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Sickle-cell disease in sub-Saharan Africa

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Background and Objectives Sickle-cell disease, over a century since its discovery, remains a great challenge in sub-Saharan Africa, where the burden of the disease is highest and where resources for managing its various complications are scarce. This paper is a general review of sickle-cell disease and, especially in Africa, focusing on its manifestations, complications and the management strategies in place.

Materials and Methods Data for this review were collected from published articles, books, and internet websites and from personal experiences.

Results The findings highlight the major clinical manifestations, the diagnostic methods and management strategies used in sub-Saharan Africa as well as some of the challenges encountered.

Conclusions Better organisation with co-ordinated multidisciplinary teams as well as government commitment is indispensable for optimal sickle-cell disease care in sub-Saharan Africa.

Key words: epidemiology, genetics, sickle-cell disease, sub-Saharan Africa, transfusion therapy

Introduction

Sickle-cell disease (SCD) refers to an inherited disorder in which red cells contain an abnormal haemoglobin, resulting from structural gene mutations of the beta-globin chain (β) due to the substitution of a single amino acid on the chain. The clinical manifestations of SCD appear to have existed for at least five thousand years under different local names in Africa before its first description in the USA (and not in Africa) in 1910 by Dr. James Herrick.

Haemoglobin (Hb) is a tetramer of four unequal polypeptide chains called globins, two of which are alpha chains and the two others beta-chains. The substitution of glutamic acid at the 6th position of the beta-chain (β6) of Hb results in haemoglobin S [1]. Other structural mutations of the β-chain include the replacement of glutamic acid, respectively, at β6 and β26 by lysine, respectively, resulting in haemoglobin C and E. However, only HbS and HbC reach high frequencies in Africa. The sickle haemoglobin (HbS) is the most common and clinically significant haemoglobin structural variant, with HbC being the second commonest abnormal Hb in Africa [2].

Although many challenges remain in our understanding of the broad spectrum of pathologies associated with SCD, the implementation of comprehensive care, including newborn screening, infection prophylaxis with penicillin and hydroxyurea therapy, has improved the survival as well as the quality of life of individuals with SCD in resource-rich countries. However, sub-Saharan Africa (SSA) is characterized by limited resources in terms of infrastructure, equipment, qualified specialists and training opportunities. These and the high frequency of other red blood cell abnormalities and malaria endemicity affect the natural history of SCD.

The purpose of this review was to provide a snapshot regarding the epidemiology, clinical features, diagnosis and management of SCD in SSA.

Epidemiology

Haemoglobin S is the most prevalent genetic disorder worldwide. In 2010 alone, more than 300 000 children

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were born with sickle-cell anaemia (HbSS), the homozygous form of HbS, and it is predicted to affect more than 400 000 newborns in 2050 [3, 4]. There are over 100 million people affected with those of African descent mostly touched. The geographic distribution of the HbS gene (sickle-cell trait) is very similar to that of malaria, occurring in SSA, the Caribbean, Middle East, Saudi Arabia, the Indian subcontinent and some countries bordering the Mediterranean Sea, especially Turkey, Italy and Greece [5, 6]. Table 1 further highlights the occurrence of HbS globally [7]. Interestingly, HbS carriers have been reported to enjoy partial immunity to malaria [8].

Most S genes occur on four haplotypes known as Senegal, Benin, Central African region (or Bantu) and Cameroon types which appear to determine the severity of organ damage [9].

Mortality in SCD is highest in the under 5-year-olds homozygous for HbS with an early-life mortality of 50–90% [10, 11], reiterating the relevance of neonatal screening programmes, which have reportedly reduced mortality by about 70%, as well as morbidity [12]. Indeed, it is suggested that where no intervention and care programmes exist, high mortality is registered amongst 90% of children, especially in the under 5-year-olds [13].

The HbS gene frequency reaches 20–40% in some countries of SSA [2], and an estimated 75·5% of all newborns with homozygous SCD occurs in SSA [3]. Hence, SSA will be the main focus of this review.

Pathophysiology

Various mechanisms have been reported in relation to the clinical manifestations and complications associated with SCD. Normal red blood cells are flexible and easily malleable when moving through all blood vessels. However, in sickle-cell anaemia, the point mutation leading to sickle haemoglobin substitutes a hydrophilic (glutamic acid) by a hydrophobic amino acid (valine) [1]. In the deoxygenated state, the valine residue on the abnormal β-chain can associate with other haemoglobin chains via hydrophobic interactions, leading to haemoglobin polymerization. When the amount of haemoglobin S is sufficient, polymerization forms long and rigid strands of haemoglobin that distort the red blood cell (RBC) to produce the characteristic sickle shape. Sickling is reversible upon haemoglobin reoxygenation. However, repeated cycles of sickling and unsickling leads to several structural and functional abnormalities of RBC including the expression of adhesive molecules, dehydration and impaired deformability [14–17], resulting in vaso-occlusion, chronic haemolysis and consequently anaemia.

Inflammation is favoured by several factors in SCD including the free haem liberated from Hb during haemolysis which has been reported to directly activate endothelial cells and macrophages [18]. Furthermore, biomarkers for inflammation also increase in SCD [15, 19], with evidence of a possible association with vaso-occlusive crises [20]. Haemostatic disorders also accompany SCD through various mechanisms [21–26].

Table 1 Births with SCD in various regions of the world

Region	Population ($\times 10^6$)	SCD[a] Births ($\times 10^3$)	% SCD births per Region
Sub-Saharan Africa	650	230	64·5
South-East Asia	3·150	120	33·6
Americas	750	5	1·4
East Mediterranean & Europe	780	1·6	0·4
Western Pacific	30	0·2	0·1
Total	5·340	356·8	100

[a]Homozygotes and compound heterozygotes.
Data source: Weatherall & Clegg [7].

Clinical manifestations and complications

Sickle-cell disease has a rich and varied symptomatology [27]. Dactylitis (hand-foot syndrome) usually manifests early (5–6 months). Painful vaso-occlusive crises are the primary reason for consultation in SCD, in 80% cases [28]. Chronic haemolysis also results in the accumulation of unconjugated bilirubin, hence jaundice, and an increased incidence of gall stones formed from bilirubinate precipitates. Some African studies have reported the prevalence of gallstone in Cameroon and Dakar, Senegal, to be, respectively, 28·9% and 10·4% [29, 30].

In SCD, by the age of 5 years old, most children already have functional asplenia accompanied by a perturbed immune system. There is dysfunctional antibody production and opsonophagocytosis in these children. In addition, splenic clearance is defective rendering them more susceptible to infections, predominantly to encapsulated organisms such as Streptococcus pneumoniae, Salmonella, Haemophilus influenzae type b (Hib) and meningococcal infections. These infections are associated with high mortality in the under 5-year-olds [31]. However, their early diagnosis, antibiotic prophylaxis and vaccination programmes would significantly reduce morbidity and mortality [31].

Several other complications are associated with SCD, especially in HbSS disease, usually involving irreversible organ damage. A few examples are reported below.

Bone complications in SCD include avascular necrosis of bone which affects about 50% of homozygous HbSS

patients by their 35th birthday [32], mainly the femoral head, and the humoral head to some extent. A recent study in patients with SCD in Nigeria observed avascular necrosis in about 13/1000 Nigerian patients with SCD [33]. Bone marrow necrosis has also been described in association with aplastic crisis and parvovirus B19 infection [34]. Parvovirus B19 affects red cell precursors resulting in a sudden, transient, but life-threatening aplasia of the marrow and reticulopenia that may last up to a week [35]. Osteomyelitis occurs in about 29% of Nigerian patients with SCD in their lifetime [36], with predominantly salmonella and staphylococcus responsible [37]. Tuberculosis and bone infarctions may also occur [38], and stress fractures have been reported in Cameroon [39].

Cardiovascular complications include pulmonary arterial hypertension, heart failure and stroke, amongst others. Pulmonary arterial hypertension occurs in about 30% of adults with SCD and associated with very high mortality rates [40]. In Nigeria, 29% pulmonary arterial hypertension was reported in adults with SCD [41], while about 10–15% of children seem to suffer from strokes, most of which are silent strokes [42]. These are asymptomatic, but are responsible for brain damage that affects the performance of children in school [43, 44]. A few African studies report strokes to be mainly of cerebral infarctions in children and cerebral haemorrhages in adults [45, 46], with prevalences varying from 3·2% to 8·7% [47, 48]. Computerized tomography and magnetic resonance imaging which should ease the diagnosis of stroke are not readily available in many settings of SSA.

Acute chest syndrome is a common complication in SCD, often associated with vaso-occlusive crisis, and accounts for about 25% of deaths in SCD [49, 50]. Studies in Congo Brazzaville and Cameroon reported acute chest syndrome in 14% and over 50% SCD cases, respectively [47, 51]. The risk factors for it include age (occurring more commonly in children than in adults), low HbF, high haematocrit, smoking, general anaesthesia and HbSS [49].

Renal dysfunction in SCD, evidenced by glomerular hyperfiltration, appears to begin during infancy [52] and associated with frequent enuresis [53]. Proteinuria is a complication of sickle-cell nephropathy that may progress to end-stage renal failure as reported in Nigeria [54]. Acute papillary necrosis in SCD has been associated with haematuria in SCD.

Proliferative retinopathy, vitreous haemorrhages and retinal detachment can result in SCD due to repeated vaso-occlusion of small vessels of the eye [55] and more frequent in double heterozygotes (HbSC, HbSβ thalassaemia) [56]. In Dakar, Ndiaye *et al.* [57] reported 75% HbSC cases with vascular retinal complications including vitreous haemorrhage. Other reports from Egypt and Nigeria have confirmed these findings [58, 59], emphasizing the need for routine eye checks in SCD to prevent sight-threatening disorders.

Acute splenic sequestration crisis is an uncommon complication of SCD adults with sudden enlargement of the spleen and a rapid decrease in haematocrit that may occur unexpectedly in HbSS [60], in HbSC [61] and in HbS/Thal disease [62], and may have fatal outcomes. In Zambia, 20·45% of deaths occurred from acute splenic crisis [63].

Other complications associated with SCD include priapism, reported in 11·6% cases in Dakar [64], leg ulcers especially in HbSS patients and alloimmunization as a complication in those receiving transfusions.

Diagnosis of SCD in Africa

The laboratory diagnosis of SCD may entail phenotypic testing for the presence of the sickle haemoglobin (HbS) as well as genotypic analysis. The physicochemical properties of HbS such as decreased solubility, deformation (sickling) under hypoxic conditions, mobility patterns in an electric field and rate of elution from a solution into an adsorbent are all used to detect its presence in the laboratory. In most settings of SSA, the 'sickling test' with sodium metabisulphite is used to demonstrate the presence of HbS in a blood sample. Sodium metabisulphite causes hypoxia to red cells and induces sickling in HbS-containing cells (homo- and heterozygous). This is affordable for most centres, but does not specify the genetic make-up of the haemoglobin. In addition, this test is effective only after the age of 6 months, since fetal haemoglobin (HbF), present at that stage, inhibits sickling. Other such non-specific tests may include the Itano solubility test, based on the low solubility of reduced HbS [65] in which HbS becomes insoluble under hypoxic conditions. Dithionite and urea-dithionite may be used to detect the presence of HbS by turbidity [66] and the Murayama test using concentrated haemoglobin haemolysates to demonstrate the hydrophobic bonds within deoxygenated HbS, by reversible gel formation at 0°C and 37°C [67].

Where available, these non-specific screening tests are confirmed using haemoglobin quantification methods that distinguish haemoglobin types including composite heterozygous forms. These include haemoglobin electrophoresis at varying pH (alkaline and acid), isoelectric focalization (IEF), capillary electrophoresis, high-performance liquid chromatography (HPLC) as well as molecular techniques. Sometimes, the association of at least two techniques is useful to separate haemoglobins presenting the same migration or elution profiles.

Alkaline electrophoresis (pH 8·6) is largely used in most settings of SSA, but because HbS and HbF tend to

migrate virtually similarly in this environment, neonates with high HbF cannot be diagnosed with this method. In an acidic environment (pH 6·0), abnormal haemoglobins that migrate similarly with haemoglobin S in alkaline electrophoresis, such as HbD, HbA and HbF, are distinguished. However, not all Hb variants are detectable by Hb electrophoresis.

Isoelectric focalization is an electrophoretic separation of Hb molecules based on the differences in the isoelectric points of proteins and used where available for distinguishing Hb types in neonates [68]. Isoelectric focalization gives good separation of HbF from HbA and variant haemoglobins such as S, C, D Punjab and O-Arab, but again may not identify all Hb variants, and is labour-intensive.

Capillary electrophoresis is an analytical technique that utilizes a combination of ion migration and electro-osmotic flow to separate protein molecules [69].

High-performance liquid chromatography is a technique that utilizes an ion exchange resin, held in a column cartridge, in conjunction with a buffer gradient. As the ionic strength and/or pH of the buffer changes, so are certain haemoglobins eluted from the column and the presence of the haemoglobin is detected using a spectrophotometric technique. It accurately quantifies Hb levels; hence, it could be used for monitoring certain therapy and transfusion regimens in SCD.

Molecular techniques provide the most accurate diagnosis, but these are relatively expensive to perform and time-consuming.

Early (neonatal) screening for SCD, combined with care and parental education, remains useful in drastically reducing infant morbidity and mortality. However, only few countries of SSA carry out systematic or targeted neonatal diagnosis including Benin, Nigeria, Congo Democratic Republic and Ghana [70–72].

Management of SCD in SSA

In SSA, few countries have national health policies and programmes regulating prevention and care for SCD, and where these exist, they do not cover national territories. Hence, SCD remains a challenge, with the huge socioeconomic impact on the patients (educational and psychological setbacks and discriminations), on the family (financial strains as there are virtually no functional health insurance schemes) and on the community as a whole. The recurrent pain and complications caused by the disease interfere with many aspects of the patient's life, including education, employment and psychosocial development. One study in Cameroon by Wonkam *et al.* [73] indicated relatively high acceptability by parents of SCD children, of the principle of prenatal genetic diagnosis (89·8%) and termination of pregnancy (62·5%), suggesting their desire to actively avoid new cases into their families, and confirming the psychosocial and emotionally stress they must go through.

In May 2006, the World Health Assembly of the WHO passed a resolution recommending that African states integrate SCD into their national health policies, to include early diagnosis, disease prevention, capacity building and comprehensive care. Nearly a decade later, countries such as Tanzania have made some implementations [74], but most lack even basic preventive measures such as penicillin prophylaxis and pneumococcal immunizations, despite established benefits. Nevertheless, it is important to emphasize the comprehensive and multidisciplinary nature of effective care for SCD, mostly lacking in SSA.

The management of patients with SCD has traditionally required non-specific care and general measures such as rest, high fluid intake and good nutrition, warm clothing in cold weather, but also the use of several therapeutic drugs ranging from analgesic (including narcotics) and anti-inflammatory drugs [75], to blood transfusion therapy, as well as managing complications.

In most settings of SSA, routine administration of folic acid during steady state is one strategy used to reduce anaemia. These patients tend to be prone to blood transfusion and up to 75% receive blood by the age of 6 years [76]. Pregnancy in SCD which is associated with worsening anaemia through plasma volume expansion and folate deficiency, intrauterine growth retardation, spontaneous abortion and pre-eclampsia, besides others, requires joint management by the haematologist and obstetrician where possible. Folate supplementation is also often routinely administered. Perioperative care in SCD varies in different settings, but again must be multidisciplinary (surgeon, anaesthetist and haematologist).

The use of hydroxyurea

The use of hydroxyurea (hydroxycarbamide) has shown very beneficial effects in reducing the frequency of painful vaso-occlusive crises, acute chest syndrome, preventing strokes and improving life expectancy [77, 78]. However, accessibility issues and other limitations make its use reduced in SSA countries [79, 80].

Role of blood transfusion in SCD

In SCD, transfusions are often required to correct anaemia, reduce the endogenous production of sickle cells and chronic haemolysis and dilute sickle haemoglobin levels. Where the oxygen-carrying capacity of blood is compromised, blood transfusions are life-saving. The main indi-

cations for blood transfusions in SCD include acute crises due to splenic sequestration, aplastic crises, folate deficiency and haemolytic crises. Chronic complications of SCD including chronic renal failure and chronic haemolytic anaemia may also require blood transfusions. A few studies in SSA suggest that about 57–80% of children with SCD required blood transfusions [76,81]. In SSA, whole blood is the major blood product used; it is now recognized by the WHO as an essential drug in these regions. It is useful in exchange transfusion and in patients needing red cell transfusions where red cell concentrates or suspensions are not available. However, there is an increased risk of circulatory overload and reactions from plasma proteins. Thus, whenever available, red cell concentrates should be preferred.

Hypertransfusion (chronic blood transfusion) regimens have proven useful in reducing the frequency of crises in homozygous SCD and preventing recurrent strokes and recurrent life-threatening acute chest syndrome, improving pregnancy outcome amongst other, in SCD [82, 83]. However, patients who receive regular transfusions run very high risks of transfusion transmissible infections, alloimmunization (blood not usually phenotyped) and iron overload. Indeed, the prevalence of alloantibodies in multitransfused patients with sickle-cell anaemia can reach 20–30% and while prevalence of HCV reaches 8% in Central and Western Africa [84–86].

Role of haematopoietic stem cell transplantation

Haematopoietic stem cell transplantation (HSCT) is curative [87], but unavailable in SSA. For example, one report of HSCT that occurred worldwide between 2006 and 2008 showed that of 146 808 transplants, only 2·7% occurred in both Africa and the eastern Mediterranean region.

Challenges and Conclusions

Prevention, care and management of SCD remain a major challenge in SSA. Co-ordinated multidisciplinary teams, including health and social workers, and non-governmental organisations are indispensable for a better impact on SCD outcome in SSA. Primary prevention of new cases of SCD through counselling services, secondary prevention of complications through early diagnosis and strategies for appropriately managing patients will not only improve quality of life in SCD in SSA, but will also reduce mortality. Local government commitments are indispensable, but also networking between regional centres of Africa, and North-South collaborations may promote better achievement in SCD care.

Conflict of interest

All authors have declared no conflict of interest.

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