A Review of Sickle Cell Disease in Kenya

Dr. Kariuki Nyambura presents an overview of SCD in Kenya and discusses important aspects of diagnosis and management of SCD including upcoming experimental new treatment modalities

Introduction

Sickle cell disease (SCD) refers to a group of autosomal recessive genetic disorders that are characterized by a single-nucleotide polymorphism in the haemoglobin molecule.[1] A heterozygous form of SCD, referred to as the sickle cell trait (SCT), occurs when an individual is a carrier of two alleles, the sickle cell gene and the wild type (HbAS). 1 SCD affects 20-25 million people globally.[2] About 75-85% of the 300,000 annual SCD births globally are children born in SSA. Unfortunately, 50-80% of these children die before the age of 5 years.[3, 4, 5]

Globally, the natural distribution of SCD covers a broad belt that includes the Mediterranean, parts of West, East and Central Africa, the Middle East, India and Southeast Asia. This distribution is attributed to the evolution of the sickle cell mutation in response to tremendous selection pressure exerted by malaria, specifically that caused by Plasmodium falciparum. The result of this is high frequencies of the mutant gene in high malarial transmission areas.[2, 3] Since those with SCT have been shown to have a survival advantage against malaria infection caused by the Plasmodium falciparum parasite, there is a high proportion of these patients in malaria endemic regions.[6, 7] On the contrary, those with homozygous SCD have a higher mortality due to malaria, especially among children aged below five years. 8 Consequently, malaria prevention plays a crucial role in managing SCD in malaria-endemic regions like Kenya .[4]

In Kenya, about 20,000 to 30,000 annual births are of babies with SCD. Distribution in the country has regional variability that mimics the pattern of malaria endemicity.3 In the western region it is estimated that as high as 18% of children are born with SCT and 4.5% end up developing SCD. In the lake region, it is estimated that about 17% children are carriers of the trait with 0.6% having SCD.3 The overall prevalence of SCD in the country is 0.9% while that of SCT is estimated to be higher with about 10 - 40% of people living in malaria endemic regions being SCT carriers.[4]

Diagnosis and Management

The clinical course of SCD differs by region because of differences in burden of malaria and other infectious diseases, the prevalence of undernutrition, limited access to screening and treatment facilities as well as socioeconomic and cultural factors. 4 Longitudinal data from a health and demographic surveillance system in Kenya revealed the overall incidence of admission to hospital among children with sickle cell anemia (SCA) aged 0–13 years is about 57.2 /100 person-years of observation. Severe anemia appears to be the most common presenting complain in the country with bacterial infections and painful crises following .[9] In one hospital, almost one out of every 10 pediatric transfusions were due to SCA.[4, 9] Contrary to the situation in high-income countries, the incidence of stroke among SCD patients is lower in Kenya and could be due to the low survival rates with few patients reaching the age where the incidence of stroke begins to rise.[9] Nevertheless, patients may still present will other symptoms of SCD including acute vaso-occlusive, hemolytic, aplastic and sequestration crises or chronic symptoms like leg ulcers, avascular necrosis of the head of the femur and gallstones.[3] Local evidence reveals that the incidence of many complications of SCD, including malaria, anemia, bacterial infections, and in-hospital death, is more among undiagnosed children compared to those on follow-up. This may due to improved disease awareness, patient care and adherence to prophylactic medication following parent education at diagnosis.[9]

Screening for SCD may be done during the prenatal period using polymerase chain reaction (PCR) DNA analysis while diagnosis can be done during or after the neonatal period. Neonatal screening of patient hemoglobin type through isoelectric focusing (IEF), high performance liquid chromatography (HPLC) or hemoglobin electrophoresis is ideal as it provides an avenue for early intervention and parent education. Diagnosis after the neonatal period is through careful assessment of the clinical features, complete blood count, reticulocyte count, peripheral blood morphology, sickling or hemoglobin solubility tests and Hb separation techniques, family studies and if necessary, genetic testing.[3] Even though SCD is primarily a disease of red blood cells, it tends to affect and manifest in several organs (Figure 1). Additionally, leucocytes and thrombocytes are equally affected and measures of these hematologic parameters are of major diagnostic significance and provide insights into the pathogenesis of the various sickle cell crises.[9,10] Additional laboratory investigations useful in screening or diagnosis and monitoring of the disease include evaluation of lactate dehydrogenase (LDH), haptoglobin, total indirect bilirubin and aspartate aminotransferase (AST).[3] Several rapid point of care tests with acceptable diagnostic performance are available in the Kenyan market and are recommended for use at lower-level facilities where conventional hemoglobin (Hb) separation techniques are unavailable. These can be used together with clinical algorithms (e.g., the Kilifi algorithm proposed by Macharia et al.[9] to identify and diagnose patients.

National guidelines recommend diagnosis during the newborn period as the baseline for comprehensive care of children born with SCD.[11] After a diagnosis is made, initiation of penicillin prophylaxis before the age of 2

Kariuki, Nyambura, Department of Paediatrics and Child Health, School of Medicine, College of Health Sciences, University of Nairobi, Kenya. Email: dr.nyambura.kariuki@gmail.com

months and up to 5 years, supplemental immunization, safe transfusion practices, psychosocial support for the patient and families,[12] nutritional support with folic acid supplementation, appropriate pain management, hydroxyurea use and screening for chronic complications of SCD are recommended.[3]

While national newborn screening would be the best way to identify children with SCD and initiate early interventions, its use in Kenya is limited by resource challenges both individually and at the health system level.[3,4,9] Penicillin prophylaxis and routine immunization are available and accessible to most patients with immunization services being offered for free as per the country's expanded programme on immunization.[3] Patients' adherence to prophylaxis is therefore dependent on parental factors. On the other hand, blood transfusion in SCD continues to be challenging in the country. Factors like the frequent use of non-leuko-depleted whole blood, limited cross-matching procedures and suboptimal storage conditions pose risks to patients with SCD.[9] Hydroxyurea has been a game changer in the management of patients with SCD in Kenya. Its use is backed by evidence from the Cooperative Study of Sickle Cell Disease study (CSSD),13 the Ped- HUG and Baby-HUG trials 14, the REACH trial 15 among others. These studies have demonstrated the benefits of hydroxyurea in reducing painful crisis, the need for blood transfusion and infection in patients with SCD, including those with comorbidities like malnutrition, with no safety concerns. Figure 2 shows the pathophysiology of SCD and action of hydroxyurea. To enhance the availability and access to hydroxyurea and improve diagnostic and treatment knowledge among healthcare workers, the Ministry of Health in Kenya, in collaboration with partners, launched a training and treatment access programme dubbed "Sickle Cell Diseases Afya Dhabiti Project" in January 2023 (https://www.health.go.ke/node/708). Such efforts are encouraging as SCD in the country has been historically neglected despite its high burden.[16] Adequate pain management remains challenging due to financial constraints on the patients' families as well as healthcare worker attitudes and practices on pain management in SCD patients and variable availability of opioids for patients with severe painful crises.[17,18]

Hematopoietic stem cell transplantation (HSCT), is the only proven treatment for SCD. The procedure is however not devoid of complications which include infection and graft-versus-host disease. Moreover, limited availability of eligible donors and the extensive resources required to carry out such procedures limits it use in resource-constrained environments like Kenya. [2] For example, In SSA, Nigeria, South Africa and Tanzania are the only countries with the capacity of providing bone marrow transplant (BMT) therapy for SCD. [19] Kenya's first bone marrow transplant center was setup in 2022 with the first transplant being conducted in October that year on a 55-year-old multiple myeloma patient. Two years later, BMTs are yet to be routinely conducted among patients with SCD in the country. Patients who can afford the treatment are referred to other international centers for the same.

New treatment modalities

New treatment modalities such as l-Glutamine (an amino acid that increases the red cell levels of glutathione), voxelotor (a hemoglobin(Hb) adjunct which reduces Hb polymerization and sickling through binding to the □ globin chain and increases its oxygen affinity) and crizanlizumab (a monoclonal antibody developed against the adhesion molecule p-selectin) have been shown to be useful in SCD(20). However, the effectiveness of these treatments is yet to be evaluated in low income and malaria endemic regions like Kenya.

Despite there being a paucity of literature on the use of gene therapy for SCD in SSA, clinicians in these countries agree that gene therapy has the potential to be the most effective approach to cure SCD in this region with a high burden .[19] Increasing the genomic research and output from the region Africa is expected to identify loci suitable for gene therapy.[19]

Novel molecular targets in the treatment of SCD focus on reducing hemoglobin-S (HbS) levels, reducing the impact of HbS polymers on red cell function, reducing the impact of membrane events which contribute to pathogenesis and, using the unique permeability of HbS-containing red cells as an access for drug delivery targeted specifically to sickle cells.20 They include drugs which modulate globin expression qualitatively or quantitatively, drugs which target HbS, drugs which target red cell dehydration (Psickle inhibitors, Gárdos channel and anion conductance inhibitors and potassium chloride cotransport inhibitors), drugs which target the red cell cytoskeleton and drugs which make use of the unique permeability of HbS-containing red cells. These have been succinctly summarized by Gibson et al. in a recently published review of emerging drug targets for sickle cell disease (20). As the promise of newer and more effective treatment modalities grows, these treatment modalities need to have their effectiveness evaluated in SSA. While their cost may initially be high, evidence on their effectiveness in the region would provide evidence useful in lobbying governments and partners to increase the access to these treatment options.

Summary

SCD remains a key public health concern in SSA and in Kenya. Despite advances in treatment and availability of evidence-based guidelines on the management of SCD patients, the burden of the disease remains high due to resource constraints and limited access to treatment options. Moreover, the effectiveness of emerging treatment modalities has not been evaluated in the Kenyan population; a prerequisite for their use in SCD patients in the country. Nevertheless, national efforts to reduce this burden have increased in the past few years raising hopes for those affected by the disease.

Figures:

Figure 1: *Figure showing acute and chronic organ complications in sickle cell disease, (adapted from Kato et al, 2018).*

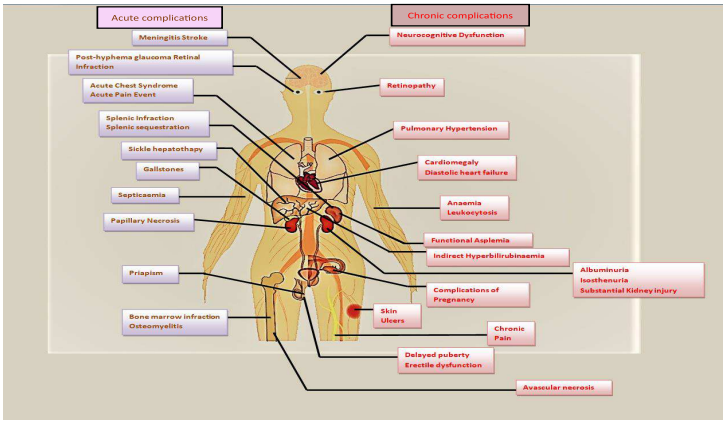
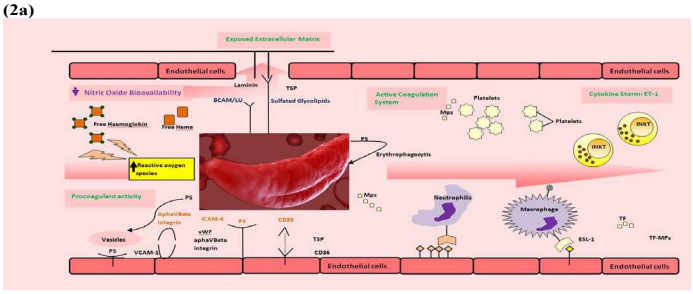
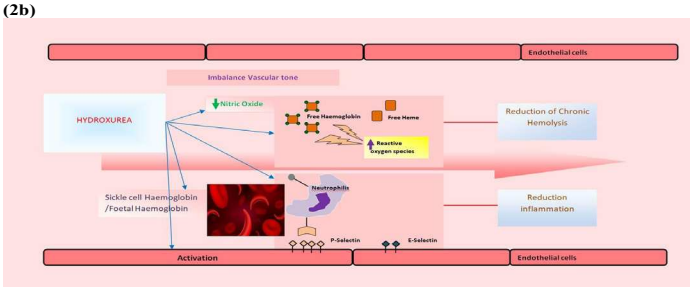


Figure 2: *Figure showing the vascular pathophysiology of sickle cell disease* ***(2a)****, and the action of hydroxyurea* ***(2b)****, (adapted from De Franchesci et al, 2011).*

(2a)



(2b)



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