Minireview Article

Sickle cell disease in East African countries: Prevalence, complications and management

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ABSTRACT

Sickle cell disease (SCD) is one of the most common life-threatening monogenic disorders affecting millions of people worldwide. The disease has a high prevalence in malaria endemic tropics, especially in sub-Saharan Africa. Although sickle-cell trait (SCT) offers protective advantage against malaria, it does not apply to homozygous individuals with sickle cell anemia but instead makes them more susceptible to not only malaria but to also other infections, causing a great deal of under-five mortality. Despite the fatal risks and high incidence rates of SCD, little attention is given, in terms of funding, management and surveillance, especially among East African countries. In addition, few works of literature exist, and less has been documented about the disease. This mini review aimed to report the current situation in terms of prevalence, mortality, diagnosis and management of SCD among East African countries; Uganda, Kenya, Tanzania, Rwanda and Burundi.

SCD is characterised by retarded growth, chronic pain attacks and severe organ damage leading to fatal complications. This, coupled with limited resources in East African countries, reduces the survival of SCD patients and most die before five years. SCD is detected through a blood test usually by Haemoglobin electrophoresis, and use of Hydroxyurea, antibiotics and blood transfusion are used to prevent complications. Early childhood detection through comprehensive new-born-screening programmes has been implemented in some countries and is key in the management of the disease.

Keywords: Prevalence; Sickle cell disease; East Africa; Management

1. INTRODUCTION

Sickle cell disease(SCD) refers to a group of inherited blood disorders (including sickle cell anemia (SCA), HbSC and Hbsβ-thalassaemia) caused by mutations in the gene encoding the haemoglobin subunit β (HBB)[1]. Hemoglobin comprises of four protein subunits, (two alpha-globin and two beta-globin). Different forms of beta-globin result from mutations in the HBB gene, which provides instructions for making beta-globin. A mutation substituting the amino acid Glutamic acid by valine results in the production of abnormal beta-globin known as hemoglobin S (HbS) [2]. Other mutations in the same gene result in abnormal versions of beta-globin such as hemoglobin E (HbE) and hemoglobin C (HbC). Beta thalassemia, a condition due to a low level of beta-globin, can also result from such mutations [3]. When oxygen levels in blood are low, the abnormal hemoglobin gene in SCD patients can cause rigid, non-liquid protein strands to form within the red blood cell, this changes the shape of the cell and cannot regain its normal disc shape in high oxygen levels, causing the sickled red blood cell that gives the disease its name. Unlike sickled cells, normal red blood cells are flexible so that they can easily move through small and large blood vessels. Sickle-shaped

cells can stick to vessel walls, and cause a blockage (vessel occlusion) that slows or stops the flow of blood, which cuts off the oxygen supply to nearby tissues. Vessel occlusion can cause sudden severe pain, called pain crises and can be triggered by dehydration, high altitude, infections, stress and temperature changes [4]. SCD is inherited as an autosomal co-dominant trait, and so individuals who are heterozygous carry SCT (HbAS), usually have no symptoms and are called carriers while the homozygous individuals have SCA, the most common form of SCD[3,4].

Common signs of sickle cell disease include swelling of the hands and feet, jaundice, symptoms of anemia (due to rapid haemolysis of sickled cells), including fatigue, or extreme tiredness. SCD is characterised by chronic episodes of pain, delayed growth, bacterial infections and stroke. Vaso-occlusion and inflammation lead to progressive damage to most organs (including the bones, brain, kidneys, lungs) and cardiovascular system, which becomes apparent with increasing age, and severity varies among individuals[4,5]. Severe complications of SCD include, but not limited to, proliferative retinopathy before the loss of eyesight, pulmonary vasculopathy associated with pulmonary hypertension, and renal vasculopathy before the onset of chronic renal disease [6].

2. DIAGNOSIS

Currently, the most common screening techniques used include sickle solubility testing, hemoglobin electrophoresis, high-performance liquid chromatography (HPLC), and isoelectric focusing (IEF), each with their advantages and limitations. The sickle solubility test is a low-cost assay that relies on the relative insolubility of HbS in the presence of a reducing agent, like sodium dithionite, so it can easily detect the presence or absence of sickle hemoglobin [7]. However, this test cannot differentiate individuals with SCD and SCT and has high chances of false negatives, making confirmatory testing essential. Solubility testing is there for best used as the first-line screening technique [8].

Hemoglobin electrophoresis, HPLC, and IEF are methods used either for primary identification of SCT or as confirmatory tests. These techniques can provide discrimination and relative quantification of hemoglobins, allowing for differentiation of SCT from SCD syndromes. Hemoglobin electrophoresis, an inexpensive and frequently used technique, uses the principles of gel electrophoresis to separate hemoglobin molecules by size and charge. However, it requires further hemoglobin discrimination, using different gels such as citrate agar or cellulose acetate or IEF methods, since co-migration of certain rare hemoglobin variants with HbS may obscure the diagnosis with standard electrophoresis [7]. IEF is an extremely sensitive, pH-based electrophoresis method that separates hemoglobins by their isoelectric point. Because of its high-discriminatory capabilities and low-cost, IEF is the primary technique used in most newborn screening programs [9]. Due to their ability to more precisely quantify hemoglobin components, HPLC and capillary electrophoresis are also used for hemoglobinopathy screening by many reference laboratories.

Urinalysis and chest X-ray are routinely performed to detect urinary tract infections and pneumonia respectively since acute sickle cell crisis is often triggered by infections [10]. Known carriers of SCD often undergo genetic counselling before having a child, and the unborn child can be tested for the disease commonly by using a sample of amniotic fluid. Neonatal screening provides a method of early detection for individuals with SCD as well as those who carry the SCT [11].

3. EPIDEMIOLOGY

Sickle cell disease distribution is closely linked to the natural protection against malaria to heterozygous individuals, and so the highest frequency is found in tropical regions, particularly sub-Saharan Africa, tribal regions of India and the Middle East. This selective

advantage has resulted in the distribution of HbS mutations closely in areas of high malaria endemicity, which are the tropics [2, 12]. However, homozygous individuals with SCA are not protected against malaria, and in fact, they are more prone compared to normal individuals, and this is worsened by the fact that most tropical countries lack the necessary resources to provide comprehensive care for SCD patients. These factors account for the high mortality attributed to SCD in such regions where by more than half of the infected children die before the age of five years, compared to developed countries where the life expectancy of SCD patients is 40-60 years [4,13,14].

4. PREVALENCE

SCD affects millions of people globally and particularly prevalent among the people in sub-Saharan Africa [1, 15]. Over 4.4 million people have sickle cell disease, while over 43 million have SCT [16]. About 300,000 to 400,000 children are born with SCD each year and over half of these die before the age of five years [17].

4.1 Prevalence in East Africa

In reviewing the situation of SCD in East African countries, 15 relevant research articles from 2008 to 2019 were found to report on the prevalence or incidence of sickle cell disease. These were quantitative original research articles and excluded studies or case-controls in which SCD was one of the study populations as well as qualitative studies. Surveillance Comparative studies reported comprehensive data (especially on mortality) of significance and were also included. Extra data on mortality, age, study group, study area, study type and test method were extracted from the selected articles and summarised in the table 1 below.

In 2016, a National Surveillance cross-sectional study by Ndeezi et al., reported that the prevalence of HbSS and HbAS was 0.7% and 13.3% respectively. A 25% mortality was reported to be attributed to SCD. The study group were 97,631 HIV exposed infants less than 18 months in all regions of Uganda [18]. Okwi et al. reported, in 2010, reported 1.58 % as the prevalence of HbSS, while that of HbAS to be 11.3% among 571 children of 6 months to 5 years, and this was a cross-sectional study conducted in Eastern and Western Uganda[19]. In 2017, Lwanira et al. reported the prevalence of HbAS to be 26.6% in a cohort study conducted among 423 children below 9 years in Iganga district of Uganda. Only one child was reported to have HbSS giving a prevalence of 0.24% [20]. In a hospital-based cross-sectional study conducted in Eastern Uganda in 2018, Mandu et al. reported the prevalence of HbAS to be 4.5% among 242 adults of 18 to 49 years [21]. In the same year, Mpimbaza et al. also reported mean prevalences of HbSS and HbAS to be 0.84% and 8.74 % respectively, this was a case-control study of 975 children (6 months to less than 10 years) conducted in Jinja Hospital, Eastern Uganda[22]. In the most recent (2019) hospital-based age-matched case-control study, Dhabangi et al. reported the prevalence of HbSS and HbAS to be 7.65% and 5.1%. The study population were 196 children of 2 months to 5 years from the East, South, West and North regions of Uganda. Although children known or suspected to have SCD were eliminated from the study at enrolment, 15 children were found to have SCD, and these had not been diagnosed before [23]. Indeed in such settings as this with a documented prevalence of sickle cell gene as high as 17%, early childhood screening of SCD is vital.

In Kenya, Komba et al., in 2009, reported the prevalence of SCD to be 1.6% as well as a 4.5% mortality. This was a hospital-based surveillance comparative study of 34,529 children below 14 years in Kilifi district, the coast of Kenya [24]. In 2013, Foote et al. reported a 1.6% and 17.1% prevalence of HbSS and HbAS respectively, in a population-based cross-sectional survey of 858 preschool children (6 to 35 months) in western Kenya [25]. Also, Byrd et al., in 2018, reported the prevalence of HbSS to be 0.2% while that of HbAS to be

16.2% in a prospective cohort study of 435 children (14 to 26 months), still in western Kenya [26].

For Tanzania, in 2018, Hau et al. reported a 12.1% prevalence of SCD and a 23% mortality in a prospective cohort study of 506 children of 2 to 12 years in Northwest Tanzania [27]. In 2017, Ambrose et al. reported a 1.4% and 19.7% prevalence of HbSS and HbAS, respectively. This was also a prospective cohort study of 919 newborns of 0 to 7 days, still in Northwestern Tanzania [28]. In a hospital-based surveillance comparative study of 157,473 births in Dares salaam, Muganyizi and Kidanto reported an incidence of 95/100,000 deliveries and 25.7% mortality of SCD among new deliveries (less than 4 weeks) [29]. Kamugisha et al., in 2011, also reported a 10.4% prevalence of HbAS in a cross-sectional study of 385 school children of 9 to 18 years in Nyamagana district, Mwanza-Tanzania [30].

For Rwanda, Gahutu et al., in 2012, reported the prevalence of HbSS to be 0.13% while that of HbAS to be 2.8% in a cross-sectional study of 749 children less than 5years in Southern highland, Rwanda[31]. Also in a screening study, of 1,825 neonates (less than 4 weeks), done in Rwanda, Burundi and East of DRC, Mutesa et al., in 2010, reported a 0.22% and 3.23% prevalence of HbSS and HbAS respectively[32]. No independent article found to report on the prevalence of SCD in Burundi.

154 **Table 1: Summary of articles that reported on the prevalence of SCD**

Author	Country	Year published	Number, N	Prevalence of SCD		Age	Study Group	Area	Mortality	study type	Test method
				HbSS	HbAS						
Ndeezi et al.[18]	Uganda	2016	97,631	0.70%	13.30%	< 18 months	HIV Exposed infants	All regions	25%	National surveillance cross sectional study	Haemoglobin Electrophoresis
Okwi et al.[19]	Uganda	2010	571	1.58%	11.30%	6months to 5years	children	Eastern and Western Uganda	--	Cross sectional study	cellulose Acetate Hb Electrophoresis
Lwanira et al.[20]	Uganda	2017	423	0.24%	26.60%	below 9years	children	Iganga district	--	Cohort study	Haemoglobin Electrophoresis, PCR-RFLP and DNA Sequencing
Mandu et al.[21]	Uganda	2018	242	--	4.50%	18 -49 years	Adults	Eastern Uganda	--	Hospital based cross sectional study	Haemoglobin Electrophoresis
Mpimbaza et al.[22]	Uganda	2018	975	0.84%	8.74%	6months to less than 10years	children	Jinja Hospital, Eastern Uganda	--	Case control study	PCR based Assays
Dhabangi et al.[23]	Uganda	2019	196	7.65%	5.10%	2months to 5years	children	East, South, West and North regions	--	Hospital based Age matched Case control study	capillary Haemoglobin Electrophoresis
Komba et al.[24]	Kenya	2009	34,529	1.60%		below 14years	children	Kilifi district, Coast of Kenya	4.50%	Hospital based surveillance comparative study	Haemoglobin Electrophoresis, PCR test
Foote et al.[25]	Kenya	2013	858	1.60%	17.10%	6 to 35 months	Preschool children	Western Kenya	--	Population based cross sectional survey	PCR
Byrd et al.[26]	Kenya	2018	435	0.20%	16.20%	14 to 26 months	children	Western Kenya	--	Prospective cohort study	PCR
Hau et al.[27]	Tanzania	2018	506	--	12.10%	2 to 12 years	children	North west Tanzania	23.00%	Prospective cohort study	_
Ambrose et al.[28]	Tanzania	2017	919	1.40%	19.70%	0 to 7 days	Newborns	North west Tanzania	--	Prospective cohort study	HPLC
Muganyizi and Kidanto[29]	Tanzania	2013	157,473	95/100,000 deliveries (incidence)	--	less than 4weeks	Newborn deliveries	Dar-es salaam, Tanzania	25.70%	Hospital based surveillance comparative	_

										study	
Kamugisha et al.[30]	Tanzania	2011	385	--	10.40%	9 to 18 years	school children	Mwanza-Tanzania	--	Cross sectional study	Haemoglobin Electrophoresis
Gahutu et al.[31]	Rwanda	2012	749	0.13%	2.80%	below 5years	children	South Highland, Rwanda	--	Cross sectional study	PCR based methods
Mutesa et al[32]	Rwanda	2010	1,825	0.22%	3.23%	less than 4weeks	Neonates	Rwanda, Burundi, East of DRC	--	Screening study	ELISA Test

Basing on the available literature, in Uganda, higher prevalence of SCD and SCT was from Eastern and Western regions as documented by Lwanira et al. 2017 and Okwi et al. 2010. North-western Tanzania also reported higher prevalence as documented by Ambrose et al. 2017 and Hau et al. 2018 as well as Western Kenya as documented by Foote et al. 2013 and Byrd et al. 2018. Generally, the low incidence is documented from highland areas, as in Rwanda and Burundi, owing to the lower malaria endemicity in such areas. Mortality of SCD was reported in national or regional surveillance studies; 25% in Uganda by Ndeezi et al., 4.5% at Coast of Kenya by Komba et al., 23% in North-west Tanzania and 25.7% in Dar-es salaam, Tanzania as reported by Hau et al. and Muganyizi and Kidanto respectively. The commonly used diagnostic tests used in the region include Haemoglobin electrophoresis and PCR tests, owing to their high discriminatory ability and low cost.

5. TREATMENT AND MANAGEMENT OF SCD

Treatment for sickle cell anemia is aimed at avoiding or reducing pain crises, relieving symptoms and preventing complications. It might also include blood transfusions as well as bone marrow transplant. Bone marrow transplant (stem-cell transplant) offers the only potential cure for sickle cell anemia. However, it is a complicated procedure with potential death risks [2, 33–36].

For proper management, correct early diagnosis, ideally during the newborn period, is key and allows early initiation of prophylactic penicillin and pneumococcal immunizations, which help to prevent complications and mortality [37, 38]. Education and counselling of families promote early recognition of disease-related complications, enabling prompt and appropriate medical intervention. Periodic evaluation by trained specialists is vital and helps to provide comprehensive care, and where recommended, blood transfusions and use of Hydroxyurea treatment represent a new treatment paradigm for SCA management [37, 39].

Long term Anti-malarial therapy is key especially to those living in endemic malaria regions; this is because SCD patients are more prone to malaria since the protective effect of SCT does not apply to them [40].

Daily use oral prophylactic penicillin among infants, annual transcranial Doppler examinations in those with SCA, and blood transfusion therapy, to prevent stroke in those with abnormal transcranial Doppler velocity, are some of the preventive recommendations. Initiation of opioids to treatment severe pain associated with vaso-occlusive crisis, as well as the use of incentive spirometry are used to avert acute complications. In the chronic stage, use of analgesics and physical therapy to treatment avascular necrosis, and use of angiotensin-converting enzyme inhibitor therapy for micro-albuminuria is recommended in adults with SCD. For those with proliferative sickle cell retinopathy, laser photo-coagulation might be considered as well as echo-cardiography to evaluate signs of pulmonary hypertension [33, 38, 41]. Treatment and management of SCD vary depending on the severity and/ patients' condition. In-spite Hydroxyurea therapy, chronic blood transfusion and haemopoietic stem-cell transplantation being the strongly recommended therapies against SCD, evidence shows that these interventions are still far less used in East African states explaining the high mortality and morbidity rates of SCD within the region.

6. CONCLUSION

Despite East Africa being in a high endemicity region, less is known about the disease basing on the scanty works of literature available. More research is still needed to establish the current burden of the disease, especially in countries of Burundi and Rwanda, as this will serve as a starting point for action against SCD. Comprehensive newborn screening programmes are also key in revealing the burden of the disease, and this should be accompanied with adequate funding to establish specialised sickle cell clinics that provide holistic care and management of sickle cell patients. This would enable more effective early infant diagnosis, treatment and management, thus improving the quality of life of SCD patients. It would also help to combat the high infant mortality rates attributed to the disease. Community and family sensitisation should be considered as a vital prevention tool to inform people about the importance of not only early childhood screening but also screening marriage partners. These would help reduce the incidence of SCD as well as prolonging lives of SCD patients as evidenced in developed countries.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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