together with retrospective screening and genetic counselling.

Option three: the best possible patient care, plus a neonatal screening program and the use of prophylactic penicillin from birth for homozygotes, alongside population screening and prospective genetic counseling.

Option four: the same as in option three, plus the availability of prenatal diagnosis, bone marrow transplantation, or both.

NBS for SCD could identify individuals with SCD at birth and subsequently enroll them into an SCD comprehensive care program. The implementation plan for NBS for SCD that is being developed includes the establishment of capacity for laboratory diagnosis of SCD, with the proposal of integrating NBS with an existing reproductive and child health program.

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PSYCHOSOCIAL CARE AND SUPPORT FOR PREVENTION AND MANAGEMENT OF SICKLE CELL DISEASE (SCD)

MOA ADEYEMO

Sickle cell disease (SCD) is one of the top ten (10) non-communicable diseases (NCDs) in most African countries including Nigeria causing significant morbidity and mortality. (1) SCD is connected with increased maternal, neonatal, infant and child mortality, stunting growth, stigmatization, job discrimination, illness related absenteeism from school or work, poverty-related inaccessibility to standard treatment, depression and other psychosocial challenges. Sometimes, it may be complicated by HIV and viral hepatitis (mainly B and C) infections because of frequent blood transfusion. (1)

Emotional and social challenges

The various emotional and social issues associated with the disease usually lead to feelings of anger, fear, guilt or helplessness in the parents of a child with sickle cell disease or the individual living with it. An individual experiencing a sickle cell episode may be overwhelmed with fear of the unknown, likewise the relatives. Ajibade, Akinpelu, Olaoye, Kolade and Makinde stated that other members of the family are usually neglected by the caregivers as a result of high demands of care from the child's illness. This is a major factor in family dysfunction. Frequent exposure to this neglect is also described as a risk factor in the psychopathology of psychosocial problems in chronic physical illness. (2)

Children living with SCD are usually absent from school due to repeated severely painful episodes of crisis requiring hospital admissions. Keeping up with school work and having good results may be problematic. Teachers have to be educated on how the condition may affect the child's daily activities and school performance. Some of the children may feel

lonely because of their inability to play with their peers due to their reduced physical strength and smaller size.

Delayed puberty, small stature and other social problems may cause low self-esteem during adolescence. Frequent absence from work due to recurrent sickle cell crises may make it difficult for adults to retain jobs or get employed. This is usually having a negative effect on the economic status of the family and individual as well as the level of care that will be received. There may also be difficulty in maintaining relationship leading to an inability to fulfill family responsibilities and loss of self-esteem. (3)

It is the responsibilities of professionals like nurses, psychologists and social workers to assist individuals and families in coping with the challenges of this disease. Familiar and peer support groups usually help the individual to cope with these challenges. The financial implication of raising a child with sickle cell disease is always enormous, and parents need to be supported to manage their financial resources prudently. The parents are to be encouraged to enroll in the national health insurance scheme to alleviate the associated financial burden.

It is a known fact that illness behaviours such as coping strategies is influenced by cultural and religious values. In Africa, the family and society's attitude to people living with sickle cell disease is affected by their cultural and religious beliefs. For instance, in Nigeria among the Yoruba and Igbo, children suffering from sickle cell disease are believed to be "abiku" and "ogbanje" respectively, who are repeatedly given birth to or reincarnated as a result of an evil spirit, therefore the family would be expected to make a sacrifice to appeal to the gods of the evil spirit. Ajibade et al. stated that some other studies have shown that religious beliefs, prayer and faith in God play a positive role in illness coping strategies and a hopeful approach to health difficulties. (2) The authors also quoted Anie et al. (2011) who mentioned that "previous research also revealed that Nigerians commonly used praying and hoping as an affective coping strategy compared with people with sickle cell disease in the United Kingdom." (2)

Nwogoh, Ofovwe and Omoti found in their study on health-related quality of life in sickle cell disease subjects in Benin City Nigeria that the energy/fatigue score and emotional being were higher in the SCD group. They attributed this to the network of psychological support from family members and healthcare workers. (4) Anie and Green corroborated these

findings by stating that psychological treatment to help people cope with sickle cell disease might complement current medical treatment. (5)

Long-term preventive care

Sickle cell disease is usually associated with a reduced life span. However, with the advancement in health care many of the people living with the disease now live to old age. There have been many opportunities to significantly improve the quality of life for people with SCD, especially adults. The ability of health workers to assist the individuals and the families to adjust their lifestyle and develop strategies to successfully manage health challenges is very vital. This chronic disease with its multiple manifestations demands a multidisciplinary approach to care and nurses are ideally positioned to coordinate care and resources for the effective reduction of the disabling effects of the disease on the individual and families. (6)

Health education: The individual should be enrolled into comprehensive care at a dedicated SCD centre where he or she and the family will be regularly educated and receive educational materials addressing the danger signs such as fever, persistent headache, abdominal pain, priapism, vomiting and diarrhoea, features of severe anaemia and chest pain with breathlessness. (1)

- The people living with SCD should also join a support group such as the Sickle Cell Association and Sickle Disease Clubs where they can interact with their mates, share experiences and counsel one another. This has been found to alleviate the psychosocial burden of the disease and consequently, improve the quality of care for people living with sickle cell disease.
- Ensuring regular checkups particularly on ears and eyes as well as keeping regular appointments are very significant in relieving emotional and social challenges.
- The individual or family should be encouraged to talk frankly in addressing their needs.

Nutrition: Encouragement of exclusive breastfeeding for the first six (6) months is highly required to be followed up with complementary feeding from six months with proteins, fruits, potatoes, yam and green leafy vegetables. Eating an adequate diet and drinking plenty of fluids should be encouraged throughout the life span. People living with SCD should be

encouraged to drink non-caffeinated beverages and avoid alcohol intake and smoking.

Recognition of early features of crises in sickle cell disease

Health care providers are expected to teach the caregivers to recognize pallor (whiteness of the palms, soles of the feet, skin and lips) and to check the conjunctivae for yellowish discoloration and the abdomen for splenic enlargement. They should also know how to assess severity of pain and early signs of ill health such as: listlessness, refusal to play and fever and seek prompt medical attention. (1)

Prophylactic therapy: Parents should be encouraged to ensure that all babies complete their immunization as scheduled. They and the people living with SCD should also ensure regular intake of recommended antimalarial and antibiotics prophylaxis. Concordance with medications may be a notable challenge. (6) Nurses need to constantly encourage both the individual and caregivers to comply with the intake of the prescribed medications.

Clothing: Ideal clothing for different weather should be worn.

Other measures to reduce the impact of sickle cell disease on caregivers: Researchers have suggested limitation of family size as a way of reducing the risk of mothers having additional sickle cell disease children. (2) Promotion of neonatal screening, genetic counselling, routine haemoglobin genotype determination and comprehensive public health education on the burden and prevention of the disease are a significant approach to the reduction of the high prevalence of sickle cell disease.

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USE OF STEM CELL TRANSPLANTATION IN SICKLE CELL DISEASE

ADEREMI, A.V

Sickle cell disease (SCD) is a chronic haematological disorder that results from an abnormal replacement of valine for a glutamic acid in the beta globulin polypeptide chain of haemoglobin. The resultant abnormal haemoglobin leads to the development of sickle-shaped red blood cells (RBCs). These cells polymerize in low oxygen environments and are capable of blocking end arteries causing painful vaso-occlusive crises, lifelong haemolysis and pan systemic end organ damage. Effort at "curing" this hereditary condition had yielded no significant results until the discovery of transplantation using haematopoietic cells in the early eighties. Currently, HLA-matched sibling allogeneic haematopoietic stem cell transplantation (HSCT) following a myeloablative or reduced intensity conditioning is unarguably the only curative option for individuals suffering from sickle cell disease. This review identifies advances that have been made in the use of HSCT in SCD and challenges associated with its availability, applicability and successful outcomes, globally. Here, effective regional and international collaborations and interventional efforts geared towards improving access, reducing cost and improving outcomes for the patients are suggested. These goals must be vigorously pursued if HSCT therapy is to enjoy any meaningful prospect especially in the less developed economies of the world.

Sickle cell disease (SCD) is an inherited haematological condition qualitatively characterized by an abnormal replacement of a glutamic acid by another amino acid called valine at the 6^{th} amino acid position of the beta-globin gene of the short arm of chromosome 11. (1) The resultant effect of this substitution is the synthesis of an abnormal haemoglobin molecule, called HbS variant. (1) When an individual expresses only one of these abnormal variants, it is termed sickle cell trait, while it is called sickle cell anaemia (SCA) when two are expressed. The abnormal haemoglobin results in characteristic "sickle" shaped red blood cells which in low oxygen situations polymerize with one another resulting in lifelong

haemolysis, vaso-occlusive crisis, ischemic changes and significant perturbations in immune systems seen in patients who suffer from the disease. (2, 3) Factors associated with early deaths, among those who are homozygous for the abnormal haemoglobin, namely SCA, include but are not limited to acute chest syndrome, kidney failure, abnormally high white blood cell counts and low levels of foetal haemoglobin. (4) Worldwide, SCA is of great public health importance. In the USA, for example, a substantial amount of money is said to be expended annually on children with SCD compared to those who are free from this condition. (5) The traditional use of blood transfusion and other supportive care, and more recently the use of hydroxyurea, although associated with a significant improvement in the patient's clinical condition, is inadequate to significantly improve prognosis and reduce the burden of morbidities and mortalities often linked with SCD. Hydroxyurea for instance has to be given over a long period of time for a patient to benefit maximally from its use, without preventing the dreaded end organ failure often seen in adults with SCD. (6) While blood transfusions offer some benefits especially in the short and medium terms, the fear of iron overload and allo-immunization with prolonged, chronic usage constitutes a major challenge in the management of individuals with this hereditary condition. (6) Consequently, the need for better approaches to managing SCD in the paediatric as well as in the young adult populations despite the availability of those effective prophylactic and treatment options had arisen. (7) So far, allogeneic haematopoietic stem cell transplant (allo-HSCT) remains the only curative therapeutic alternative available for individuals living with the disease. (7, 8, 9) While stem cell technology has enjoyed wide acceptability and recorded huge successes among the paediatric population with SCD, it is becoming increasingly popular also among young adults suffering from this chronic medical condition. (8) Because significant cases of graft rejection occur from donor-host-mismatch, getting the right donor is one of the major challenges associated with the use of this approach. (10) The thinking now is looking beyond the use of the traditional HLA-matched siblings as donors to the use of donors who may not be related to the patients but have the same stem cell type, as well as the use of peripheral venous blood and blood from the umbilical cord at the time of delivery instead of relying on bone marrow as the only source of stem cells. (11) Because there are not always enough stem cells from cord blood, a combination of these cells and those from the donor's bone marrow has also been recommended. (12)

Type of Haematopoietic Stem Cell Transplantation

For many years now, bone marrow stem cells have been used as transplants in the management of a number of medical conditions such as malignancies, immunological and haematological disorders. (11) In general, there are three main types of haematopoietic cell transplantations: autologous, allogeneic and syngeneic. In the autologous type, the individual is given their own stem cells whereas the cells are harvested either from a sibling (called HLA-matched, allogeneic stem cell donors) or someone who is unrelated but with white cell antigen that closely matches the recipient's (11) in the allogeneic type. In the later circumstance, donors are identified either through a donor registry or from a National Marrow Donor Program. (11) Syngeneic stem cell transplantation is very rare and involves the use of stem cells from a patient's own identical twin. The allogeneic stem cell transplant option, in the form of allo-HSCT, is the only proven approach in use for patients with SCA (7), although with differing post-transplantation outcomes across various HbS variants. The goal of HSCT is to correct the abnormal RBCs by replacing the patient's blood forming (haematopoietic) cells with those of a disease-free donor. (13)

Pre-transplantation Evaluation and Preparation

To ensure successful transplantation, both the patients and the donors must be properly evaluated and the patients must be adequately prepared. Although there are no known, clear cut, indications yet for the use of stem cells as transplants in SCD patients, some selection criteria have been suggested. (14) These criteria include: the presence of human lymphocyte antigen (HLA)-matched siblings as potential donors, the patient's age of not less than 16 years, and the presence of at least one of the following clinical presentations: recurrent severe episodic pain, acute chest syndrome, a CNS episode such as stroke, associated bilateral retinopathy, nephropathy or lung disease, osteonecrosis involving several joints, or red cell allo-immunization resulting from long term blood transfusion. (15) Once screened, the patients are then offered drugs in order to suppress their immune system to ensure the grafts are not rejected. (16) These pre-treatments, popularly called conditioning regimens, vary just as the case of their outcomes. Examples of drugs with established efficacy in the preparation of patients for HSCT include busulphan, cyclophosphamide, antithymocyte globulin, fludarabine, cyclosporine A, and methylprednisolone at various combinations and dosages depending on the

patient's clinical status. (15, 17, 18) Granulocyte colony-stimulating factors and antithymocyte globulin have also been employed in some instances to reduce the rate of rejection and the risk of developing graft-versus-host-disease (GVHD) as much as possible. (19, 27) Other supportive care given to enhance engraftment and reduce toxicity includes the use of hydroxyurea, simple and exchange red-cell transfusions, use of penicillin V, cyclosporine A, and mycophenolate mofetil. (20, 21) Broadly, three kinds of conditioning regimens have been proposed based on the duration of cytopenia and support care that may be required for the transplantation: myeloablative conditioning (MAC), reduced intensity conditioning (RIC) and non-myeloablative conditioning (NMAC). (18, 35) While MAC followed by allo-HSCT has been made use of widely among children below the age of 16 years with significant overall survival rates, the NMAC approach has been shown to be associated with significant positive results among adults with SCD. (9, 22) The MAC regimen is represented by a combination of busulphan with cyclophosphamide and antithymocye globulin (ATG), or busulphan with cyclophosphamide and fludarabine, while RIC is exemplified by a combination of melphalan, fludarabine with either ATG or alemtuzumab. (18) As evidenced by very high disease-free and overall survival rates, Walters et al. demonstrated a successful utilization of the MAC regimen when they treated a cohort of 22 SCD patients with HSCT following a combination of busulphan, cyclophosphamide and ATG in the nineties. (15) A number of studies thereafter have reported similar and even much better outcomes using this regimen prior to stem cell transplantation in SCD patients. Talano et al., however, have shown that RIC results in better outcomes especially with regard to donor chimerism, rapidity of transplant engraftment, GVHD severity and TRM, compared to MAC in SCD patients who were treated with HSCT. (3) Figure 1 is a summary of how donors and patients are screened and those eligible are included in the management of SCD with HSCT.

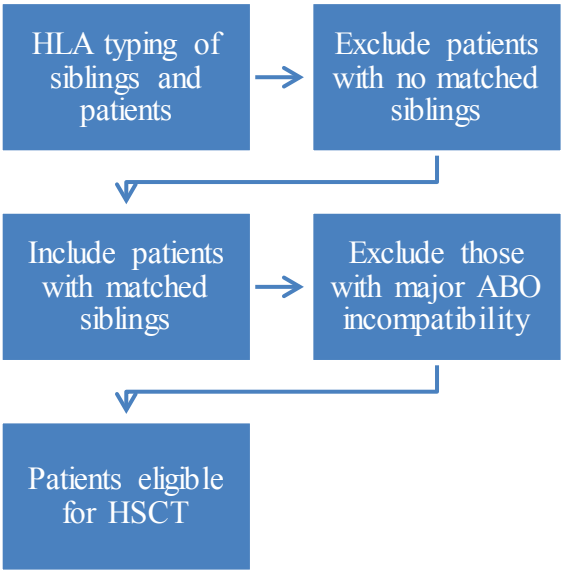

Figure 1: Screening and Eligibility of Patients

Stem Cell Transplantation Use in SCD: Supporting Evidence

Since the first reported case of successful transplantation of bone marrow (BM) stem cells by Johnson et al. in the early 1980s (23), there have been several other reports of the successful use of stem cell therapy for managing patients with SCD (see Table 1). The majority of these therapies, involving the usage of HLA-matched, allo-HSCT following a myelo-ablative pre-treatment conditioning, have reported significant disease-free and overall survival rates that are well over 80%! In a cohort of patients treated in Nigeria between 2010 and 2014, Isgro et al. reported that 28 out of 31 SCA patients who received BM transplants following MAC, survived with no SCD symptoms, accounting for about a 90% disease-free survival rate. (16) 1n a 2017 review of 1000 children aged below 16 years who had HSCT from HLA-matched siblings following either a myeloablative regimen or RIC between 1986 and 2013, Gluckman et al. reported a 5-year overall survival rate of about 95% and an event-free survival rate of about 93%. (24) More interesting however is the study of Dedeken et al. (25) In their report, they noted that following a three-

month administration of hydroxyurea prior to BM transplantation from HLA-matched donors, the 50 HSCT recipients had an eight-year overall survival rate and event-free survival of about 97.4% following the utilization of hydroxycarbamide. A similar but more encouraging HSCT outcome has been reported by a group of Italian scientists in which they replaced busulfan with treosulfan in their MAC regimen and compared this with the traditional MAC-based regimen. (26) On the whole, they noted an overall survival rate of about 100% and a disease-free survival rate of about 93% among the 30 SCD individuals treated following a seven-year post-transplantation follow up. It should be noted however that the majority of the above findings are seen in SCD children treated with HSCT. Among adults, studies are still very scant and this is because MAC which is the most commonly employed conditioning regimen is often associated with increased toxicity. (20) With this in mind, Hsieh et al. in 2009 carried out HSCT using an NMAC protocol that included the use of total body irradiation, alemtuzumab, and sirolimus amongst adults with SCD aged between 16 and 45 years old. (20) Their findings showed that all of the 10 patients who received this protocol were alive after a 30-month follow up, with 9 (90%) of them having donor lympho-haematopoietic engraftments that could be described as stable and capable of reversing the SCD phenotype in the recipients. (20) Similarly, Schleuning et al. had demonstrated significant mixed haematopoietic chimerism in a 22-year-old adult patient after 30 days post transplantation with stem cells using the RIC regimen that included fludarabine and cyclophosphamide. (21) Another approach which has been employed among adults is using haplo-identical donors rather than the usual HLA-matched siblings. For example, in a study from the United States of America, Saraf et al. utilized haplo-identical peripheral blood stem cell transplants and reported that 7 out of the 10 adult patients treated were alive after a 16-month follow up, accounting for an 87.5% survival rate. (27) Table 1 is a summary of a few scientific evidences in support of the application of HSCT in paediatric as well as adult patients with SCD.

Use of Stem Cell Transplantation in SCD: Drawbacks

It is an irrefutable fact that allo-HSCT has gained wide acceptability as a curative choice especially for SCD patients with severe clinical presentations. Nonetheless, challenges abound associated with its use in this chronic medical condition. These drawbacks stem from several factors that could range from the procedure itself, to patients' own peculiar characteristics, including their age and HbS phenotypes. The following,

among other things, have been acknowledged as requiring special attention for improvement: organ toxicity related to the use of HSCT, GVHD, graft rejection and availability of potential donors. (7) Cerebral thrombosis, CNS haemorrhage, end organ failure, infection and GVHD (which may be acute or chronic) have particularly been identified as resulting in transplantation-related deaths among the recipients of HSCT. (8, 18, 19) Organ toxicities and transplantation-related mortalities (TRM), for instance, are a major concern for the use of matched related siblings with myeloablative conditioning regimens especially among individuals with a very severe form of SCD prior to transplantation. (22) Expectedly, these untoward events would be worse with alternative donors. (8) With regard to the source of stem cells to be used, umbilical cord blood has been shown to be associated with reduced incidences of GVHD but the fact that it takes a longer time for the graft to take is seen as a downside to this approach. (28) The need for RIC or NMAC for adults with SCD also arose because the traditional MAC often used in children is associated with too much toxicity and increased mortalities. (20)

Table 1: Evidences in support of the use of HSCT in SCD patients

Country	Study period	No of Patients	Age (in years)	Conditioning type	Donor type	Stem cell source	EFS (%)	OS (%)
Nigeria (17)	2010-2014	31	2-17	MAC	HLA-matched sibling	BM	90	90
USA (27)	2014-2017	10		Modified MAC	Haploidentical	PB		87.5
France (19)	1988-2004	87	2-22	MAC	HLA-matched sibling	BM/CB	86.1	93.1
France (18)	1996-2009	16	1-17	MAC or RIC	Matched Unrelated	CB	50	94
(32)	1991-1999	50	3-16	MAC	HLA-matched sibling	BM	84	94
CIBMTR (33)	1989-2002	67	-	MAC		BM	85	97
Belgium (25)	1988-2013	50	1.7-15.3	MAC	HLA-matched siblings	BM/PB/CB	97.4	94.1
France (24)	1986-2013	1000	9 (Median age)	MAC/RIC	HLA-matched siblings	BM/PB/CB	91.4	92.9
Italy (26)	2000-2014	30	1.7-18.8	MAC	HLA-matched siblings/MUD	BM/PB/CB	93	100
USA (20)	-	10	16-45	NMAC	HLA-matched siblings	PB	90	100
Germany (21)	-	1	22 years	RIC	HLA-matched sibling	PB	100	100

CIBMTR = Center for International Blood and Marrow Transplant Research; MAC = Myeloablative Conditioning; RIC = Reduced Intensity Conditioning; BM = Bone Marrow; CB = Cord Blood, PB = Peripheral Blood

Use of Stem Cell Transplantation in SCD: Future Perspectives and Recommendations

Globally, there have been reports of significant successes using stem cells as transplants to cure SCD, but a greater proportion of these are from the developed nations of the world such as China, Europe and the Americas, compared to the developing economies. (29) In Africa, only Egypt has shown serious commitment in the areas of developing SCT programs. (29) With about 8 transplant centres carrying out well over 200 allo-HSCTs each year, Egypt is indisputably taking the lead, but there is a serious need for regional cooperation if the efforts at achieving a cure for SCD in the continent are to yield any meaningful results. (29) Since the costs of accessing HSCT is a big issue, such collaborations are germane to ensuring more SCD patients, especially residing in the developing nations of the world, are reached with this curative technology at reasonably affordable costs. The current endeavours, geared towards expanding the donor base to include unrelated cord blood donors and gene-editing of the patient's own stem cells to allow for autologous stem cell transplantation and reduce the risk of GVHD that often characterizes the use of allo-HSCT, must be sustained. Stem cell gene therapy should be explored especially for individuals lacking appropriate matched bone marrow stem cell donors. (30) Researchers have shown that this approach is very possible in the nearest future. For instance, in a preclinical study involving the use of a lentiviral vector encoding a human haemoglobin gene, scientists at the California Institute of Regenerative Medicine had shown that the vector, namely CCL-betaAS_3-FB LV, is capable of efficiently transferring and consistently expressing an effective anti-sickling β-globin gene in human SCD bone marrow progenitor (CD34+) cells, as well as significantly improving the resulting RBC physiology. (31) Therefore, individuals, government establishments and corporate organizations are encouraged to commit enough resources to research and other interventional programmes that could aid in the use of HSCT as a therapeutic option for these patients.

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National Policies and Programmes on Sickle Cell Disease

Asekun-Olarinmoye, EO,
Usman, AB, Faramade, IO,
Olarewaju, SO and
Asekun-Olarinmoye, TF

In the World Health Organization's (WHO) African region, Sickle cell disease (SCD) is the most common genetic disease. Every year, more than 300,000 babies are born with severe forms of haemoglobinopathies worldwide with a third of these occurring in Nigeria alone. Of all patients with SCD,75% live in sub-Saharan Africa.

Most developing countries have inadequate national health policies and plans, and scarce facilities, diagnostic tools, treatment services and trained personnel. There is a need for urgent interventions to address this public health problem. Harmonization of the situation analysis on SCD with the policy goals is essential in order to be able to make a good judgment on where to focus attention.

In Africa, SCD is still associated with substantially high morbidity and mortality, hence the need for effective and definite national policies, programs and control measures. An overview of national policies and programs on SCD in selected developing and developed nations is presented in this chapter.

Sickle cell disease (SCD) is one of the most common genetic diseases worldwide and its greatest burden is found in sub-Saharan Africa especially Nigeria. In most parts of West Africa, the prevalence of sickle cell trait ranges between 10% and 30% of the population. Nigeria, India and the Democratic Republic of Congo host the majority (90%) of the world's SCD population. (1,2,3,4) The majority of the 300,000 babies with SCD born annually worldwide are delivered in resource limited

environments in sub-Saharan Africa, where access to medical care and preventive strategies are not uniformly available. (1,4-7) This incidence is on the increase and may increase up to 400,000 individuals by 2050.(1)

Policy Development

National health policies, strategies and plans play an essential role in defining a country's vision, policy directions and strategies for ensuring the health of its population. The development of National Health Policies, strategies and plans is a complex and dynamic process.

Key Health Care Policy messages

1. Reduce health inequalities in terms of equitable access to services,
2. Networks to share best practice,
3. Evidence based interventions,
4. Improve access to essential medicines,
5. Prioritize population wide strategies,
6. Control and evaluate resource utilization,
7. Accurate and reliable data collection and analysis,
8. Technical capability, use of technologies, and
9. Competencies of health personnel.

The following are the policies and programs in place for developing countries:

The WHO African Regional Strategy for Sickle Cell Disease (8)

The SCD strategy for the WHO African region seeks to increase individual and community awareness about SCD, strengthen primary prevention, reduce disease incidence, morbidity and mortality, and improve quality of life. The Strategy also contributes toward the achievement of the Millennium Development Goals 4 and 5.

Aim, objectives and targets

The aim of the strategy is to contribute towards the reduction in incidence, morbidity and mortality due to sickle cell disease in the African region.

The specific objectives are:

(a) to identify priority interventions for Member States to develop and implement programs and policies for SCD prevention and control at all levels;

(b) to provide a platform for advocacy to increase resource allocation for prevention and control of SCD through multisectoral collaboration and action; and

(c) to establish mechanisms for monitoring, evaluation and research of SCD and apply the findings in policies and programs.

Targets for 2020 are that:

(a) 50% of the 23 Member States with a high SCD prevalence should have developed and be implementing a clearly designed national sickle cell disease control program within the context of a national health strategic plan;

(b) 25%of the countries in the African region should have adopted the concept of comprehensive health care management of SCD; and

(c) at least 50% of all sickle cell trait countries will have established an SCD surveillance system with adequately trained staff**.**

Guiding principles

The principles that guide this strategy are:

(a) country ownership, leadership, fairness and community participation in the implementation of this regional strategy;

(b) effectiveness, cost-effectiveness and availability of proven interventions and services, especially for the poor and for rural dwellers;

(c) integrated and evidence-based interventions and a prevention-focused population-based approach for the step-by-step execution of significant interventions as part of the national health plan;

(d) partnership, team building and coordination involving all players at various levels; coordination should foster a vibrant description and understanding of roles, responsibilities and mandates; and

(e) cultural sensitivity, ingenuity, resourcefulness and accountability involving individuals and patients.

Priority interventions

SCD control interventions for member states of the African region evolve around primary health care and health promotion approaches to ensure policy development and implementation, legislation and regulation, and expansion of primary and secondary prevention.

These interventions include:

(a) improvements in health care provision: clinical and laboratory management at all levels of the health system, screening of newborns, training of health professionals, and development of protocols;
(b) genetic counselling and testing;
(c) geographical and financial accessibility to health-care services;
(d) public awareness in schools, communities, health institutions, media and associations; and
(e) establishment of patient support groups; advocacy.

Roles and responsibilities

Countries should:

(a) develop, implement and reinforce comprehensive national integrated SCD programs oriented towards the socioeconomic environment where the health system operates;
(b) mobilize and allocate resources for SCD programs;
(c) promote community awareness and involvement in SCD prevention, patient care and support;
(d) integrate SCD surveillance within the national health information system;
(e) improve the knowledge and skills of health and non-health care providers in SCD control;
(f) collaborate with partners to undertake basic and applied research; and

(g) support and coordinate national associations working in SCD prevention and control policies on employment for SCD patients.

Interventions

The following interventions for the African region should be adapted to local settings.

Advocacy for resource mobilization and increased awareness

Member States should develop and implement effective advocacy interventions to create awareness of SCD and enhance efforts for local and international resource mobilization in order to ensure the availability of appropriate infrastructure, equipment, supplies and medicines. The WHO and countries should collaborate in developing regional networks and global alliances to help reduce the burden of SCD. High-level advocacy should be explored and encouraged.

Partnerships and social impact

Partnerships between health professionals, parents, patients, relevant community interest groups, non-governmental organizations (NGOs) and the media should be nurtured. This will facilitate public education which will increase awareness and encourage screening among members of the community. Partners should support the prioritization of SCD interventions such as widespread provision of screening, laboratory equipment, and specific vaccines that are not part of routine national immunization programs; the development of appropriate interventions to strengthen existing health delivery systems; and a multi-disease approach.

Creation or strengthening of national SCD programs within the framework of non-communicable disease prevention and control in harmony with national maternal and child health programs

The development of these interventions is the basis for improving the health care of those affected by SCD. Essential areas of work include advocacy; prevention and counselling; early identification and management; data collection, surveillance and research; community education; and partnership. An integrated multisectoral and multidisciplinary team involving health and social workers, teachers, parents and concerned NGOs could be established to work on the practical aspects of care delivery as well as program implementation and monitoring.

Capacity-building

Health professionals should be given pre-service and in-service training in SCD control including prevention, diagnosis and management of cases, and complications. The basic requirements to meet these service needs at various levels of the health system should be provided. All members of the health-care team are important for successful program establishment and implementation.

Supportive activities for special groups–children under five years, adolescents and pregnant women

Member States should reinforce national SCD supportive activities for vulnerable groups such as children under five years, adolescents and pregnant women who should benefit from financial packages for case management. Other supportive measures include early diagnosis and treatment of complications; special transfusion regimens; surgery; immunization; prophylactic antibiotics, folic acid and antimalarials; and special programs for prenatal care, psychosocial and professional support to patients, and adaptive educational interventions.

Primary prevention including genetic counselling and testing

Prevention entails setting up genetic counselling and testing interventions in high prevalence countries to reduce partnering between carriers. Genetic counselling and health promotion activities can lead to a substantial reduction in the number of children born with the disease. Widespread community involvement and support are essential.

Early identification and screening

Ideally, the disease should be identified at birth as part of routine newborn screening or at any subsequent contact the child has with a health facility. Depending on national policy, early identification can be done by the universal screening of all newborns, targeted screening of babies born to carrier mothers, and screening of pregnant women. Screening of babies should be done by collecting blood from a heel prick; testing can be done using iso-electric-focusing or high-performance liquid chromatography. These services should be offered in conjunction with counselling and health education since diagnosis raises serious medical, ethical and cultural issues which may vary from country to country.

Comprehensive health care management (CHCM) for SCD patients of all ages

CHCM consists of the following: parent and patient education; adequate nutrition; adequate hydration; use of prophylactic antibiotics and antimalarials; folic acid supplementation; use of specific vaccines; continuous medical follow-up; and early detection and management of complications. These measures will reduce morbidity, prevent complications and improve quality of life. According to the Ouagadougou Declaration, CHCM should also be integrated into health systems using the PHC approach to meet the needs of both rural and urban dwellers, including prevention of complications and patient referral to higher care centres when necessary. Family and community-based care should be integrated into the national program. Implementation of CHCM requires trained personnel, adequate facilities and interventions adaptable to the local needs of communities.

Provision of affordable medicines for SCD management and pain relief

The use of quality generic medicines as part of the national essential medicines list should be promoted. Sub regional economic entities can help in the manufacture and purchase of these medications. Since many SCD patients tend to revert to traditional medicinal practices, traditional pharmacopoeias should be fostered after proper testing, validation and standardization. Traditional health practitioners should be involved in SCD management and referral whenever possible.

Strengthening laboratory and diagnostic capacity and supplies with nationwide coverage

Tools for the diagnosis of SCD should be made available according to their complexity at all levels of the health system starting at the primary care level. A system for maintenance and uninterrupted provision of supplies should be developed. Diagnostic and imaging facilities should be made available for early detection of complications.

Initiate and enhance sickle cell disease surveillance

Community-based activities including surveillance and supervision, monitoring at all levels of operation, and periodic evaluation at national level should be undertaken to reduce the burden of SCD. These

surveillance data will give information that is useful for daily evidence-based decision-making and policy making in the management of the program.

Research promotion

It is important to describe the history of SCD, its clinical evolution and association with malaria and other diseases. In line with the Algiers Declaration, there is a need to promote innovative research in SCD directed towards basic knowledge and its transformation into new tools such as medicines, vaccines and diagnostic tools; it is also important to identify knowledge gaps and evaluate strategies. It is necessary to promote research in both conventional and traditional medicine to produce evidence of safety, efficacy and quality.

National Guidelines for the Control and Management of Sickle Cell Disease in Nigeria(9)

Preamble

In Nigeria, sickle cell disease is among the ten (10) priority non-communicable diseases (NCDs) and it contributes significantly to both child and adult morbidity and mortality. By virtue of its population, Nigeria stands out as the most sickle cell endemic country in Africa with an annual infant death rate of 100,000 representing 8% of infant mortality in the country. A survey done in South-south Nigeria in 2011 found a prevalence of 2.39% of SCD among the population. It is also estimated that about 24% of Nigerian adults have sickle cell trait.

Despite the high burden of SCD in Nigeria, a national policy to combat the disease is still awaiting ratification and many of the new modalities of management are not accessible or affordable. In 2010, the Nigerian SCD Network (NSCDN) was established as a cooperating body bringing together Nigerian physicians, non-governmental organizations (NGOs) and other interested bodies both within the country and in the Diaspora. One of the first tasks of the network was a survey to document the available facilities and the prevalent management practices in SCD clinics in the country in order to put the current situation in perspective and to enable planning and rational research projections. (10)

Considering the huge burden of SCD in Nigeria, focusing on tertiary care will probably not make an appreciable impact in improving the overall

outcome but a more practical strategy would be to tackle the problem at the primary healthcare (PHC) level by putting in place an appropriate national policy. Interestingly, a policy has been formulated in the context of non-communicable diseases in the country and is awaiting ratification. Some practical steps have been taken in the last few years to pursue programs of SCD control and management. There is now an SCD desk, with a designated officer at the Non-communicable Diseases Division of the Federal Ministry of Health, that controls SCD-related programs in the country. There is a commitment to newborn screening and six comprehensive SCD centres have been established in the different geopolitical zones of the country. (10)

Management protocols and guidelines have also been prepared to ensure uniformity and accepted management of SCD in the country. A national SCD policy has been prepared and should be ratified soon. Also, a Bill for the Control and Management of Sickle Cell Disease, which provides comprehensive provisions for SCD, was presented to the National Assembly in 2011, and it is hoped this will eventually become a legislated Act. The explanatory memorandum of the bill seeks to provide a legal framework for the prevention, control and management of SCD and to draw the attention of the public to the health burden arising from the disease in Nigeria. The Federal Ministry of Health says it will include point-of-care testing of sickle cell disease among children aged 0-9months in the National Policy and the Strategic Health Plan for Prevention and Control of SCD in Nigeria point-of-care test kit was presented by the SC support society of Nigeria, an NGO, in collaboration with Silver Lake Corporation Study Asuza, California, USA. (11)

The bill (12) has seven parts:

In Part 1, government is to engage in the prevention, control and management of SCD through the provision of support for patients suffering from the disease and also encourage participation of the stated LG in its program.

Functions and duties of the Ministry in respect of this program shall include

(a) The establishment and coordination of a Sickle Cell Screening program, with counselling by trained individuals with specific knowledge of the disease.

(b) Provide and improve access to quality care for Sickle Cell Disease patients. Linking laboratory results in deliverable ways to the provision of clinical care by creating properly staffed approved local health institutions.
(c) Raising awareness about the disease at local, national and governmental levels.
(d) Ensuring program support from governmental and non-governmental organizations, including private companies.
(e) Advocacy to draw the attention of international health agencies to the public health problem and cost burden, with a view to attracting international collaborative assistance.
(f) Developing a database of Trait carrier frequency and disease prevalence for evidence-based planning and calculation of the burden of disease. Clinical data on patterns of disease presentation, treatment regime and treatment outcome shall be collated and audited.
(g) Managing clinical networks adapted to local needs and resource availability and the building of care networks into existing hospital services. Enhancement of the partnership between primary care clinics and community-based Sickle Cell Disease organizations.
(h) Improve and expand patient, patient family and provider education.
(i) Ensure continuity and coordination of service delivery for individuals with the disease.
(j) Such other functions and duties that are provided for it under this Act.

Part II is in furtherance of the above in that the Ministry may accredit public or private hospitals and medical clinics or health centres for the purpose of implementation of the program which includes

(a) Serving for the delivery of medical treatment for the disease
(b) Providing for genetic counseling and blood genotype testing of the public.
(c) Keeping, collating and transmitting to the Ministry or its designated agency monthly or periodic records of persons who have undergone a genotype test, genetic counselling and medical treatment for the disease. Such records shall include the names, ages, and addresses of the persons attended to and the dates of the visits.
(d) Keeping a register of all Sickle Cell patients, as well as that of carriers.

Part III provides for the establishment of registering (sickle cell registry and a surveillance system) with the goal of establishing a sickle cell data system that will be used to describe the epidemiology and characteristics of the disease.

These data can be used for research, information dissemination policy decisions, and health care planning at the local, state and national level.

Part IV describes strategic components of the program. The main components of SCD prevention, control and management shall include:

(1) The SCD Newborn Screening Program (SCD-NBS). The screening of all newborns of mothers who are identified carriers of the sickle cell trait or suffering from the disease shall be encouraged.
(2) The genetic testing of parents, siblings or other appropriate relatives of children with Sickle Cell Disease and of adults with the disease.
(3) The genetic testing of all pregnant mothers is to be encouraged.
(4) Genetic counselling and testing, particularly of intending couples.
(5) Primary and secondary preventive medical strategies including prophylaxis, and treatment and services for individuals who have sickle cell disease.
(6) Training of health professionals (including doctors, nurses and other health staff) on genetic counselling.
(7) Education of parents and family members of persons suffering from the disease in counselling programs.
(8) The free treatment of the complications of sickle cell disease in this program shall come into effect when the National Health Fund is established. It shall then be financed from the fund without prejudice to the Act establishing the FUND.
(9) The Government of the Federation in collaboration with the States shall encourage the education of children born with the disease at least to the senior secondary school level.

Part V establishes a governing body known as “the council” which shall be responsible for general supervision and provision of guidelines for the control of expenditure of the program.

The members of the council will comprise;

(a) the Minister of Health, who shall be the Chairman;
(b) the Minister of State for Health, who shall be Vice-Chairman;

(c) the Executive Director, National Primary Health Care Development Agency;
(d) the Head of the National Coordinating Centre, who shall be the Secretary;
(e) the Director, Planning, Research and Statistics of the Ministry;
(f) a haematologists and a Sickle Cell Disease expert from tertiary health institution;
(g) a representative of the Ministers for Education and another in charge of Women Affairs respectively;
(h) two other Nigerians (one of whom must be a woman) who have or are members of a non-governmental organization working in the control and management of sickle cell disease.

This section also describes the powers of each council member.

Part VI summarizes the financial requirements of the program while Part VII gives a list of staff of the National Coordinating Centre.

Part VIII offers special services to intending couples via accredited centres, such services shall include:

(1) Accredited centres under this Act shall run special services for persons intending to get married which include genotype tests and genetic counseling particularly for those that are carriers of the sickle cell trait or have sickle cell disease.

(2) Where it is learned or found through a genotype test that intending couples may bear children prone to the disease, the medical personnel or centre attending to the couple shall – (a) advise such intending couple not to go into the marriage due to the likelihood of occurrence of the disease in children that may be born; (b) reduce such advice in writing and issue the written advice to the persons concerned and keep records of the full names, addresses and other particulars of such persons so counselled.

(3) No action or claim for breach of promise to marry shall be brought against anyone withdrawing from an intended or planned marriage in compliance with the written advice of appropriate medical personnel.

(4) No intending couple shall be forced to comply with the written advice of medical personnel while those in marriage shall however

bear the burden of medical services of all children born with the disease in such marriage.

(5) Nothing in this section shall be construed to warrant, support or justify any divorce or withdrawal by any person from an already subsisting lawful marriage or from any obligation. Lastly, there are miscellaneous provisions in Part IX where the Ministry may assign or request any non-governmental organization or accredited body to carry out advocacy or to perform any specified function permitted by the Act for the prevention and control of the disease in the federation.

Also, accreditation of any centre, organization or body may be withdrawn by the Ministry due to any of the following:

(a) It does not satisfactorily perform its functions or those assigned to it by the Ministry;
(b) It has become affected by any of the disqualifications from accreditation under this Act or was not qualified for accreditation under this Act at the time it was accredited; and
(c) It diverts to its private use or is found to be unfair in the dispensation or administration of any drugs or material or any part thereof made available or donated to it for the benefit of the public.

Primary Health Care Level of Care for SCD Patients

The care of SCD patients at the PHC level should revolve around the following:

(1) Training: PHC workers should be trained in the aetiology, presentation and common complications of SCD. They should also be able to provide basic genetic counselling to dispel the myths and stigma that surround the disease. Such trained personnel should be available in every PHC clinic.
(2) Awareness and education: massive awareness drives organized with the involvement of the media, community/religious leaders, committed advocates from the political class, sports and other celebrities, and key players in the private sector. This should be on an ongoing basis in each local government area. Learning about SCD should also be incorporated into the primary school curriculum.

(3) Early diagnosis, preferably through universal newborn screening, has to be introduced, with the registration of identified patients in a follow-up clinic.
(4) Health surveillance: all patients should be seen in a clinic on a regular basis. They must have access to a minimum level of care, which should include malaria prophylaxis, folic acid supplementation, penicillin prophylaxis and pneumococcal vaccination in children.
(5) Referral to a secondary or tertiary institution as necessary. The latter should focus on providing specialist care, including hydroxyurea therapy when indicated, and screening for patients at risk for stroke using TCD. A reliable blood supply should also be available for acute and chronic needs.

Tanzania

SCD in Tanzania has been recognized as one of the diseases of public health importance which however has shown evidence of reduction in under five mortalities following the introduction of SCD programs and interventions. Tanzania is among the 20 high-mortality countries that has achieved a 57% reduction in its under-five mortality rate (U5MR) from 158 per 1000 live births in 1990 to 68 in 2011. Although most efforts targeted infectious causes of mortality, the WHO projects that when the U5MR falls to below 50 per thousand live births, countries will need to develop policies to directly reduce mortality due to non-communicable diseases. Many African countries such as DRC, Tanzania and Nigeria have established SCD centres but Tanzania strategically decided to integrate SCD into its NCD program due to limitation of resources. (2,13) Comprehensive, dedicated SCD programs that provide NBS, follow-up care, family and patient education and counselling, and prevention and treatment of complications can have a significant impact in reducing morbidity and mortality. The most dramatic reduction of up to 70% of deaths in the age group 0–3 years has been linked with the results of early identification of newborns with SCD by NBS and prevention of infection. Tanzania is working to implement interventions to provide services for individuals diagnosed clinically with SCD, as well as penicillin prophylaxis and will be working to establish NBS and prevention of infection by promoting the use of penicillin and pneumococcal vaccination. NBS for SCD could identify individuals with SCD at birth and subsequently enroll them into SCD comprehensive care programs. The implementation plan for NBS for SCD that is being developed includes the

establishment of capacity for laboratory diagnosis of SCD, with the proposal of integrating NBS with the existing reproductive and child health program. (14,15)

As in many African countries, prophylactic penicillin or pneumococcal vaccination has not been introduced amongst individuals with SCD. Phenoxymethyl penicillin is cheap and included in the National Essential Medicine List (NEMLIST). With the inclusion of SCD in the national strategy for NCDs, the recommendation has been included in the training manual. Training of health workers all over the country started in 2013, which ensured that the implementation of its recommendation reaches all levels of health care. With regard to the prevention of infections by vaccination, also in 2013, Tanzania included PCV in the expanded program of immunization available to all children. (16) It is hoped that widespread use of PCV should lead to a reduction in the burden of U5 deaths from bacterial sepsis in children who receive PCV even without a diagnosis of SCD. Preventing infections and death from malaria is also an important component of preventing mortality in SCD, as malaria has been shown to be related with high mortality. (13)

Options for management of sickle cell disease

Option one: Retrospective genetic counselling in combination with prophylactic penicillin use after diagnosis.

Option two: Neonatal screening program and the use of penicillin for all homozygous babies, together with the most effective patient care, in combination with retrospective screening and genetic counselling.

Option three: most effective patient care, in combination with neonatal screening and the use of prophylactic penicillin from birth for homozygotes, and population screening with prospective genetic counselling.

Option four: as it is for option three, including accessibility to prenatal diagnosis, bone marrow transplantation, or both.

NBS for SCD could identify individuals with SCD at birth and subsequently enroll them into SCD comprehensive care programs. The implementation plan for NBS for SCD that is being developed includes creating capacity for laboratory diagnosis of SCD, with the proposal of integrating NBS with the existing reproductive and child health program.

A pilot program for the implementation of NBS for SCD was planned in 2015, with the aim of integrating the NBS policy into the reproductive and child health (RCH) program.

SCFT – the Sickle Cell Foundation of Tanzania was launched recently. SCD has been listed as one of the 6 problems in the government's plan on NCDs and as part of the broad medium-term strategic plan (MTSP) 2009-2015 which is also part of the broader Tanzanian Vision 2025. This marks the national/government response to the WHO's call for Action for the country to invest in the prevention of chronic illnesses including SCD. There are also policies with good intestates in place if well interpreted, for instance, policy (user fee exemption policy) in relation to SCD related medical care services. (14,15)

India

Sickle cell anaemia is highly prevalent in the tribal belt of Central and Southern India. The public health implications of sickle cell anaemia are significant leading to poor quality of life, lower life expectancy and higher rates of infant mortality. Unfortunately, India does not have any comprehensive national program to tackle the problem of sickle cell disorder. In most states, sickle cell disease receives scant attention from government health services. (17)

However, in 2006 the Department of Health and Family Welfare, Government of Gujarat initiated the Sickle Cell Anaemia Control program to control the menace of the disease in five districts of the state. Today, the program has been extended to all 12 tribal districts of Gujarat. Sickle cell disease does not have any cure; therefore, any strategy to deal with the disease should focus on prevention and early diagnosis to ensure effective management of the disease and put off a crisis situation. The Sickle Cell Anaemia Control Program does just that by focusing on early diagnosis of the disease, treatment and counselling of patients.

From 2006 till March 2011, a total of 1,396,904 tribal people have been screened through the program. The screening helped in identifying 10,673 sickle disease patients and aided in ensuring that adequate treatment and guidance are delivered to the victims. It concludes by discussing how the program has widened the scope of public health service delivery in Gujarat.

The Sickle Cell Anaemia Control program aims to:

1. Prevent the spread of sickle cell disease by reducing sickle cell births through screening and genetic counseling.
2. Identify sickle cell anaemia in newborns and infants as early as possible.
3. Provide early treatment to sickle cell patients.
4. Offer counselling to patients and relatives so they understand the scope of the problem and participate in the management of the disease.
5. Create awareness about the disease among the entire community.

The clinical management of patients with sickle cell disease and thalassaemia has become increasingly multi-disciplinary and complex. This trend calls for the development of guidelines for the management of specific clinical problems and protocols for various therapeutic procedures; to facilitate uniformity and standardization of care across different disciplines.

The guidelines provided guidance on different approaches to managing SCD such as the

- **Diagnosis of SCD**: This section looks at the clinical presentations, laboratory diagnosis, sickling test, interpretation of the sickling test, solubility test, cellulose acetate electrophoresis, blood film, high-performance liquid chromatography, isoelectric focusing, algorithm for definitive laboratory diagnosis of SCD, quality assurance and laboratory standards.
- **Management of Acute Complications in SCD:** Objectives of clinical management of SCD are to maintain a steady state of health, prevent and reduce the number of crises and complications, treat crises and complications promptly and effectively and promote a healthy lifestyle and a positive self-image. The policy looked at acute clinical presentations such as sickle cell crisis, priapism, acute chest syndrome and stroke, predisposing factors for sickle cell crisis, initial evaluation of an SCD patient in crisis and management of various crises, priapism, acute chest syndrome and stroke.
- **Special Situations:** This section is about special situations in managing SCD patients such as the use of hydroxyurea for managing SCD, suggested indications for hydroxyurea therapy in Nigeria, contraindications, dosage of hydroxyurea, prophylaxis and

antimicrobial therapy, management of osteomyelitis, blood transfusion, and peri-operative management of patients with SCD,

- **SCD and Pregnancy:** Sickle cell crises are unpredictable in or out of pregnancy. The guideline discussed effects of SCD on pregnancy, documented complications of pregnancy with SCD, a multidisciplinary team approach to the management of SCD in pregnancy, pre-conception counselling, pre-natal diagnosis, ante-natal care, prophylactic transfusion admission criteria, discharge criteria following treatment for sickle cell crisis, intrapartum, postpartum and contraception.
- **Management of Chronic Complications of SCD:** Problems of the musculoskeletal system are prominent in the life of the individual with sickle cell disease. Management of chronic complications such as osteonecrosis (Avascular Necrosis), ocular complications, renal complications and chronic leg ulceration in Sickle Cell Disease.
- **Care in Steady State of SCD:** Routine prophylactic measures, growth and development monitoring in children with SCD, home care and recommended regular clinical assessment of patients in steady state at the out-patient clinic are discussed in this section.
- **Genetic Counselling and Testing in SCD:** Genetic Counselling is a non-directive art of providing accurate, full and unbiased information in a caring relationship to an individual or family affected by a genetic disorder to enable them come to terms with and cope better with the disorder. This section discussed the reasons for genetic counselling and testing in SCD, the procedures/counselling process and challenges of counselling in SCD.
- **Newborn Screening and Diagnosis in SCD**: Newborn Screening (NBS) is done at birth or in the neonatal period to enhance early detection of sickle cell haemoglobin. There is discussion of steps in the collection of samples, the movement and transportation of collected samples, laboratory testing of newborn blood samples for haemoglobinopathy screening, protocol for processing laboratory samples, coverage of newborn screening.

Other Programs (18-20)

- **Centre of Excellence for Sickle Cell Research and Training Abuja:** The University of Abuja Centre of Excellence in Sickle Cell Disease Research and Training was instituted to undertake multidisciplinary research that will involve faculty from health,

social, computer sciences, education and mass communication with the aim of actualizing the control of sickle cell disease.

- **Sickle Cell Foundation Nigeria**: The National Sickle Cell Centre (NSCC) is strategically located opposite the Lagos University Teaching Hospital, for the purpose of facilitating and enabling ease, desirable and effective collaboration with a tertiary care hospital and university research centre. The Foundation has initiated a database of people living with Sickle Cell Disorder (SCD) in Nigeria. This would be a valuable resource for planning for better health care, for essential communication and for monitoring the survival trend.
- **The Nigerian Sickle Cell Expert Advisory Committee (NISEAC)**: This committee of the Sickle Cell Foundation Nigeria was set up to examine all matters related to sickle cell disorder and the standard of service to be delivered to save as well as improve the quality of lives of those affected. The Committee presently has about 30 members spread across the 6 geo-political zones in Nigeria. At its first meeting, the committee arrived at decisions and recommendations summarized hereunder;
    - The Federal and State Governments as well as the organized private sector in Nigeria and the International Aid Agencies should urgently allocate funds annually for financing appropriate training, service, and research programs to seriously address sickle cell disorder.
    - The Federal and State Governments, should introduce newborn or infant screening for the early diagnosis of sickle cell disorder in Nigeria.
    - Prophylactic anti-infective measures against pneumococcal, meningococcal and other prevalent bacteria should be freely provided to infants and children with sickle cell anaemia in order to reduce the high death and illness rates caused by these infections.
    - Adequate safe blood for transfusion should be provided in all States of the Nigerian Federation to save and support lives.
    - The training and recognition of a cadre of Sickle Cell Nurse Specialists should be introduced in order to improve our capacity to deliver better health care and educational coverage to affected individuals and families.
    - Serious concern that numerous drugs are freely marketed in Nigeria with unproven claims of curative or palliative properties in the treatment of sickle cell disorder.

- **Nigeria Global Health Initiative, CDC:** is collaborating with many partners to plan and implement programs to tackle the public health burden of SCD in Nigeria**:**
  - "Preventing Infectious Disease Deaths in African Children with Sickle Cell Disease" Partners: Association of Public Health Laboratories, Michigan State University, National Hospital (Abuja).
  - "Improving Hemoglobinopathy Prevention and Management Efforts through the Development and Evaluation of a Global Hemoglobinopathy Needs Assessment Tool" Partners: Guys and St. Thomas Hospital (London, UK), Katsina State Government, Sickle Cell Cohort Research, SCORE (Nigeria).
  - "Assessing an Association between Lead Poisoning and Sickle Cell Disease" Partners: USAID, National Center on Environmental Health, Healthy Homes and Lead Poisoning Prevention Branch.

Programs and Policies in Developed Countries

The National Sickle Cell Anemia Control Act of 1972 arrived to address the early identification of individuals with SCD and their ongoing truculence in a comprehensive manner. (21)As part of public health activities addressing SCD, increasing knowledge awareness through activities by community-based organizations, support groups, and advocacy organizations also may provide effective avenues to reach people with SCD.

Depending on state policies, NBS programs vary as to whom they report positive screening results and whether all, some, or no carriers of haemoglobinopathies are actively followed up with an in-screening and information disclosure – related consent procedures.

The Sickle Cell Treatment Act of 2003 in the United States of America

The Sickle Cell Treatment Act (SCTA) provides an important opportunity to work with federal and state policymakers to implement public policies that will ultimately lead to a better quality and an enhanced care and health outcome for those living with sickle cell disease (SCD). In 2003, Senators Jim Talent (R-MO) and Charles Schumer (D-NY) and Representatives Danny Davis (D-IL) and Richard Burr (R-NC) garnered bipartisan support for the SCTA, which was signed into law by President George W. Bush in

2004 as an amendment to the American Jobs Creation Act (Public Law Number 108-35). The SCTA was the first major legislative initiative in more than 30 years focused on SCD. (22) As groups move forward to act under this law, it will benefit SCD stakeholders to understand the law's key provisions as well as to identify opportunities for advocacy created by the law that can result in implementing policies that will improve health outcomes for individuals with SCD.

Provisions of the Sickle Cell Treatment Act of 2003

The SCTA includes three major provisions. These are:

1. Creating a new, optional Medicaid benefit that explicitly allows states to increase reimbursement for SCD treatments including chronic blood transfusions and stroke prevention, in addition to adding genetic counselling and testing as reimbursable services. (23)
2. Making available Medicaid reimbursement (at the 50 percent federal administrative matching rate) for public education campaign activities specifically related to SCD. (23)
3. Authorizing the Sickle Cell Disease Treatment Demonstration Program to improve access to services for those with SCD in addition to improving and expanding patient and provider education around SCD. (24)

Each of these provisions is discussed in greater detail below.

Provision 1: New Optional Medicaid SCD Benefit

The new optional Medicaid benefit created by the SCTA clarifies that states can cover both key primary and secondary preventative services related to SCD through Medicaid. Although states generally could have covered these services prior to the law's enactment, the SCTA both makes it absolutely clear that these services can be covered by state Medicaid programs and gives states additional flexibility around the services. For example, states can now reimburse providers for services aimed at treating SCD (such as transcranial Doppler studies and blood transfusions) at a higher rate than it would pay for similar services aimed at treating other diseases. (25) Missouri was one of the first states to implement the optional Medicaid benefit in 2007, effectively increasing access to a broader spectrum of services for individuals with SCD who receive coverage from Medicaid. In particular, Missouri's inclusion of SCD in its

chronic care improvement program (CCIP) extended access to a variety of chronic disease management services to patients with SCD. Maryland convened a task force that encouraged legislators to add the optional benefit to their Medicaid programs but have not yet successfully implemented them. (26)

Provision 2: Medicaid Reimbursement for Education and Other Services Related to SCD Prevention and Treatment

In general, Medicaid is not used for financing public education campaigns. However, the SCTA makes it clear that if public education campaigns are specifically targeted around individuals who have SCD or carry the sickle cell trait, the non-medical expenditures—including administrative expenses – associated with such campaigns can be reimbursed by the federal government under the standard Medicaid administrative matching rate of 50 percent (i.e., for every dollar spent on an SCD public education campaign, the federal government will reimburse a state for half the cost). Activities that are considered related to public education campaigns include services, such as genetic screening and counselling, that will identify individuals with SCD or sickle cell trait who are likely to be Medicaid eligible and provide them with information related to prevention of SCD complications. In creating a new service bundle, this provision allows organizations to conduct outreach with non-medical personnel to educate high-risk communities about SCD and carriers of sickle cell trait, providing new opportunities to include this population in a system of care. It also allows non-medical personnel, such as counsellors, to spend time with sickle cell trait carriers and SCD patients and families to discuss disease management. This flexibility to fund SCD public education campaigns remains unique and specific to SCD. For other conditions, the Center for Medicare & Medicaid Services (CMS) has made it clear that "Expenditures related to any public education campaigns not specific to SCD remain unallowable under Medicaid". (27) Under the bill, states could pay for outreach, counselling, and other non-medical services in a variety of ways. In one scenario, payment could resemble fee-for-service reimbursement for medical services. States might also designate certain entities to serve as contractors for the program and provide them a lump sum payment upfront. There are few federal constraints except that the activity must relate to Medicaid. Thus, it would not be permissible to use the Medicaid money to pay for public service announcements (PSAs) aimed at the general population rather than the Medicaid beneficiary population specifically.

Provision 3: Creation of a Demonstration Program to Establish Systematic Mechanisms for SCD Prevention and Treatment

The SCTA also authorizes the Sickle Cell Disease Treatment Demonstration Program which has as its goals increasing access to treatment for those with SCD, ensuring that consumers and providers are better educated about SCD, and improving the coordination of services for those with SCD. To further these goals, the SCTA provides for grants to be made by the United States Department of Health and Human Services (HHS) Health Resources and Services Administration (HRSA) during each Federal fiscal year (FFY), to up to 40 eligible entities where the program is conducted to aid in the development and creation of systems to improve SCD prevention and treatment.(16,27)Selected entities may use their grant for purposes including education, treatment (including genetic counselling and testing), and improvement of continuity of care for people with SCD. Grantee organizations may also use funds for training health professionals and identifying and securing additional federal funds to continue SCD treatment.

Standards for Clinical Care of Adults with Sickle Cell Disease in the United Kingdom(28)

The first edition of the "Standards for Clinical Care of Adults with Sickle Cell Disease in the UK" (Sickle Cell Society, 2008) has contributed immensely to the improvement of care for patients with sickle cell disease (SCD).However, there was a need to update the document in 2018 due to the enormous quantity of clinical and academic research into SCD globally. These researches included clinical research trials, new insights into pathophysiology, many new drug therapies, and potentially curative treatments. Regrettably, these new developments have not always translated into an improvement of care in quality of life or outcomes. Furthermore, patient survey reports indicated that many of the issues that patients raised in 2008, including the timeliness of pain relief, inadequate education of health professionals and inequity of care still exist. The 2018 document was divided into three sections; Section A (General Principles) deals with the organization of care and health and well-being, Section B is on the management of acute and chronic complications, and Section C includes other management issues and treatments.

General principles

1. Adults with sickle cell disease (SCD) should obtain care near their homes where possible, but accessibility to highly specialist multidisciplinary care including specialist nursing support should also be available.

2. Linkage should exist between all local hospitals and specific specialist centres with agreed pathways and protocols for advice and referral for acute and chronic complications.

3. Specialist haemoglobinopathy teams should participate in a quality review program of haemoglobinopathy services against nationally agreed standards.

4. All consenting patients should be registered on the National Haemoglobinopathy Registry (NHR) and annual review data and adverse events should be reported to the NHR.

5. All patients should have access to specialist psychology support.

6. Core staffing of Specialist Centres for SCD should include a psychologist with a special interest and experience in SCD.

Transition

7. Specialist teams should have a policy and a dedicated team for transition, which should include a named transition-lead.

8. Further and higher education institutions, universities and colleges should develop and monitor policies for supporting students with SCD with respect to their education, their health and their careers.

Primary care

9. All adults with SCD should be registered with a general practitioner (GP).

10. Each SCD patient should be offered routine primary health care services at their GP surgery.

11. All adults with SCD should have access to community nursing support**.**

Acute pain

12. Patients presenting as a medical emergency with an acute painful episode should be offered appropriate analgesia within 30 minutes of presentation to the emergency department.

13. All hospitals with emergency departments should have protocols to guide management of uncomplicated acute presentations of SCD.

Acute complications

14. All hospitals with emergency departments should have protocols to guide management of uncomplicated acute presentations of SCD including when to seek specialist advice.

Chronic complications

15. All patients should be offered regular outpatient review to ensure screening for chronic disease complications and early initiation of treatment according to local protocols and national guidance.

16. All patients with evidence of chronic organ dysfunction should have access to review in multidisciplinary or specialist clinics.

17. Patients with complex pain needs should be referred to a multidisciplinary chronic pain team with experience of SCD, offering both pharmacological and nonpharmacological interventions**.**

Prevention of infection

18. Specialist and local haemoglobinopathy teams and GPs should ensure that adults with SCD are adequately vaccinated against the following infections according to advice in the Green Book:

    - Invasive pneumococcal disease,
    - Haemophilus influenza type B,
    - Neisseria meningitis ACWY and B, and
    - Hepatitis B.

Patients should be periodically warned about the increased risk of invasive pneumococcal disease (IPD) and other forms of sepsis. They should also be educated about symptoms which might indicate infection and to attend for medical assessment if temperature ≥380C.

Annual Review

20. All adults with SCD should be offered comprehensive review from a specialist centre at least annually.

21. A pro forma should be used for the annual review visit to ensure systematic, detailed, and consistent care and to facilitate data collection.

Pregnancy

22. Pregnant women with SCD should be managed by a multidisciplinary team of obstetricians, midwives and haematologists with an interest in SCD in a unit that manages high risk pregnancy.

23. Units which manage SCD pregnancy should have a clear protocol for patient management. Hydroxycarbamide (HC).

24. All hospitals looking after adults with SCD should have a prescribing and monitoring protocol for hydroxycarbamide (HC) (also known as hydroxyurea) to maximize benefits and safety.

25. Specialist centres should audit their use of HC to ensure it is discussed with all patients who may benefit from its use.

Transfusion

26. All hospitals that admit SCD patients should have protocols and training in transfusion for SCD including manual exchange procedures.

27. Automated exchange transfusion should be available to all patients with SCD and should be provided by specialist centres.

28. Specialist centres should audit their use of blood transfusion in the acute and chronic setting to ensure its use is consistent with national guidance.

Emerging therapies

29. The National Health Service (NHS) England should ensure that all patients have equitable access to high cost interventions.

30. Trials for haematopoietic stem cell transplantation (HSCT) in adults with SCD should be available in the UK.

31. All patients with SCD should have access to information regarding current clinical trials, to enable participation if the patient so chooses**.**

United Kingdom

Sickle cell disease and thalassaemia major are serious health problems for inner city populations in Britain, but services are inconsistent and policy guidance is unclear. (29-31) The NHS Health Technology Assessment Program commissioned two systematic reviews to identify the objectives of the screening programs and to determine whether, and in which populations, screening using haematological tests should be either selective or universal. The decision on who to screen in areas where not everyone is tested is based on questions to identify ethnic origin. Continuous monitoring and evaluation are crucial to the success of SCD control programs and should be based on process, outcome and impact measures. These indicators should meet the requirements of national health management systems and be reportable to relevant international forums over the next 5 to 10 years.

United Kingdom screening policy – haemoglobinopathy and sickle cell disease (29)

The goal of the Screening Programme for Sickle Cell and Thalassaemia is to develop a linked program of high-quality screening and care in order to:

- support people to make informed choices during pregnancy and before conception,
- improve infant health through prompt identification of affected babies,
- provide high quality and accessible care throughout England, and
- promote greater understanding and awareness of the disorders and the value of screening.

UK National Screening Committee:

- Offer screening pre-conceptually,
- Offer screening as early as possible, but at least by 8-10 weeks of pregnancy,
- Offer all pregnant women screening for sickle cell and thalassaemia,
- Observing local policy, base screening on the Family Origin Questionnaire and blood test results, and
- All babies can be screened for sickle cell disorders on the newborn bloodspot.

Cuban programme for prevention of sickle cell disease (30)

The percentage of carriers of the sickle cell gene in Cuba ranges from 3 to 7% in different regions. In 1983 the National Medical Genetics Centre initiated a program for the control of sickle cell disease, which was started in Havana and later extended nationwide. The program is based on mass education, screening and supportive genetic counselling, care of affected individuals, and availability of prenatal diagnosis.

Screening for hemoglobinopathies in Copenhagen (31)

Increased immigration to the Nordic countries of people from areas in which haemoglobinopathies are common diseases has resulted in an increased frequency of individuals heterozygous for serious haemoglobin disorders such as beta-thalassaemia and sickle cell disease. Thus, in Copenhagen County, about 4 per cent of the immigrants from these countries are carriers of one of these diseases. A centre for haemoglobinopathies has been established in Copenhagen County, dealing with diagnostics, screening procedures, genetic counselling, prenatal diagnosis, education and treatment of various haemoglobin disorders. In collaboration with Rigshospitalet and the laboratory serving general practitioners, a screening program for pregnant women of relevant ethnic origin has been established, capable of servicing the entire Copenhagen area**.**

Conclusion

The majority of countries in sub-Sahara Africa are yet to develop a national policy while some are faced with challenges toward the implementation of an existing legal framework. Indicators for monitoring

progress will include availability and enforcement of SCD control policies, legislation, regulations, programs and guidelines. Outcome and impact indicators will include the reduction of SCD incidence, mortality, morbidity and risk factors; educational achievements; and job security of SCD patients. Implementation of the interventions suggested for each country and the WHO would ensure prevention, care and support at all levels and result in improved quality of life and life expectancy of those affected individuals.

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Future Perspectives for the Treatment of Sickle Cell Disease

Falana BA and
Adeyemo MOA

The main focus of this review is to evaluate treatment modalities for people living with sickle cell disease in the developing world, the psychosocial implications and effects of this disease compared to that of the developed world. The most important challenge is improving prospects for the patients with sickle-cell anaemia in developing countries. The provision of comprehensive care for patients is early intervention for preventable problems with pain medication, antibiotics, nutrition, folic acid supplementation and high fluid intake. Tragically the majority of these individuals will die in childhood due to lack of basic care and those who survive into adulthood often face a life of chronic disability and premature death unless disease-modifying therapy can be provided. What are the current future perfectives and best practices in the management and care of this disease? The establishment of health programs is solicited for developing countries at the national level to promote access to affordable medical services for people affected by the disease. People with the disease have two copies of the sickle globin gene, which produce an abnormal haemoglobin and a red blood cell that have haemoglobin S instead of haemoglobin A. In sickle cell anaemia, the most common form of sickle cell disease, the body makes sickle-shaped blood cells that contain abnormal haemoglobin. These red blood cells are less functional and block blood flow, causing pain and organ damage and increasing the risk for infection.

The Epidemiology and Psychosocial Burden of Sickle cell Anaemia in the Developing World

Sickle cell anaemia is one of the most common severe monogenic disorders in the world presenting with characteristic abnormal, rigid, sickle shaped red blood cells. Haemoglobin polymerization involves a point mutation on the 6th codon of the beta-globin gene located on the short arm of chromosome 11 which is central to the pathophysiology of this disease. (1) This mutation produces a defective beta globin chain, which under low oxygen tension polymerizes into long fibres that eventually lead to abnormally deformed sickled red blood cells characterized by rigidity and vaso-occlusion. (2) The latter is responsible for the painful crises that characterize the disease. There is also a chronic vasculopathy triggered by free haem resulting in nitric oxide scavenging and up regulation of adhesion molecules in reticulocytes, neutrophils and endothelial cells. (3) In normal states, the erythrocytes are elastic, and this characteristic morphology enables them to pass through blood vessels and even at capillary sites in human organs and systems. The sickled red blood cells make it difficult to pass through these blood vessels and low oxygen tension results thereby promoting sickling effects. Hence erythrocytes become sticky, adhere to the endothelium and clump together plugging smaller vessels and also damage large blood vessels that can become severely stenotic and/or occluded. (2)

The World Health Organization (WHO) estimates sickle cell anaemia affects nearly 100 million people throughout the world, with over 300,000 children born with this condition. Tragically the majority of these individuals will die in childhood due to lack of basic care, and those who survive into adulthood often face a life of chronic disability and premature death unless disease modifying therapy can be provided. The World Health Organization (WHO) has also made some commitments for promoting awareness of this disease such as:

a. Increasing effective awareness of sickle cell anaemia as a major health issue worldwide.

b. People living in each and every community all around the world should become aware about:

i. Myths and stigmas about the disease are removed.

ii. All developing and member countries should establish various health programs to provide easy access to the treatment for this disease at the national and regional levels.

iii. The availability of satisfactory access to technical support and medical services for all people suffering from this disease must be promoted.

iv. Medical professionals should be provided with wellness training facilities for better prevention, research, work and accurate implementation of the resources minimizing disease complications.

v. New health strategies to completely eradicate this disease from the world should be implemented.

Malformation of haemoglobin protein structures, mainly thalassaemias and sickle cell anaemia is globally widespread. In the year 2017 about 7% of the world's population carry genes responsible for haemoglobinopathies out of which about 400,000 neonates are born with major haemoglobin disorders, including more than 300,000 cases of sickle cell anaemia in Africa. (2) Globally, there are more healthy people who have inherited only one mutant gene from one parent of thalassaemia carriers than of sickle cell anaemia, but the high frequency of the sickle cell gene in certain areas leads to a high rate of affected newborns. Sickle cell anaemia is particularly common among people whose ancestors come from Saudi Arabia, sub-Saharan Africa, India, and Mediterranean countries. (2) Migration raised the frequency of the gene in the Americas. In some areas of sub-Saharan Africa, up to 4% of all children are born with the condition. (2, 3) In broad terms, the prevalence of healthy carriers who have inherited the mutant gene from only one parent ranges between 15% and 40% across Africa and decreases to between 1% and 2% on the North African coast and less than 1% in South Africa. (3) The environmental conditions that lead to the emergence of the S mutation ensure – at least in equatorial Africa – that the highest prevalence of SCD is found in regions where the malaria parasite is still endemic. (3)

Malaria is a major erythropoietic stress factor and profoundly alters the clinical expression of SCD in sub-Saharan Africa. In Ghana and Nigeria, the frequency of the trait is 15% to 35% whereas in Uganda it shows

marked tribal variations, reaching 45% among the Baamba tribe in the west of the country. (4) Frequencies of the carrier state determine the prevalence of sickle cell anaemia at birth. (4) For example, in Nigeria, by far the most populous country in the sub region, 24% of the population are carriers of the mutant gene and the prevalence of (5) sickle cell anaemia is about 15 to 25 per 1000 births. This means that in Nigeria alone, about 150,000 children are born annually with sickle cell anaemia. The public health consequences of sickle cell anaemia are enormous. Its impact on human health may be assessed against the yardsticks of infant and under-five mortality. As not all deaths occur in the first year of life, the most valid measure is under-five deaths. An increasing proportion of affected children now survive past five years of age but remain at risk of premature death. The people living with sickle cell anaemia as well as their doctors, nurses, and relatives are faced with several challenges such as daily use of routine drugs, recurrent or frequent illnesses, need for blood transfusion, regular clinic attendance and hospitalization. Hence, parents or caregivers of these children tend to have a worse health-related quality of life (6) compared to those without sickle cell disease children which impacts negatively on their behaviour and self-esteem. (7, 8) The financial burden of SCD on the caregivers and their families is very high. In a study by Adegoke and Kuteyi in 2012 (9), more than half of the caregivers reported that the expenses of the child's illness adversely affected the family's basic needs such as basic life needs and housing. This is not surprising considering the rising trend of inflation in most countries in Africa and the world at large. In Nigeria, and many other developing countries, national programmes on health insurance and social welfare systems are absent, making caring for a child with chronic illnesses such as SCD a great financial burden. Furthermore, about 70% of the caregivers in this study lost income or financial benefits due to time spent caring for their children. In Nigeria, the predominant form of health-care financing is out-of-pocket. As observed previously, job loss, underemployment and/or unemployment arising from time spent caring for a child with SCD, will significantly contribute to the financial burden experienced by caregivers and their family. (8) They also reported that about 40% of the caregivers sometimes or frequently neglected other members of the family because of the demands caused by the child's illness. It is known that the way parents relate with their ill children and the feeling of neglect this generates in other siblings are a major factor in family dysfunction. (10) This neglect especially when experienced too frequently has been described as a risk factor in the psychopathology of psychosocial problems in chronic physical illness. (11) Depression, frequent school absenteeism as a result

of recurrent crises and suboptimal health are other major problems of SCD children (11). It is important therefore, that adequate and concrete educational plans should be developed for them. This is consistent with a study on psychosocial and family functioning in children with SCD and their mothers in Atlanta Georgia where they found that sickle cell patients and their caregivers experienced more depressive symptoms than the controls. (12) Treatment with hydroxyurea has reduced many of the major complications. Even well-organized holistic care including expert counselling and access to needed care, irrespective of patients' ability to pay, can significantly reduce illness and deaths and improve the quality of lives of people living with sickle cell anaemia in developing countries. The World Health Organization (WHO) estimates, that sickle cell anaemia affects nearly 100 million people throughout the world, with over 300,000 children born with this condition annually.

Genetics of Sickle cell Anaemia

Human Haemoglobin (Hb) is a tetramer globin polypeptide (a pair of chains "α-like" and one pair of chains "non-α") over a portion of haem for each chain, this portion consisting of a ring of protoporphyrin IX forming a complex with a single atom of ferrous ion (Fe2+). The haem group can connect to a single oxygen molecule, giving the haemoglobin molecule the ability to carry up to four oxygen molecules – hence its importance in the metabolism of organisms (13). The production of various human haemoglobins is controlled by two groups of closely related genes. The genes of α-like globins are on the short arm of chromosome 16, between the band 13,2 and the telomere, and consist of two globin genes α (alpha) and a single copy of gene ξ (zeta). The genes of non-α globin are on chromosome 11, band P15, near the end of the short arm, and consist of a single gene ε (epsilon), in the foetal globin genes GA and the genes (delta) and (beta) adult haemoglobin. (13) There is still consensus that sickle cell anaemia is a monogenic disease caused by a single mutation in the beta globin gene, characterized by the substitution of glutamic acid by valine at position 6 (*6*Glu→Val). This change alone causes the resulting abnormal haemoglobin, the haemoglobin S (HbS), when deoxygenated and in high concentration, to provide reduced solubility with a paracrystalline structural formation, leading to a sharp rise of blood viscosity. (14) Characteristically, sickle cell anaemia presents obvious phenotypic variability and, to elucidate this phenomenon, research has shown that the pathogenesis of this disease is quite complex. In addition to the factors themselves and the erythrocyte haemolysis, inflammation, endothelial

activation and changes in vasoactive factors seem to play a role in triggering the clinical phenomenon typical of SCA, such as vaso-occlusion. (14) The sickle gene results from a mutation punctiform causing substitution of amino acid-glutamic acid in the sixth position of the chain of β globin (β□) to valine (β^{6} Glu→Val), thereby haemoglobin S is represented by α2A β26 Glu→Val 6. This substitution is due to a change in the second base of the codon of the encoding glutamic acid, in other words, GAG to GTG. (14) Although all patients with sickle cell disease presents the same genetic mutation the relative diversity on the severity of the clinical manifestations is remarkable. Several modifying factors have been studied in order to determine why this diversity happens (15). Those currently most important are: levels of foetal haemoglobin (Hb F), the coexistence of other hereditary haemoglobinopathies (e.g., thalassaemia) and finally, the different haplotypes of HbS. The association of sickle cell disease with other hereditary haemoglobinopathies is relatively frequent and leads to a variety of clinical presentations, ranging from asymptomatic to the most severe. Among its most common types are included: Sickle Cell Disease (SCD), wherein individuals are homozygous for the gene for haemoglobin S; Sickle Cell Trait wherein the patient has a gene that synthesizes polypeptide chains; Normal Globin and an abnormal gene, with production of both haemoglobins (A and S), predominantly haemoglobin A (HbA) (15).

Clinical Features of SCD

Sickle cell anaemia covers a wide range of illnesses. Most affected people have chronic anaemia with a haemoglobin concentration of around 8 g/dl. The main problems arise from the tendency of the red blood cells to become sickle-shaped and plug capillaries and also damage large vessels that become severely stenotic or occluded at low oxygen tension. In children, sickle-shaped red blood cells often become trapped in the spleen, leading to a serious risk of death before the age of seven years from sudden profound anaemia associated with rapid splenic enlargement or because lack of splenic function permits an overwhelming infection. Between 6 and 18 months of age, affected children most often come down with painful swelling of the hands and/or feet (hand-foot syndrome). Survivors may also suffer recurrent and unpredictable severe painful crises, as well as “acute chest syndrome” (pneumonia or pulmonary infarction), bone or joint necrosis, priapism or renal failure. For most patients the incidence of complications can be reduced by simple protective measures such as prophylactic administration of penicillin in

childhood, avoiding excessive heat or cold and dehydration, and contact as early as possible with a specialist centre. These precautions are most effective if susceptible infants are identified at birth. Some patients have such severe problems that they need regular blood transfusion and iron-chelation therapy. These changing manifestations of sickle cell anaemia in developing countries create an urgent need to develop models of care appropriate to the management of the disease.

Current Sickle Cell Management Practices in the Developing World

In most developing countries where SCD is a major public health concern, its management has remained inadequate, national control programs do not exist, the basic facilities to manage the patients are usually absent, regular systematic screening is not a common practice and the diagnosis is usually made when a patient presents with a severe complication. Simple, cheap and very cost-effective procedures such as the use of penicillin to prevent infections are not readily available in many countries. Some of the management practices include:

Nutrition

Sickle cell patients have an increased metabolic rate and protein turnover which are balanced by high calorie intake. Folic acid requirements are increased by haemolysis above normal levels of 50 g/day and as much as 500 ng daily is necessary to reverse established megaloblastic change (16). Because of low availability of folic acid and the cooking practices, folate deficiency is common and supplemented with drugs. Erythrocytes are rich in zinc and people living with sickle cell tend to acquire an increased total body iron burden especially if they receive blood transfusions. Iron salts are not prescribed routinely.

Prophylaxis against Infections

Regular immunization against the common viral and bacterial infections of childhood is especially important and diligence is necessary to ensure that vaccine schedules are completed. A tetanus toxoid "booster" should be given at regular intervals because of the prevalence of leg ulceration. Prophylactic penicillin is essential in early childhood to prevent pneumococcal septicaemia.

Therapy of Infections

Once infections occur, diagnosis and therapy should be as prompt as possible. The hazards of overwhelming septicaemia are well recognized and must be remembered in any child with a high fever, or who looks lethargic and ill, and treated accordingly.

Avoidance of Adverse Climatic Conditions

The commonest precipitating factor for the painful crisis is cold and education and proper clothing may minimize its effect so that patients understand the importance of cold and keep warm at the cold wet periods of the year, and at night.

Hydration

Dehydration and haemo concentration are known to precipitate a painful crisis in some patients. The maintenance of adequate hydration is very important where febrile conditions increase fluid loss, especially in countries with high ambient temperatures.

Oxygen

The use of oxygen is frequently recommended for people living with sickle cell anaemia during the therapy of acute complications. The disease usually lowers arterial oxygen saturation in the steady state and this may fall further during acute illness, especially in acute chest syndrome, under these conditions, high levels of inspired oxygen can only be beneficial.

Blood Transfusion

It is invaluable in the management of acute exacerbation of the disease. Also, in normal hazardous cases of blood transfusion, there are additional dangers of haemosiderosis and precipitation of crisis. Generally, the indication of blood transfusion is a haemoglobin level less than 4 g/dl to 5 g/dl in selected cases, for electric or emergency surgical operations, and the presence of formidable complicating infections. Normally packed cells are transfused simply to raise the haemoglobin concentration level without increasing the blood volume.

Anti-malarias

Malaria has been reported as the commonest precipitating cause of crisis in Africa, it is also known that malaria parasitaemia is associated with a fall of 2 g/dL in haemoglobin concentration level (17). Malaria is therefore lethal to sickle cell patients and a special effort is required to prevent it and to render prompt treatment when prophylaxis fails. The drugs used are paludrine and proguanil.

Analgesics

Relief of pain is an important aspect in the management of painful crisis. Mild to moderate pain often respond to paracetamol. For more severe pains, pethidine or codeine have reduced the frequency of emergency room visits. (17) Pentazocine or morphine can also be used for severe pains necessitating hospital admission. Intravenous infusion of these drugs gives better and more sustained pain relief but the occurrence of drug dependence in some sickle cell populations has led to reservation in the use of narcotic analgesics.

Steroids

Adreno corticotrophic hormone and corticosteroids have been helpful in some cases for controlling pain, swelling and muscle spasm. (18)

Cyanate

Dietary cyanate, from foods containing cyanide derivatives, has been used as a treatment for sickle cell anaemia. In the laboratory, cyanate and thiocyanate irreversibly inhibit the sickling of erythrocytes drawn from sickle cell anaemia patients. However, the cyanate would have to be administered to the patient for a lifetime as each new red blood cell created must be prevented from sickling at the time of creation.

New Therapeutic Frontiers and Future Perspectives

The following are the current trends in the care and management of sickle cell disease in patients recently, though they require great expertise and they are very costly.

1. Gene Therapy: A panoply of potential new therapies for sickle cell disease has emerged in just the past five years. Pharmaceutical companies

are now actually interested in SCD. Gene therapy for SCD has always been made available recently. Now it is actually here for humans, albeit on an extremely limited and experimental basis. (20) Five individuals with SCD have undergone some form of gene transfer therapy to date, but the durability of clinical benefit of the current generation of gene therapy methods remains to be demonstrated. (20) Even so, next-generation gene therapy techniques are already being studied in preclinical models. An ideal gene therapy for SCD would avoid the problems of insertional mutagenesis and difficulty achieving proper spatiotemporal expression of a transgene by permanently correcting the sickle mutation *in situ*. In an effort to achieve this goal, Hoban et al. (20) used specifically engineered zinc-finger nucleases and a donor nucleotide template to effect cleavage of the β-globin locus and homology-directed repair of the sickle mutation in haematopoietic stem and progenitor cells (HSPCs). (20)s These modified HSPCs could engraft in immunodeficient mice and produce cells from multiple lineages. Moreover, gene-corrected CD34+ cells from the bone marrow of individuals with SCD could produce wild-type haemoglobin tetramers. (20) Clearly, more work needs to be done until this gene correction technique is ready for studies in humans, including elimination of off-target cleavage and non-homologous end joining.

2. Bone Marrow Transplantation: The first sickle cell patient who underwent bone marrow transplantation also had acute leukaemia. (21) Fourteen (14) years after this intervention the patient remains cured of both the leukaemia and the sickle cell disease. Encouraging experience with marrow transplantation in SS patients (without leukaemia) was reported from Belgium. (21) A collaborative protocol is enrolling sickle cell patients in Brazil, Canada, France, Germany, the UK and the USA to evaluate the role of bone marrow transplantation as a definitive treatment of sickle cell disease. In 1998, about 100 children (22-23), with an average age of 7–10 years, received allogeneic bone marrow grafts from HLA-matched relatives as curative treatment of their sickle cell disease. Ablation of recipient bone marrow is accomplished with busulphan and cyclophosphamide, without total body irradiation. Following early experience with frequent neurologic post-transplant events careful attention is given to prevention of hypertension, seizures and thrombocytopenia. (24) Early, procedure-related mortality ranges between 5% and 10% and will probably become lower in the future. Cure rates range from 71% to 82% and chronic graft-versus-host disease develops in <15% of patients. The median periods of follow-up reported vary between 23 and 60 months. These are very positive results, at least for those sickle cell patients who have an HLA-compatible and healthy related donor. Still,

issues dealing with patient selection and with long-term outcomes need to be considered. Because there is no simple reliable index of severity in sickle cell disease, a wide range of complications is used to define patient eligibility in the collaborative transplantation protocol mentioned above. (22) Qualifying complications include both intermittent events (stroke, frequent painful crises) and evidence of chronic organ damage (eyes, lungs, kidneys, bones). Parent and physician opinions on the validity of some of these inclusion criteria are likely to vary widely. While some would consider the procedure for all sickle cell patients who have a marrow donor. (25) Others might take a position that transplantation will help only very few SS patients. It is not unreasonable to speculate that parents, patients and doctors face this dilemma. The best transplantation outcomes are expected early in the life of the sickle patient, before significant organ damage has occurred, and also in those young patients with the mildest disease. Yet it is precisely these patients who have the highest probability of "event-free" long-term survival without transplantation. Such patients have the most to lose if, despite being at the lowest risk for transplant complications, they are still unfortunate enough to die early of a transplant-related event or to develop chronic graft-versus-host disease (GVH). Transplantation with umbilical cord haemopoietic stem cells is associated with a lower incidence of GVH. Preliminary data in three children with this type of haemopoietic graft suggest that the procedure will become a useful alternative to bone marrow transplant. (26) Long-term adverse effects of bone marrow transplantation also are significant but need to be seen in the light of the long-term effects of sickle cell disease itself, or of those of its alternative treatments. Long-term transplant complications include sterility and acute leukaemia from the high-dose anti-neoplastic drugs required for the procedure.

Open Issues and Future Perspectives

The past few decades have seen service organization for patients with SCD in several developing countries. (11) While high-level research is conducted in many centres and excellent care is routinely delivered, very few data report outcomes of healthcare delivery and utilization in these countries. No up-to-date data on the burden of SCD across the EU are available, due to the absence of an organized system of data collection and to the lack of widespread newborn screening in many countries. Information on the rate of hospitalization, length of stay, readmission rate, outpatient service utilization, and outcome data, including mortality, is

limited to some centres. A great deal of literature on healthcare utilization, service delivery, and costs of care for SCD is available for the USA, but similar data have not yet been produced from several developing countries and this is a gap that should be filled to allow better service implementation. Further aspects of care require coordinated action. Cerebrovascular complications are not limited to stroke prevention; silent infarcts and cognitive impairment pose a great burden on the health and quality of life of children with SCD, and will greatly impact them in later life. Investigations and interventions in this field have been performed in some countries but need to be expanded. Transition to adulthood is challenging and the mortality peak is shifting from early childhood to late adolescence and young adulthood. In 2017, the FDA ended a nearly 20-year drought in new therapies for sickle cell when it approved a supplement, L-glutamine oral powder (Endari) to help prevent acute complications of the disease. In a phase 3 trial, patients who received L-glutamine have 25% fewer hospital visits for crisis, were hospitalized 33% less often, were discharged an average of 4.5 days sooner, and were 65% less likely to experience acute chest syndrome compared with the placebo group (26), many more sickle cell therapies are on the horizon, and some already are in late-stage trials. One promising candidate is rivipansel, a small molecule that stops sickle erythrocytes from adhering to the vascular endothelium by inhibiting the adhesion molecules P-selectin and E-selectin. (27)

Conclusions

With proper treatment, sickle cell disorder can be managed. A combination of folic acid and penicillin seems to work for many and managing the pain with pain killers under medical supervision is strongly advised. They are also advised to reduce stressful environment and situations as these can ignite crisis. Drinking water regularly is very good to keep the person hydrated and short and regular exercises can ease some of the joint pains associated with complications of the disease. In addition, support groups should be created in various health units worldwide most especially in developing countries so that those in crisis are often fast tracked at accident and emergency so they can receive treatment as soon as they arrive in hospital, thus arresting the severity of the crisis as well as potentially save lives.

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SICKLE CELL DISEASE PROGNOSIS

OMOBUWA O

Sickle cell disease (SCD) is usually present at the birth of a newborn who has the condition, but the majority of affected infants show no symptoms or signs of the disorder until after the fourth month of life. Sickle cell disease symptoms are multiple and diverse in terms of expression and severity, being mild in some individuals, while they are moderate or severe in others, and may require hospital admissions. (1)

The commonest clinical features of SCD are usually related to anaemia. Anaemic persons typically experience hypoxia as a result of inadequate amounts of red blood cells needed for the purpose of oxygen transport and tissue oxygen delivery in the individual. Consequently, affected persons may experience tiredness or a feeling of weakness (fatigue has been identified as one of the commonest symptoms of SCD, especially HbS (sickle cell anaemia)). When anaemia is severe enough or becomes chronic, it can result in damage to very important and vital body organs such as the brain, heart (it can result in anaemic heart failure), lungs (may give rise to respiratory distress), kidneys, spleen, as well as other body organs. When anaemia is very severe in an SCD patient, it greatly increases the risk for mortality from the condition. (1)

Making the diagnosis of SCD very early in life is crucial because it will give an opportunity for the early institution of preventive measures against many of the complications that may result; hence early diagnosis and treatment will ultimately lead to a significant improvement in the prognosis of the condition. In the USA, all the state governments are statutorily required to conduct sickle cell disease testing as part of their newborn screening programs. The test is carried out using blood collected for the purpose of conducting routine newborn screening tests; hence sickle cell disease or even the carrier state (sickle cell trait) can be easily detected in the newborn. If the screening test shows evidence of the presence of sickle haemoglobin, another blood test is conducted for the purpose of confirmation of the diagnosis. Prenatal diagnosis of SCD can

be done in the early gestational period via amniocentesis or placental tissue sampling. (2)

Individuals suffering from SCD tend to have a lower life expectancy when compared to the general population. However, the severity of the disease varies markedly in the affected individuals as the penetrance and expression of the disorder tend to vary appreciably from person to person. Some people with SCD may remain asymptomatic for several years of their lives while others may not survive beyond infancy or early childhood as a result of infections (SCD patients, especially children, are much more susceptible to infections when compared with the general population) or repeated occurrence of sequestration crises. New therapies for SCD management are known to contribute significantly to improvement in the life expectancy and quality of life of SCD patients. Individuals with SCD can live or survive beyond their 5^{th} decade of life if they have access to new, optimal care and management of the condition. (2)

Factors Important in the Determination of SCD Prognosis

Sickle cell disease is known to cause both acute and chronic illnesses in sufferers, and ultimately lead to a significant reduction in the median life expectancy of the affected individuals (by at least 30 years globally), with the highest reductions in life span occurring in the low-income countries of the world, especially in the sub-Saharan African (SSA) region. A wide spectrum of severity of the condition exists, with some patients being totally asymptomatic or showing only a few, mild symptoms while others suffer frequent, life-altering and life-threatening complications often requiring hospitalization and sometimes, intensive care. Much of this marked variability occurring in SCD-affected individuals remains unexplained, despite advancement in research, including the conduct of highly sophisticated research works on genetics. Major factors that have been recognized as being possibly influential on the prognosis of SCD include the following: genetics, the environment, socio-economic status of individuals and families, tobacco use, exercise and other lifestyle characteristics, frequency and severity of infections as well as availability and quality of healthcare services. The aforementioned factors are possibly very important determinants of SCD prognosis, as shown by the clear distinctions in the resultant outcomes of SCD patients in the developing world (Africa) when compared to some western countries (USA and Europe). (3)

Genetic Factors Capable of Influencing the Prognosis of SCD

Virtually every individual with SCD has the one same genetic mutation in which a thymine has replaced an adenine in the DNA encoding the ß-globin gene. As a result, valine takes the place of glutamic acid at position six in the ß-globin chain. (4) This change gives rise to a recessive phenotype feature which manifests as deformed, sickled red blood cells which are capable of occluding the microvascular circulation, thus causing blood vessel damage, reduced blood supply to vital organs which may result in organ infarcts, painful vaso-occlusive crises and other symptoms known to be associated with SCD. Irrespective of the fact that all individuals with SCD share the same specific, constant genotypic mutation, there is usually an astounding variability in the clinical pattern and severity of expression of the disease in affected individuals. (5)

The Role of Foetal Haemoglobin as a Determinant of SCD Prognosis

Boosted post-delivery expression of foetal haemoglobin (HbF) is possibly the most extensively recognized and validated modulator of SCD symptomatology and severity. The foetal haemoglobin, in congruence with its name, is the principal haemoglobin found in the foetus from the mid to late trimester of gestation. (6) Foetal haemoglobin is known to bind oxygen much more tightly than the normal adult haemoglobin (HbA), an attribute that allows the growing and developing foetus to extract oxygen from the maternal circulation. Following birth, this characteristic is no longer needed and eventually, the generation of the gamma-subunit reduces while the production of the ß-globin subunit goes up. The ß-globin subunit then replaces the gamma-globin subunit in the haemoglobin tetramer to the extent that adult haemoglobin, HbA, ultimately replaces HbF as the key constituent of the human red blood cells. (6) Haemoglobin F levels tend to stabilize during the first year of life at less than one percent (1%) of the total haemoglobin in the individual, with the exception that occurs in cases of hereditary persistence of foetal haemoglobin, a situation in which the HbF percentage in the individual is much higher. This persistence of HbF in an individual with SCD substantially ameliorates the severity of the manifestations of symptoms and signs of SCD in the individual. (6)

The effect of α-Thalassaemia on the Prognosis of SCD

Studies have shown that the deletion of one of a pair of closely connected α-thalassaemia genes (heterozygous α^{+}-thalassaemia) in sickle cell anaemia (haemoglobin SS disease) lowers the mean corpuscular haemoglobin concentration (MCHC), a determinant of HbS polymerization, and is likely to decrease intravascular red blood cell (RBC) sickling. Deletion of the two closely linked α-thalassaemia genes (α^{+}-thalassaemia, homozygous state) tends to a greater extent to reduce the MCHC but any resulting reduction in sickling may be neutralized by an overall rise in total haemoglobin. Hence, α-Thalassaemia may provide a very good model to differentiate the impacts of preventing sickling in the micro vessels and the potentially dangerous effect of a higher packed cell volume (haematocrit) impairing blood flow in the macrocirculation. (7)

The Role of Environmental Factors in SCD Prognosis

The important role of the environment (climate, etc.) as a determinant of the prognosis of SCD is not in doubt, when considered in relation to several factors such as climate, skin cooling which could trigger bone pain crises or obviously random occurrences such as exposure to infective organisms like *Streptococcus pneumoniae* or Parvovirus B19. Malaria remains a markedly significant determinant of morbidity and mortality for SCD patients in malarious areas such as sub-Saharan Africa and central India. Increased susceptibility to other potentially more serious infections by organisms such as *Salmonella* spp. may suggest SCD carriage rates in the populace.

A Comparison of Genetic and Environmental Factors Modifying Sickle Cell Disease

An existing classical method for differentiating the role of genetic factors from that of environmental influences in the study of diseases is the study of monozygotic (identical) twins. On a global scale, it has been documented that the birth of identical twins occurs in 0.3%–0.4% of all deliveries. In order to find usefulness in studies of haematological and clinical characteristics of diseases, both twins being studied need to survive long enough to be able to provide adequate, relevant data for the purpose of the given study. These criteria are often not met; the largest available, documented series for SCD study in Jamaica contained only six pairs of identical twins. A comparative study of twin pairs revealed that

genetics plays a significant role in the growth and haematological indices of identical twins whereas the study also showed that clinical events in the twin pairs were often at variance, suggesting that non-genetic influences are also of significant importance in the determination of the prognosis of SCD in affected individuals. (8)

A Brief Comparison of the Various SCD Genotypes

Sickle cell anaemia (HbSS disease) and sickle cell β^0-thalassaemia ($S\beta^0$-thal) are the most severe clinical and haematological forms of SCD although both genotypes may vary markedly in terms of their severity in manifestation. Haemoglobin SC disease tends to be usually mild but it is known to be more prone to proliferative sickle retinopathy (PSR). The haemoglobinopathy S-β^0-thal exhibits a very broad clinical range of features based on the molecular mutation for the β-thalassaemia gene and the amount of adult haemoglobin produced in the affected individual. In West African peoples, the $S\beta^0$-thal gene is generally associated with a slight decrease in normal β-chain synthesis and HbA levels ranging from 15% to 25%. These result in a mild clinical course of the condition, although this genotype is also known to be more prone to PSR. The association of an increased risk of PSR in the generally milder variants of SCD, *vis-à-vis* SC and $S\beta^+$-thalassaemia, remains poorly understood. There is marked variation in the frequency and severity of complications (clinical) between the different SCD genotypes but there is an identified pattern for symptoms to be more pronounced in the commonly more severe SCD variants (SS and $S\beta^0$-thal) whereas it is much less severe in SC disease and the West African variant of $S\beta^+$-thalassaemia. (9)

Socio-economic and Healthcare Determinants of SCD Prognosis

- Socio-economic factors are important determinants of health in all people of the world. Numerous studies have shown and established that an increased poverty level is associated with worse health. (10) This is particularly relevant to SCD which is much more prevalent in the poorest countries of the world, especially sub-Saharan Africa. (11) Lack of, or inadequate household financial resources will ultimately compromise the quality of care an SCD patient will receive in settings where healthcare financing is mainly done through out-of-pocket expenses, as occurs in many developing countries, including Nigeria. (10) Socio-economic status may

determine families' access to communication, transport, and medical services.

Other important socio-economic factors which may influence SCD prognosis include the following:

- Nutrition: adequate nutrition is highly essential for health and wellbeing in every individual and is more importantly so in the SCD patient. Good nutrition, including adequate intake of water, fruits and vegetables is of immense benefit in SCD.
- Access to public health measures such as immunization: vaccination is adjudged to be one of the most cost-effective health interventions of our time. Since SCD patients are particularly susceptible to infections from disease organisms (especially vaccine-preventable diseases – VPDS), they should receive all required vaccines in order to protect them from VPDs and so reduce their chances of crises and haemolysis induced by infection.

Tobacco Smoking and SCD

Several studies have provided convincing evidence that active and passive smoking are harmful in SCD. The adverse pulmonary effects of environmental tobacco exposure in the universal population have been elaborately described. Tobacco smoke may have particularly adverse consequences for children with SCD because research in otherwise healthy individuals has demonstrated a strong relationship between tobacco smoke and inflammation, oxidative stress, and endothelial dysfunction. (3) Young children and adolescents with SCD who had repeated exposure to passive tobacco smoking were found to have higher frequencies of acute pain and hospital admissions. (12)

Life expectancy in SCD

Chronic organ damage secondary to SCD tends to result in many medical complications, although some prophylactic treatment measures are capable of reducing the incidence of these complications. Without bone marrow transplantation (the only potentially curative treatment for SCD), median age at death is 42 years for men and 48 years for women in patients with sickle cell anaemia (HbSS disease); whereas life expectancy is 60 years for men and 68 years for women with haemoglobin SC disease. (13) In some parts of Africa, 50-80% of children with SCD die before they attain

the age of 5 years. (14) Morbidity and mortality rates associated with SCD are now observed to be declining in recent times and this has been attributed to recent improvements in the management of infections and other SCD complications in childhood, new health interventions as well as active health maintenance for adults, and patient counselling. More than 90% of patients of all phenotypes will survive past the age of 20 years, and significant numbers of SCD patients now live beyond 50 years of age. (13)

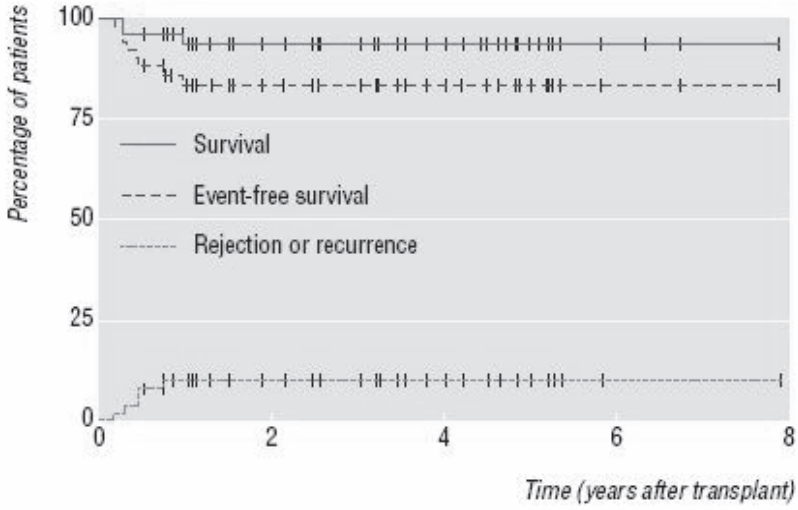

Fig. 1. Survival and recurrence rates for sickle cell disease patients following bone marrow transplantation (Source: Claster S, Vichinsky EP. BMJ. 2003; 327:1151–1155)

Causes of Mortality in Children with SCD

Sickle cell disease (SCD) is typically characterized by multi-organ disease and an increased risk of early (premature) death. Many studies have shown that the survival of children with SCD has improved over the past few decades. (15) This improvement in survival has been attributed to the introduction and implementation of newborn screening, use of prophylactic antibiotic (penicillin); vaccinations against *Haemophilus influenza* type b and *Streptococcus pneumonia*, with possible contributions from advances in red blood cell transfusion medicine, iron chelation therapy, and transcranial Doppler screening to identify SCD patients who

are at an increased risk of cerebrovascular accident. (16) Complications of SCD constitute an important cause of mortality in children especially in the SSA region and India where bacterial infections lie at the root of the many cases of mortality occurring among under-five children. Previous studies have described the association of dactylitis with more severe outcomes in children diagnosed with SCD. (17) Also, diagnosing SCD before the eighth month (following manifestations of suggestive clinical features) of life and a haemoglobin level of <7 g/dl have been identified as risk factors for mortality in young children with SCD. The quality of, and accessibility to healthcare are also recognized factors influencing mortality as a result of SCD. (18)

Risk Factors for Mortality in Adults with Sickle Cell Disease

As patients with SCD grow older and age, they begin to manifest evidence of end-organ damage which makes some contributions to an increase in morbidity and early mortality in SCD sufferers. (16) Hydroxyurea, a drug approved by the United States Food and Drug Administration in 1998, has remained the only drug that has been shown to beneficially and significantly alter the natural history of SCD, according to peer-reviewed studies. (16) Although several studies have shown survival improvement in adult patients with SCD following hydroxyurea treatment, the mortality rate remains relatively high for patients aged 18 years and older following transition to adult care (19), a possible reflection of a lack of access to high-quality care at that stage of life.

Chronic organ disease (COD) has become increasingly important as a cause of morbidity and mortality in older SCD patients, especially in developing countries (19). Recent studies have also shown the associations of the following parameters: elevated tricuspid regurgitant jet velocity (TRJV) on echocardiogram (20), pulmonary hypertension (PHT) (21), elevated levels of N-terminal pro-brain natriuretic peptide (NT-pro-BNP), history of asthma and/or wheezing, end-stage renal disease requiring dialysis (22), worsening of haemolysis (23), and prolongation of QTc interval (24) with a significantly increased risk of death in patients with sickle cell disease.

A vast majority of the early mortality cases in SCD patients are largely preventable by careful implementation of inexpensive health interventions. In addition, patients identified to have risk factors for a severe clinical

course of the disease or at risk of early death from the condition may benefit from closer monitoring in the clinic, and the earlier use of therapies like hydroxyurea. These potential risk factors could be considered in the making of the final decision when contemplating the use of expensive and relatively high-risk treatments like bone marrow transplantation (BMT) or gene treatment. (25)

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List of Contributors

Professor Olutayo Christopher ALEBIOSU. B.Sc., MB.Ch.B, FWACP
Department of Medicine, College of Health Sciences,
Osun State University, Osogbo.
+2348038237500
olutayo.alebiosu@uniosun.edu.ng

Professor Michael Olabode BALOGUN. BSc, MBChB, FMCP, FWACP, FRCP (GLASG.), FSM, FESC, FNCS
Department of Medicine, College of Health Sciences,
Obafemi Awolowo University, Ile-Ife
08100579080
bodebalogun@yahoo.co.uk

Professor Patience Olayinka AKINWUSI. B.Sc., MBChB, FWACP, FAHA, FESC, FNCS
Department of Medicine, College of Health Sciences,
Osun State University, Osogbo.
+2348037219451
pat.akinwusi@uniosun.edu.ng

Professor Esther Olufunmilayo ASEKUN-OLARINMOYE. B.Sc., MD, FWACP
Department of Community Medicine, College of Health Sciences,
Osun State University, Osogbo
+2348033602184
esther.asekun-olarinmoye@uniosun.edu.ng

Professor Rasaaq Ayodele ADEBAYO. MBChB, FWACP, MPA, CERT. In Interventional Cardiology (Alexandria), FNCS.
Department of Medicine, College of Health Sciences,
Obafemi Awolowo University, Ile-Ife, Osun State.
+2348037149610.
aderasaaq@yahoo.co.uk

Dr. Tope Gafar ATERE. B.Sc., MPhil., Ph.D.
Department of Biochemistry, College of Health Sciences,
Osun State University, Osogbo.
+2348035796643
tope.atere@uniosun.edu.ng

Dr. Olayemi Olutobi OLADOKUN. B.Sc., M.Sc., Ph.D.
Department of Physiology, College of Health Sciences,
Osun State University, Osogbo.
+2348037282899
olayemi.oladokun@uniosun.edu.ng

Dr. Akinlolu Gabriel OMISORE. MB.Ch.B, MPH, FWACP
Department of Community Medicine, College of Health Sciences,
Osun State University, Main Campus, Osogbo.
08036247712
akinlolu.omisore@uniosun.edu.ng

Dr. Olatokunbo Olupelumi OGUNS. MB.ChB
Department of Haematology,
Obafemi Awolowo University Teaching Hospital Complex Ile-Ife.
+2348160694476
oginniolatokunbo@gmail.com

Dr. Kehinde Joyce OLUFEMI-AWORINDE. MB.BS, FMCPath, FWACP
Department of Haematology and Blood Transfusion, College of Health Sciences,
Bowen University, Iwo
08035730533
kehinde.aworinde@bowenuniversity.edu.ng

Dr. Opeyemi Olalekan ONI. MBBS, M.Sc., FWACP
Department of Medicine, College of Health Sciences,
Bowen University Teaching Hospital, Ogbomoso
+2348060450458,
oniopeyemi64@gmail.com

Dr. Taiwo Adekemi ABAYOMI. B.Sc., M.Sc, Ph.D.
Department of Anatomy, College of Health Sciences.
Osun State University, Osogbo
+2348164375232
taiwo.abayomi@uniosun.edu.ng

Mr. Opeyemi Samson ADELEKE. B.Tech., M.Sc.
Department of Anatomy, College of Health Sciences
Osun State University, Osogbo
+2348131323268
opeyemi.adeleke@uniosun.edu.ng

Dr. Oluyomi OKUNOLA. MBChB, FMCP
Department of Medicine, College of Health Sciences,
Obafemi Awolowo University, Ile-Ife.
08037211495
yok8t@yahoo.com

Dr Oyekunle Olayanju OYEBISI. MB, BS, FMCP
Department of Medicine,
Olabisi Onabanjo University Teaching Hospital, Sagamu.
08053371431
oyebisi_oyekunle@yahoo.com

Dr. Samuel Ademola ADEGOKE. MBChB, FWACP, MPH, PhD
Department of Paediatrics and Child Health, College of Health Sciences,
Obafemi Awolowo University, Ile-Ife.
08035037560
adegoke2samade@yahoo.com

Dr. Busayo Gideon OLOGUN. MBChB
Department of Paediatrics,
Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife.
08032522258
ologunbusayo100@yahoo.com

Dr. Damilare Adedayo ADEKOMI. Ph.D.
Department of Anatomy, College of Health Sciences,
Osun State University, Osogbo
08038441671
adedayo.adekomi@uniosun.edu.ng

Dr. Michaeline Asuquo ISAWUMI. MB.ChB, FMCOph, FWACS, M.Sc CEH, FICS
Department of Surgery, College of Health Sciences,
Osun State University, Osogbo.
+2348033912103
michaeline.isawumi@uniosun.edu.ng

Dr. Mustapha Busuyi HASSAN. MBBS, FMCOph, FWACS, FICS
Department of Surgery, College of Health Sciences,
Osun State University, Osogbo.
+2348023050965
mustapha.hassan@uniosun.edu.ng

Dr. Abiona Oluwadamilola ODEYEMI. MBBS, FMCP
Department of Medicine, College of Health Sciences,
Bowen University, Iwo
07032512473
abiona.odeyemi@bowenuniversity.edu.ng

Dr. Oluwafemi OJO MBBS, FWACP
Department of Medicine, College of Medicine,
Lagos State University
08038344342
ojofemi911@yahoo.com

Dr. Adeseye Abiodun AKINTUNDE. MBChB, FWACP, FMCP, Dr. med., FACC, FESC
Department of Medicine, Faculty of Clinical Sciences,
Ladoke Akintola University of Technology, Osogbo.
08033932076
aaakintunde@lautech.edu.ng

Dr. David Adesanya OFUSORI. Ph.D.
Department of Anatomy & Cell Biology, College of Health Sciences,
Obafemi Awolowo University, Ile-Ife, Osun State
+2348034455715
davidofus234@yahoo.com

Dr. Benedict Abiola FALANA. B.Sc., M.Phil., Ph.D.
Department of Anatomy, College of Health Sciences,
Osun State University, Osogbo.
+2348067033706
Benedict.falana@uniosun.edu.ng

Dr. Joseph Babatunde DARE. B.Sc., M.Sc., Ph.D. PGDE
Department of Anatomy, College of Health Sciences,
Osun State University, Osogbo
+2348077805474
babatunde.dare@uniosun.edu.ng

Dr. Adedayo Olugbenga OLAOSUN. MBChB, DLO (WACS), FWACS, DOHNS(RCS), MPH, MSc (Epid. & Med. Stat.), Grad. Cert. Org. Leadership
Department of Otorhinolaryngology, College of Health Sciences,
Ladoke Akintola University of Technology, Osogbo
+2348033736113
aoolaosun@lautech.edu.ng

Dr. Emmanuel Oludele FARINLOYE. MD, FWACS
Department of Obstetrics and Gynaecology, College of Health Sciences,
Osun State University, Osogbo
+2348033886130
emmanuel.farinloye@uniosun.edu.ng

Dr. Najemdeen Ajao ADELEKE. MBBS, FWACS.
Department of Obstetrics and Gynaecology, College of Health Sciences,
Osun state University, Osogbo.
+2348033933434.
najemdeen.adeleke@uniosun.edu.ng

Oluwapelumi Deborah ADEYERA. BSc, MPH
Population Council, Abuja, Nigeria.
+2348068997573
adeyeraoluwapelumi@gmail.com

Dr. Olanrewaju Ibikunle IBIGBAMI. MB.CHB, M.CLIN. PSYCHOL., MSC. CAMH. FWACP (PSYCHIATRY).
Department of mental health, College of health sciences,
Obafemi Awolowo University, ile-ife.
+2348030652116
oibigbami@oauife.edu.ng

Dr. Tolulope OPAKUNLE. MBBS, FMCPsych
Department of Mental Health,
State Specialist Hospital, Asubiaro, Osogbo, Osun State.
+2348034006843.
toluopakunle@gmail.com

Temitope Feyisayo ASEKUN-OLARINMOYE. B.Sc., MPH
Department of Public Health, Faculty of Basic Medical Sciences
Adeleke University, Ede, Osun State
+2349032181738
temitope.asekunolarinmoye@adelekeuniversity.edu.ng

Dr. Moridiyat Omolara Adeyinka ADEYEMO. RN, B.Sc., Ph.D.
Department of Nursing science, College of Health Sciences
Osun state University, Osogbo
+2348038033257
moadeyemo@uniosun.edu.ng

Dr. Adewale Victor ADEREMI. MBBS, MPH, M.Sc.
Department of Biochemistry, College of Health Sciences,
Osun State University, Nigeria
+2348065850304
adewale.aderemi@uniosun.edu.ng

Dr. Aishat Bukola USMAN. MBBS, MPH, FWACP, Ph.D.
Department of Community Medicine,
Ladoke Akintola University Teaching Hospital, Osogbo.
+2348035449691
ishaatu@gmail.com

Dr. Ifedola Olabisi FARAMADE. MBBS, MPH, FMCPH
Department of Community Medicine.
Ladoke Akintola University of Technology Teaching Hospital.
Osogbo.
+2348060101894
ifemade2k9@gmail.com

Dr. Sunday Olakunle OLAREWAJU. MBBS, MPH, FMCPH.
Department of community medicine, College of Health Sciences,
Osun State University, Nigeria.
+2348033799676
sunday.olarewaju@uniosun.edu.ng

Dr. Olubukunola OMOBUWA. MBCh.B, MPH, FWACP
Department of Community Medicine, College of Health Sciences,
Osun State University, Osogbo
+2348037394566
olubukola.omobuwa@uniosun.edu.ng

Dr Abiodun Omoniyi Moses.
MBBS, FWACS, FMCOG
Dept of Obstetrics & Gynaecology, College of Health Sciences, Osun State University
E mail: omoniyi.abiodun.uniosun.edu.org

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