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Sickle Cell Disease in Nigeria ----------A Review

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***Abstract**: Sickle cell disease, a genetically determined disease is a major cause of mortality and morbidity in Nigeria, a country with the highest burden of the disease in the world. Information cited in this article was mainly from published works on this subject in Nigeria and elsewhere. The information was extracted over a period of 5months from May 2015 to September2015, from hard copies of scientific Journals, Google search, Pubmed and Hinari websites.*
Despite recent advances in the management of this disorder in the developed countries, little has changed in Nigeria. It remains a major cause of mortality and morbidity among children in Nigeria. In conclusion, recent breakthroughs in the management of sickle cell disease such as genetic screening for pre-implantation and prenatal diagnosis, counseling and fetal selection are not readily accessible in Nigeria
***Keywords:** Sickle Cell Disease, Nigeria.*

I. Introduction

Sickle cell disease (SCD), a genetically determined haematological disorder is common in Nigeria.[1] It was first observed about 1904 by Dr JB Herrick in the blood of an anaemic West Indian medical student. [1]
It is not known exactly when and how or where the mutation producing sickle cell gene occurred, but it is speculated that it originated in the Middle East amongst the Veddoids in the Arabian Peninsula.[2]Sickle cell gene spread from there into Africa, Southern Europe and India.[2] The sickle cell trait is found throughout tropical Africa, Southern Europe, Middle East and people of African descent.[2] as shown in Fig I

The patient with sickle cell trait is relatively resistant to the lethal effects of falciparum malaria.[3] The high incidence of this deleterious gene in equatorial Africa is thus explained by the selective advantage for survival it confers in an environment of endemic falciparum malaria.

II. Epidermiology

Earliest study among adults and children in south-east Nigeria by Lehman and Nwokolo[I][4] in 1959 reported sickle cell trait prevalence of 24.3% but did not report about homozygous SS. The two commonest haemoglobin variant reported in Nigeria are haemoglobin S (HbS) and haemoglobin C (HbC). HbS is fairly well distributed in Nigeria but HbC seem to be concentrated in western Nigeria and decreases as one move eastward from the west. From 10% in Ghana to 3.6% in Yoruba land of western Nigeria, to almost non existence in east of the river niger.[5] By 1982 it was estimated that in Nigeria about 30,000 infants are born each year with SCD.[1,6] It is currently estimated that about 25% of adult Nigerians have sickle cell trait and 1 to 3% have SCD.[1][1,6-7] Kaine et al[5] found among preschool Igbo in Eastern Nigeria 22.5% AS, 1.6% SS and 0.1% AC. This similar to zero prevalence found among the Igallas east of river Niger in the northern border of Igbo land.

III. Genetics/Pathophysiology

Sickle Cell Disease is a haemoglobinopathy in which there is substitution of a single amino acid in the beta chain of adult haemoglobin resulting in haemoglobin S, C, D or E depending on amino acid sustitution.[8,9]
Haeamoglobin S and C are present in Nigeria while haemoglobin G (HbG), haemoglobin D (HbD) and haemoglobin E (HbE) rarely exist in West Africa.[10] These abnormal haemoglobins are transmitted as autosomal recessive genes.[8,11]

Heterozygous inheritance of an abnormal haemoglobin with a normal one results in a symptomless carrier state or 'trait'. Inheritance of haemoglobin S (HbS) with any other abnormal haemoglobin like beta-thalassemia (B^o or B^+), HbC, HbS results in SCD. However homozygous inheritance of HbSS is called SCA.[12]

In HbS, valine replaces glutamic acid at position 6 in amino acid sequence of beta chain.[11] In haemoglobin C (HbC) lysine replaces glutamic acid at position 6 in the beta chain.[9] While in haemoglobin D (HbD) glutamine replaces glutamic acid at position121 in the amino acid sequence.[9] These amino acid

substitutions lead to decreased solubility of the haemoglobin molecule in low oxygen tension. Oxygenated HbA and

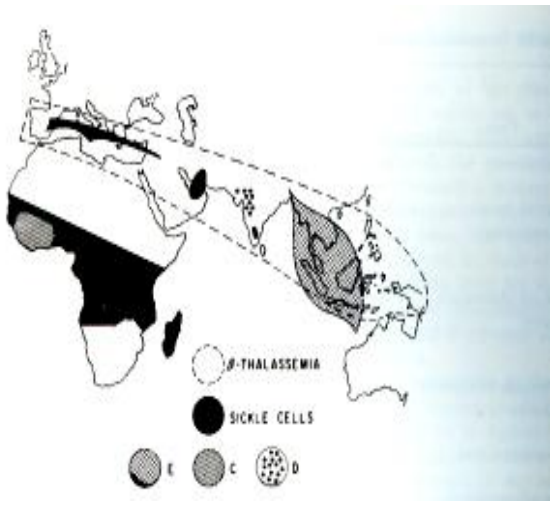

Figure I [2]

HbS have the same solubility, but upon deoxygenation the solubility of HbA falls by one half whereas that of the sickle cell haemoglobin becomes 50 times less soluble.[13] The intra erythrocyte electrolyte concentration is disturbed, with higher sodium, lower potassium and loss of adenosine triphosphate (ATP) leading to red blood cell (RBC) membrane stiffening due to influx of calcium into the cell.[14] High intracellular calcium causes most of the defect characteristic of irreversible sickled cells.[13,14] The most common and most severe haemoglobinpathy is homozygous SS, also called sickle cell anaemia.[9] Other haemoglobin variants in their homozygous state leads to mild anaemia and a number of phenomena that seem to be specifically related to sickling phenomenon (circulatory catastrophes and infarcts) are not caused by their possession.[14] Combination of HbS with other abnormal haemoglobin leads to clinical state similar but milder than homozygous SS. The spectrum include sickle cell haemoglobin C disease HbSC disease),sickle cell B^{o}-thalasemia, sickle cell B^{+}-thalassemia and sickle cell haemoglobin D Punjab (HbSD).[9]

Co-polymerization of B6 valine and complimentary region on B chains of adjacent molecule is responsible for the brittle character of sickle erythrocyte under conditions of decreased oxygenation. [9]
Virtually all signs and symptomatology of SCD is attributable to this phenomenon.[9,10]There is a chronic haemolytic anaemia resulting from premature destruction of the brittle poorly deformable erythrocytes. Other manifestations of SCD are attributable to ischaemic changes resulting from vascular occlusion by masses of sickled cell.[9,10] The clinical course of affected children is typically associated with intermittent episodic events often referred to as crisis.[9]
The clinical manifestations of SCD result from two key pathological processes: vaso-occlusion and hemolysis.[15,16]Sickle cells, along with non-sickled RBCs, leukocytes, and platelets, form heterocellular aggregates, which adhere to the vascular endothelium, causing obstruction of the lumen of small blood vessels.[17,18] This microcirculatory occlusion leads to acute and chronic tissue ischemia and infarction, with multisystem effects, particularly in bone, lungs, brain, kidneys, and spleen. It is responsible for acute painful episodes and crises and many of the long-term complications seen in SCD.[19,20] Sickled RBCs are more readily destroyed by the reticulo-endothelial system, partly as their rigidity makes them more easily filtered in the spleen and partly due to changes in the structure of the lipid bilayer (with exposure of anionic phosphatidylserine on the RBC surface), which promotes phagocytosis.[21] With sickle cell anemia (HbSS), this causes a chronic anemia (a steady state Hb of 6–8 g/dl) with a resultant increase in cardiac output and workload, which produces cardiomegaly and reduced exercise tolerance.[22] The increased energy demands due to this and the chronically elevated rate of hematopoiesis contribute towards poor growth in children, and individuals are susceptible to any factor exacerbating the anemia, which can precipitate circulatory failure.[23] Intravascular hemolysis also leads to release of free hemoglobin–an important scavenger of nitric oxide.[24] Reduced levels of this potent vasodilator and the hyperdynamic circulation contribute further to vascular damage and occlusion, including within larger vessels.[24]

There is altered splenic function with reduced phagocytic and reticuloendothelial function.[25,26] There is also reduced serum opsonins of the alternate complement pathway and these lead to increased

susceptibility to infection especially to encapsulated organisms.[26] There is also increased susceptibility to salmonella osteomylitis due mainly to bone necrosis.[9,25]

IV. Clinical Presentation

Most SCD patients do not manifest clinically till about age of 6 months when the level of haemoglobin F (HbF) begins to fall.[26] They may present with pallor, jaundice, hepatosplenomegaly, and swelling of dorsa of hands/feet (hand foot syndrome) failure to thrive, infections, sickle cell habitus etc.[26] There are two major crises which patients might present with, namely: vaso-occlusive crisis (VOC) and anaemic crises.

4.1 Vaso occlusive crises

Vaso occlusive crises is also called pain or thrombotic crises due tovascular occlusion by sickled cells and can affect any part of the body but is more common over the long bones, abdomen, chest, and the back. Central nervous system involvement leads to cerebro vascular accident.[27]

Precipitating factors include physical exertion, exposure to extremes of weather, fever, dehydration, acidosis, infection, emotional disturbance and sometimes the cause is not known.[9,26]

Hepatic crisis which is also called right upper quadrant syndrome and consists of right upper quadrant pain, fever, jaundice, elevated transaminases and hepatic enlargement, occurs in about 10% of patients with vaso occlusive crisis.[27]The rapid decrease in transaminases during the recovering phase differentiate this condition from slower decline characteristic of acute viral hepatitis.[14,27,28]. Acute viral hepatitis has the same clinical course in these patients as in the general population but with higher peak bilirubin level because of additional haemolysis from haemoglobinopathy [14,29]. Another manifestation of vaso-occlusive crisis in the chest is known as acute chest syndrome, young children will present with chest pain, fever, cough, tachypnoea, leukocytosis, and pulmonary infiltrates in the upper lobes ,often difficult to different from pneumonias; adults are usually afebrile, dyspneic with severe chest pain, with multilobar/lower lobe disease. Pulmonary hypertension is increasingly being recognized as a serious complication of SCD.[27]

4.2 Anaemic crisis can be caused by hyperhaemolysis, aplastic crisis and acute sequestration crisis.[26]

i. Hyperhaemolysis is precipitated by infections, glucose-6-phosphate dehydrogenase (G6PD) deficiency, acidosis and dehydration.[21,26] There is increased pallor, jaundice and hepatosplenoemgally[28-29]

ii. Aplastic crisis is characterized by an acute failure of erythropoiesis often following viral infections especially parvovirus $B_{19.}$[26] The patient will present with weakness, progressive pallor and pancytopenia.[30] During this crisis the patient may have associated bone and joint pain. Blood transfusions are often necessary in order to preserve the patient's life.[30]

iii. Acute sequestration is caused by pooling of blood in the spleen and the liver characterized by sudden onset of progressive anaemia, spleenic enlargement, abdominal pain and shock..[9]

Various crisis and increased susceptibility to infections are responsible for recurrent illness in patients with SCD.

V. Diagnosis

Diagnosis is made by haemoglobin (Hb) electrophoresis with cellulose acetate at Ph 8.6. However HbD and HbG migrate at the same rate as HbS while HbE and O Arab migrate at the same rate as HbC.[26] Citrate electrophoresis at Ph 6.3 is a better alternative to cellulose acetate as it gives better separation of common haemoglobin variants since they migrate at different speed while isoelectric focusing can be used in children below 6months. Hemoglobin solubility and red blood cell sickling tests are useful in establishing the diagnosis of SCD.[26,29]

Other investigations that are useful in the management of various complications, these patients may develop, includes full blood count with differential count and reticulocyte count, peripheral blood smear, serum electrolytes, pulmonary function tests (trans-cutaneous oxygen saturation).[31]

Renal function tests like serum creatinine, blood urea nitrogen and urinalysis. Also done is hepatobiliary function tests like alanine transaminase and fractionated bilirubin.[32]

Transcranial, ultrasound is used to detect children at high risk of cerebro-vascular accident especially among children below 2 years, and those found to be at high risk of stroke are given regular blood transfusions.[33]

Prenatal diagnosis of sickle cell anaemia is the current method of diagnosis of SCD. Amniocentesis, chorionic villus sampling (CVS), and fetal blood sampling are used to obtain fetal cells for genetic diagnosis.[34-35] These procedures are not without risk of abortion of the fetus. Ideally, the disease should be identified during the prenatal period or at birth as part of a routine screening programme. Such services should be available alongside counseling and health education services since diagnosis raises serious ethical and cultural issues. When result of prenatal test confirms HBSS, the mother is faced with the decision to terminate

the pregnancy and try again for an unaffected child or choose to continue the pregnancy and prepare her mind for the challenges of management.

VI. Complications Of Sickle Cell Disease.

Sickle cell disease has a profound effect on the liver. This effect of SCD on the liver manifests as liver dysfunction often referred to as sickle cell hepatopathy.[36] It occurs predominantly in patients with SCA and to a lesser extent in patients with HbC diseases and HbS thalassemia.[36-37] This liver dysfunction encompasses a range of hepatic pathology arising from the primary SCD process and complications of its treatment.[11,14,36]

The primary disease process that may lead to liver dysfunction includes, anaemia, sickling of red cells in the sinusoids, swollen kupffer cells, fibrin deposits and hyaline thrombi leading to obstruction to blood flow in the liver.[11,36]

Liver injury can be caused by the adherence of deformed or haemolysed erythrocytes to vascular endothelium.[14] Chronic haemolysis leads to development of pigment stones with consequence of cholecystitis acute and chronic biliary obstruction.[11,14,36-37]

Consequences of treatment such as blood transfusion and antibiotics therapy can also lead to liver dysfunction.[14] Complications of multiple blood transfusions like iron overload, acute and chronic infection with hepatitis B and C are also important causes of liver dysfunction in SCD.[36-38]Third generation celphalosporins are known to sometimes crystallize in the gallbladder leading to cholelithiasis.[36]

Barrett-Connor [38] in 1968 was one of pioneer workers that studied the role of hepatitis B virus (HBV) infection in liver dysfunction in SCD. Liver biopsy specimens in four cases showed necrosis, cellular disarray with balloon cells and leucocyte infiltration suggestive of viral hepatitis. The study concluded that unrecognized viral hepatitis B infection in SCD may be responsible for 20-40% prevalence of cirrhosis reported in patients with SCD.

Abnormal liver function tests are common in patients with sickle cell disease. Raised bilirubin levels, predominantly unconjugated, are universal in sickle cell patients due to chronic haemolysis.[36,39]Total bilirubin concentrations are usually less than 6mg/dl.[36] Plasma lactic dehydrogenase and aspartate transaminase levels are elevated and usually related to the degree of haemolysis and ineffective erythropoiesis.[36]Elevated serum alkaline phosphatase are commonly seen in SCD patients during vaso-occlusive crisis.[14] Plasma alanine transaminase levels, when they are elevated accurately reflect hepatocyte injury in SCD patients.[36,40]

Kaine et al,[40] in liver histology of 6 patients with hepatic crisis reported that all specimens showed dilated hepatic sinusoids, containing numerous sickled red cells. The Kupfer cells were markedly hypertrophied and many contained phagocytosed red cells. There were areas of patchy liver cell damage with cellular infiltration in the lobular parenchyma. Liver cell damage was more prominent in the areas adjoining the central veins. There was mild fibrosis in the lobular parenchyma as well as portal tracts in two specimens. They also found that in patients who were positive for hepatitis B antigen (HBsAg), cellular infiltration was more aggressive, particularly in the portal tracts and extended beyond the limiting plate in some areas. [40-41]

Yohannan et al,[42] in Saudi Arabia studying 34 children with fulminant hepatic failure from hepatitis A virus (HAV) and HBV infections found that children with SCD may have higher morbidity and mortality from it.

VII. Malaria and infections

The relationship between malaria and SCD is an intriguing one. The persistence of the sickle mutation at such high frequency in African populations in spite of the severity of SCD has been attributed to the fact that heterozygous sickle trait confers protection against severe and life-threatening malaria (in particular cerebral malaria caused by Plasmodium falciparum). The presence of HbS is associated with reduced parasitic invasion 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.[43]It might be assumed that homozygous SCD would confer greater resistance to malaria, however co-existence of the two is associated with increased mortality and morbidity, and malaria is the most common precipitating cause of crisis in endemic countries.[44]

Infection is a significant contributor to morbidity and mortality in sickle cell disease (SCD). The sickle gene confers an increased susceptibility to infection, especially to certain bacterial pathogens.[45] Infections also provokes a cascade of SCD-specific patho-physiological changes, that often manifest as crises. Also individuals with SCD typically suffer from functional hypospenism or asplenism, impaired splenic function resulting from repeated infarctions that heals by fibrosis thereby replacing spleenic tissues with fibrous tissues. As a result of deficiency of tufts in synthesis, an immune-stimulatory peptide, and properdin, which participates in complement activation they are predisposed to infection.[46] Opsonized bacteria are removed

efficiently by macrophages in the spleen or liver, but poorly opsonized bacteria are only cleared effectively by the spleen. Such pathogens include encapsulated bacteria, in particular Streptococcus pneumoniae (pneumococcus) and Haemophilus influenzae. These cells persist after an initial infection and rapidly produce antibody on subsequent exposures.[47]. Several specific clinical conditions commonly associated with infection in SCD are caused by particular pathogens as shown in table 1[48]

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

Pathogen	**Predisposing factors**
Encapsulated bacteria *(e.g.,* Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis, Salmonella spp*)*	Impaired splenic function
	Impaired opsonization
Salmonellae	Recurrent vaso-occlusion with intestinal infarct, necrosis and increased gut permeability
	Decreased neutrophil killing
Malaria	Decreased deoxyhemoglobin 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

Table 2 Other complications of SCD[49]

Growth retardation, delayed sexual maturation, being underweight
Avascular necrosis of the femoral or humeral head: This is due to vascular occlusion
CNS involvement: Most severe manifestation is stroke
Ophthalmologic involvement: Ptosis, retinal vascular changes, proliferative retinitis
Cardiac involvement: Dilation of both ventricles and the left atrium
Digestive system: Cholelithiasis is common in children; liver may become involved
Genitourinary system involvement: Kidneys lose concentrating capacity; priapism is a well- recognized complication of SCD
Dermatologic involvement: Leg ulcers are a chronic painful problem

VIII. Treatments

Bone marrow transplant, ultimately is the cure for SCD. But finding a HLA matched donor is often difficult and the procedure is costly and sometimes, leads to life threatening complications.[50] Treatment for sickle cell anemia is aimed at avoiding crises, relieving symptoms and preventing complications. Patients with SCD need regular follow ups.

9.1 Medications

Drugs that are used in the management of sickle cell disease include:

Antibiotics**.** In children with sickle cell disease, penicillin should be commenced at 2 - 4 months of age and continued until they're at least 5 years old. This is a good prophylaxis against life-threatening infections by encapsulated organisms. Antibiotics may also help adults with sickle cell anemia fight certain infections.[51] Analgesics**, l**ike non steroidal anti inflammatory drugs to relieve mild to moderate pain during a sickle crisis, while opoids are used in severe cases.[52] Hydroxyurea **.** When taken daily, hydroxyurea reduces the frequency of painful crises and may reduce the need for blood transfusions by stimulating production of fetal hemoglobin. Hydroxyurea increases risk of infections, it is speculated that long-term use of this drug may cause tumors or leukemia in some patients. However, no case has been reported.[53] Nitric oxide**.** In sickle cell disease there is low levels of nitric oxide in their blood. Nitric oxide, helps in dilating blood vessels and reduces the stickiness of red blood cells. Treatment with nitric oxide may prevent sickle cells from clumping together. Studies on nitric oxide have had mixed results so far.[54]

Statins are normally used to lower serum cholesterol, but may also reduce inflammation. In sickle cell anemia, statins may improve blood circulation through the tissues.[55]

9.2 Vaccinations to prevent infections

Apart from routine childhood immunizations, vaccinations, such as the pneumococcal vaccine and the annual flu vaccinations, are also important for patients with sickle cell disease.[56] as shown in Table 3

Table 3 Recommended immunization schedule for sickle cell disease[48]			
	Pneumococcus	**Meningococcus and Haemophilus influenzaetype b**	**Influenza**
Under 2 years	Routine immunization	Routine immunization	Annual
Age 2–5 years (fully immunized)	Single dose PPV	Booster dose given as the Hib/MenC vaccine	Annual
Age 2–5 years (unvaccinated or partially vaccinated)	Two doses of PCV given 2 months apart, followed 2 months later by PPV	Two doses of the Hib/MenC vaccine given 2 months apart	Annual
Age >5 years (fully vaccinated)	Single dose PPV	Two doses of the Hib/MenC given 2 months apart	Annual
Age >5 years (unvaccinated)	Single dose PPV	Two doses of the Hib/MenC vaccine given 2 months apart	Annual
Reinforcing immunization	PPV every 5 years	MenC vaccine every 5 years, Hib vaccine not currently recommended	Annual

Note: Schedule summarized from Salisbury D, Ramsay M, Noakes K. Immunization against infectious diseases (The Green Book). London: Department of Health; 2006.[49]
Hib, Haemophilus influenzae type b; MenC, meningococcus group C; PCV, pneumococcal conjugate vaccine; PPV, pneumococcal polysaccharide vaccine.

9.3 Blood transfusions

In children with sickle cell anemia at high risk of stroke, regular blood or exchange blood transfusions are indicated, while sequestration syndrome, hyperhaemolytic anaemias and refractory vaso occlusive crisis will receive blood transfusion on pro rata basis.[57-58] Regular blood transfusions may lead to iron overload hence chelating agent like desferoxamine should be given orally to such patients.[59]

9.4 Supplemental oxygen

Oxygen by face mask or nasal prongs is indicated in sickle cell crisis especially anaemic crisis.[60]

Control of SCD

Control of SCD by selective mating appears so logical and simple that many individuals, religious bodies and charitable organizations have tried to implement it themselves by screening young people and discouraging marriage among carriers.[61] Awareness is being developed by the formation of Sickle Cell Foundations and Clubs, with attendant publicity in Nigeria. Peers and relatives of the affected individuals because of improved survival now have the opportunity to observe their periodic pain crises and sadly deaths. This familiarity has heightened awareness.[62]

Pre-implantation genetic diagnosis is good but expensive option.[63]Prenatal diagnosis and abortion is also an option, but remain unacceptable majority Nigerians. Although there are no legislations outlawing marriages between sickle cell trait in Nigeria, most churches in the south-east Nigeria demand for documented result of genotype screening before couple are wedded.[61]. Creation or strengthening of national sickle-cell disease control programmes within the framework of national programmes for prevention and control of non-communicable diseases is necessary in affected countries.[64] Essential areas of work should cover advocacy; prevention and counseling; early detection and treatment; data collection, surveillance and research; and community education and partnerships. A multidisciplinary team involving health and social workers, teachers, parents and concerned nongovernmental organizations could be established to work on the practical aspects of implementation and monitoring of the programme.[64]

IX. Conclusion

Setting up sickle-cell screening and genetic counseling programmes in countries such as Nigeria with high prevalence rate of the disease cannot be overemphasized. These services should be made accessible and affordable to the population at risk. Genetic counseling and screening can lead to substantial reduction in the number of children born with the disease and trait

X. Conflict Of Interest

There is no conflict of interests among authors. All the authors contributed in different aspects of the article.

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