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Sickle cell disease among children in Africa: An integrative literature review and global recommendations

Lucky L. Mulumba [a], Lynda Wilson [b,*]

[a] Intensive Care Unit, 60th Medical Group, Travis Air Force Base, CA, USA
[b] The University of Alabama at Birmingham School of Nursing, Birmingham, AL 35294-1210 USA

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ABSTRACT

Sickle cell disease (SCD) is a genetic blood disorder affecting red blood cells, with high morbidity and mortality rates. The United Nations has recognized SCD as a global public health concern, and the World Health Organization (WHO) recommends that 50% of member states will have established SCD control programs by 2020 (World Health Organization, 2006).

This paper presents an integrative review of 63 references related to SCD among children less than 18 years of age in Africa, published between 2000 and 2015. The review focuses on the incidence, prevalence, morbidity, and mortality; current practices and challenges related to screening, diagnosis, and treatment; and recommendations for practice, policy, and research to improve health outcomes of children with SCD in Africa.

There have been significant improvements in the morbidity and mortality rates for children with SCD in high resource countries such as the United States due to factors such as early diagnosis through newborn screening programs, prophylactic therapy, comprehensive care programs including hydroxyurea therapy, and bone marrow transplant. Many of these interventions can confer the same benefits to SCD patients in Africa. Newborn screening for SCD, developing partnerships between high resource countries and countries in Africa to support training of healthcare workers, research, and sharing of knowledge can help to reduce the SCD burden in Africa.

Contents

* Corresponding author. Tel.: +1 205 934 6787.
E-mail addresses: nlukiah@yahoo.com (L.L. Mulumba), lyndawilson@uab.edu (L. Wilson).

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1. Introduction

Sickle cell disease (SCD) is a genetic blood disorder affecting red blood cells, with high morbidity and mortality rates. Sickle haemoglobin (HbS) is a structural variant of normal adult haemoglobin (HbA) (Chakravorty & Williams, 2015). SCD includes a series of pathological genotypes resulting from the inheritance of HbS. SCD affects 20–25 million people globally, and 50–80% of infants born with SCD in Africa die before the age of 5 years (Aygun & Odame, 2012). It is estimated that 240,000 children are born with SCD annually in sub-Saharan Africa (Makani et al., 2011).

The United Nations General Assembly has recognized SCD as a global public health concern due to the morbidity and mortality caused by the disease and the significant social and economic impact that results (United Nations General Assembly, 2009). The purpose of this paper is to review the literature related to SCD among children less than 18 years of age in Africa. The review focuses on the incidence, prevalence, morbidity, and mortality of SCD among children in Africa; current practices and challenges related to screening, diagnosis, and treatment; and recommendations for practice, policy, and research to improve health outcomes of children with SCD in Africa based on the literature and on global guidelines.

The integrative review method proposed by Whittemore and Knafl (2005) guided the process used for this review. This method consists of five steps: (a) identification of the problem; (b) identification of search strategies; (c) evaluation of data quality; (d) data analysis; and (e) synthesis and presentation of the data. The inclusion criteria included full-text reports, web pages, or articles (research-based or descriptions of existing programs or policies), published between 2000 and 2015, and focused on SCD prevalence, morbidity, mortality, screening, treatment, and/or policy guidelines for children less than 18 years of age in Africa. Data-bases included in the initial search included Medline, CINAHL, PubMed, and Google Scholar, using the key words: "Sickle Cell Disease (SCD)", "Sickle Cell Anemia (SCA)", "SCA/SCD Screening, Treatment, and Policies," cross-listed with keywords "Children" and "Africa." Additional sources were identified by examining reference lists of each paper that was reviewed. A total of 63 references were identified that met inclusion criteria.

After the articles were retrieved, their strengths and limitations were assessed by both co-authors, and key concepts were identified. This paper presents a synthesis of the articles reviewed, and a discussion of implications of the findings for practice, policy, and future research. The articles were analyzed and grouped according to the following categories to facilitate the final synthesis: epidemiology, prevalence, and global health significance; mortality rates; morbidity; genetic counseling and newborn screening; management; and recommendations for policy, research, and global partnerships.

2. Epidemiology

Of the 330,000 babies born with a major hemoglobinopathy worldwide, 275,000 have SCD, making it the major global hemoglobinopathy (Aygun & Odame, 2012; Modell & Darlison, 2008; Weatherall, 2011). SCD patients in the developed world account for only 10% of the world's SCD patient population (Aygun & Odame, 2012). In 2008, Aliyu et al. (2008) reported United Nations estimates that there are between 20 and 25 million people worldwide living with SCD, of which 12–15 million live in Africa. It is estimated that 75–85% of children born with SCD are born in Africa, where mortality rates for those under age 5 range from 50% to 80% (Aygun & Odame, 2012; Makani et al., 2011).

The highest prevalence of sickle-cell trait (SCT) in Africa occurs between the latitudes of 15° North and 20° south, where the prevalence ranges between 10% and 40% of the population (Agasa et al., 2010). In 2010, Rawezula reported results of a study of records of over 2000 newborns at a hospital in Tanzania (Rwezaula, 2010). Findings indicated that 18.2% of the neonates had abnormal hemoglobin levels and that the incidence of abnormal hemoglobin levels differed based on the geographical regions of the newborns' parents. The incidence of SCT among infants whose parents were from the coastal areas was 35.6%, compared with 6.7% for infants whose parents were from the northern region.

The incidence of the SCT in Cameroon, the Democratic Republic of Congo, Gabon, Ghana, and Nigeria ranges from 20% to 30%, and in some parts of Uganda, the prevalence is 45% (Afolayan & Jolayemi, 2011; Agasa et al., 2010; Anie, Egunjobi, & Akinyanju, 2010; Serjeant & Ndugwa, 2004; World Health Organization, 2006). Chakravorty and Williams (2015) suggested that there are few places where the carrier rate for SCD is greater than 25% because of the disadvantages conferred by homozygosity.

Because many births occur outside of hospitals and many children die before diagnosis with SCD, there are limited statistical data on the incidence of SCD in Africa (Serjeant, 2010; Serjeant & Ndugwa, 2004). There is a need for additional research to gather accurate data about SCD prevalence in order to direct appropriate health care policies (Munyanganizi, Cotton, Vertongen, & Gulbis, 2006; Odunvbun, Okolo, & Rahimy, 2008). One approach to generating more accurate data about the incidence and prevalence of SCT and SCD was reported in 2010 by Piel et al. (2010), who developed a geo-statistical mapping model based on the frequency of the hemoglobin S (HBS) allele and population data.

It has been suggested that one factor associated with the high incidence of SCD in tropical Africa is the protection against Plasmodium malaria associated with having the SCT (Aygun & Odame, 2012). However, that protection seems not to extend to people with SCD (Komba et al., 2009; Rahimy et al., 2003). The theory that the SCT offers some immunity against the malaria parasite was found to be strong in tropical Africa through a geostatistical mapping study, but could not be explained in other parts of the world (Aidoo et al., 2002; Piel et al., 2010). Migration from Africa and other regions with high rates of SCT and SCD has contributed to the global spread of SCD to areas such as North America and the Caribbean (Weatherall, 2011; Wonkam et al., 2011).

3. Mortality rates

Mortality rates associated with SCD vary widely across the globe. Children born in high-resource countries with major

hemoglobinopathies (including SCD) have higher chances of survival and lower mortality rates than those born in poor resourced countries (Aygun & Odame, 2012). The higher life expectancies for SCD patients in high resource countries may be due to earlier diagnosis, greater access to care, education of caregivers, and better disease management (Aygun & Odame, 2012; Modell & Darlison, 2008). The life expectancy for people with SCD in the United States (U.S.) is 42 and 48 years for men and women, respectively. Quinn and colleagues (Quinn, Rogers, McCavit, & Buchanan, 2010) reported a 93.9% survival to adulthood of children diagnosed with SCD who were followed in Dallas, Texas (Quinn et al., 2010). In Jamaica, life expectancy stands at 53 and 58.5 years for men and women, respectively (Wierenga, Hambleton, & Lewis, 2001).

In contrast, in 2010 Aygun and Odame reported estimates that 50–80% of children born with SCD in Africa die before the age of 5 years (Aygun & Odame, 2012), although accurate statistics are often not available (Grosse et al., 2011; Serjeant & Ndugwa, 2003). The high mortality rates in Sub-Saharan Africa are influenced by multiple factors including limited resources leading to poor access to care, and lack of comprehensive SCD management programs. Interventions that have been effective in reducing mortality among SCD patients in high resource countries such as newborn screening, and prophylactic penicillin administration are not available in most low resource countries (Odame, 2010).

4. Morbidity

The disease process in SCD causes complications in multiple body organs. Some of the most common morbidities associated with SCD include chronic pain and intermittent painful episodes, musculoskeletal problems, stroke, pulmonary hypertension, and septicemia. These complications often co-exist, affecting the quality of life for patients, and if untreated, they may lead to death.

Pain associated with vaso-occlusive crises is due to microvascular occlusions triggering the activation of nociceptive afferent nerve fibers (Stuart & Nagel, 2004). Children younger than 3 years are prone to painful swelling of the hands, known as hand-foot syndrome or dactylitis. Long bones and joints are often areas of necrosis leading to pain. Micro vaso-occlusion in the mesenteric blood vessels also causes intense abdominal pain (Stuart & Nagel, 2004). In 2003, Komba and colleagues published findings from a study of 236 SCD children (age 8 months–2 years) in Benin, and reported that that 77.5% experienced painful vaso-occlusive crises, with an average of 3.3 episodes per patient.

Many children with SCD experience musculoskeletal complications due to avascular necrosis, osteomyelitis, and septic arthritis. Balogun et al. (2010) published findings in 2004 from a study of 318 SCD patients in Nigeria. Study participants ranged from 1 to 45 years of age, and 46% below age 10. These authors noted that children below age 10 years were more likely to have multiple musculoskeletal problems, and reported that among the children younger than 10 years in this study, 95% had septic arthritis, 63.3% had osteomyelitis, and 7.2% had avascular necrosis of the femoral head. Among children between 11 and 20 years of age, 46.4% had avascular necrosis of the femoral head, 30.6% had osteomyelitis, and 5% had septic arthritis.

Stroke due to vascular occlusion is one of the most serious complications of SCD (Kolapo & Vento, 2011). In high resource countries, it is estimated that the risk of developing a stroke among SCD patients is 250 times higher than for those without SCD (Makani, Williams, & Marsh, 2007). In 2009, (Verduzco & Nathan, 2009) reported findings from a study in the U.S. indicating that 24% of patients with SCD suffer a stroke by the age of 45 years. In 2001, Makani, Williams and Marsh estimated that the rate may even be higher in Africa due to the high prevalence of several risk factors including low hemoglobin, leukocytosis, and the Bantu haplotype (Makani et al., 2007). Recommended stroke prevention interventions include screening using the Trans-cranial Doppler assessments and chronic blood transfusions for higher risk patients (Stuart & Nagel, 2004), but these interventions may not be available to patients in Africa due to limited care accessibility. Makani et al. (2007) identified the need for more studies to document the scope and risk factors for stroke among children with SCD in Africa.

Pulmonary hypertension (PH) results from the chronic hemolysis that occurs with SCD. This complication affects 30% of patients with SCD in the U.S. with a mortality rate of 40% within 40 months of diagnosis (Aliyu et al., 2008). Although most information about PH in SCD patients is derived from studies on adults, new evidence suggests that PH is also a problem in the pediatric population (Aliyu et al., 2008). Although data about the incidence of PH among children in Africa is limited, the high incidence of known infectious risk factors for PH (HIV/AIDS, Hepatitis B and C, and malaria), may contribute to high rates of this complication in Africa (Battersby, Knox-Macaulay, & Carrol, 2010; Serjeant, 2005; Williams et al., 2009).

Findings reported in articles published from 2005 to 2010 indicate that bacterial infections leading to septicemia are also major causes of morbidity and mortality for children with SCD in Africa, particularly those below age 2 years (Battersby et al., 2010; Obaro, 2010; Serjeant, 2005; Williams et al., 2009). Children with SCD are more likely to suffer from pneumococcal disease than those who do not have SCD (Battersby et al., 2010; Obaro, 2010; Williams et al., 2009). Even though *Streptococcus pneumoniae* is the widely causative agent of infections in SCD children, findings from studies published in 2005 and 2010 suggest that bacteremia in African children with SCD may be caused by other bacteria (Battersby et al., 2010; Obaro, 2010; Serjeant, 2005). In 2007, Kizito, Mworozi, Ndugwa, and Serjeant (2007) reported findings from a study of 155 children with SCD in Uganda, indicating that *Staphylococcus aureus* accounted for 60% of the 47 positive blood cultures. Other organisms identified included *Haemophilus influenza*, *Staphylococcus epidermis*, *S. pneumonia*, *Streptococcus viridans*, and *Escherichia coli*. In 2010, Battersby et al. reported that septicemia due to *nontyphi Salmonella* species and *Klebsiella* species was the most common cause of death in children below 5 years of age with SCD in Nigeria (Battersby et al., 2010). In 2009, Williams et al. reported findings from a study of 1749 children with SCD younger than 14 years in Kenya (Williams et al., 2009). Findings from this study indicated that the most common causes of bacterial infection were *S. pneumonia* (41%), *non-Typhus Salmonella* (18%), and *Haemophilus influenza* (12%). Other causative organisms included *Acinetobacte*r species (7%) and *E. coli* (7%). The findings from these studies suggest that the types of bacteria causing infections in children with SCD differ from country to country. In 2007, Kizito and colleagues emphasized the importance of identifying the organism causing bacterial infections in order to develop effective management strategies (Kizito et al., 2007). In 2005, Sergeant questioned the effectiveness of pneumococcal prophylaxis in SCD children in Africa where there is infrequent isolation of *S. pneumonia* (Serjeant, 2005).

A final complication of SCA and SCD that may contribute to both morbidity and mortality is malaria. In 2009, Komba and colleagues published findings from a study conducted in Kenya to examine the prevalence and outcome of malarial infections among children (ages 0–11 years) admitted to a hospital in Kenya from 1998 to 2005 (Komba et al., 2009). The authors noted that although it has long been assumed that malarial infection is a major cause of morbidity and mortality among SCD patients, findings from this study indicated that the incidence of malarial parasitemia was lower among children among children with SCD compared to children

without SCD. In 2010, Makani and colleagues reported similar findings from a prospective surveillance study conducted in Tanzania between 2004 and 2009 (Makani et al., 2010), Findings from this study indicated that the prevalence of malarial parasitemia was lower in patients with SCA than patients without SCA. However, among patients who were hospitalized, parasitemia was associated with higher mortality rates. Makani and colleagues stressed the importance of effective treatment for malaria during hospitalizations among SCA patients, and both groups of researchers identified the need for further studies to guide policy about malarial prophylaxis for SCD patients in Africa (Komba et al., 2009; Makani et al., 2010).

5. Prevention, neonatal screening, and treatment strategies

Effective management of SCD revolves around genetic counselling, neonatal screening and early diagnosis; prophylaxis with immunizations; providing anti-malarial medications, antibiotics, and hydroxyurea; and prompt management of complications. Bone marrow transplantation in a selected segment of patients is the only proven cure for SCD to date (Walters et al., 2001), but this is an expensive treatment and in 2004 Sergeant and Ndugwa noted that this option is not feasible as a public health approach in low resource countries (Serjeant & Ndugwa, 2004).

6. Genetic screening and counselling

Several authors have suggested that prenatal screening and diagnosis could reduce the burden of haemoglobinopathies in poor resource countries (Kafando, Sawadogo, Cotton, Vertongen, & Gulbis, 2005; Weatherall, 2011). In 2008, Modell and Darlison suggested that the use of genetic epidemiological data can help to assess SCD health care needs (Modell & Darlison, 2008). In 2006, the World Health Organization (WHO) identified a variety of medical genetic screening programs that are appropriate for low- and middle-income countries and that could help to reduce the incidence of SCD (World Health Organization, 2006). These programs include carrier identification using family pedigrees and screening tests, and postnatal screening for sickle cell disorders. The success of SCD prevention through heterozygote detection and premarital screening is influenced by the knowledge and attitudes of health care providers and community members about SCD and its treatment (Abioye-Kuteyi, Oyegbade, Bello, & Osakwe, 2009). In 2009, Abioye-Kuteyi et al., 2009 reported results of a survey of 320 government workers in Nigeria. Findings indicated that 69% had poor knowledge about SCD, although 95% had positive attitudes towards premarital screening. These researchers also reported that 86.7% of respondents and 74% of their partners had had sickle cell screening. Although 25% of the married and engaged respondents did not know their partner's sickle cell status, 33–66% indicated that they would continue the relationship with their partner if either or both had haemoglobinopathy (Abioye-Kuteyi et al., 2009).

Prenatal genetic testing as a means of prevention and control of genetic diseases including SCD has been suggested as one of the effective ways of eradicating genetic haemoglobinopathies. However, in 2006, Ahmed, Atkin, Hewison and Green noted that such testing may result in ethical and moral challenges because positive results may suggest termination of the pregnancy (Ahmed, Atkin, Hewison, & Green, 2006). In 2005, Animasahun, Akitoye and Njokanma reported findings from a cross-sectional survey of health workers at a teaching hospital in Nigeria. Although 91.3% had heard about SCD prenatal screening, only 75.3% knew that SCD could be prevented by prenatal screening. A total of 48.2% of these health workers were not aware that prenatal screening was available in Nigeria; and 42.1% would not allow preventive termination of pregnancy for positive screening results (Animasahun, Akitoye, & Njokanma, 2009).

In 2011, Wonkam et al. (2011) reported a high level of acceptability of pre-natal diagnosis and pregnancy termination for SCD among Cameroonians parents, even though Cameroon had not implemented a national SCD control program (Wonkam et al., 2011).

7. Neonatal screening

In 2008, Tshilolo and colleagues noted that in high resource countries where newborn screening has been introduced, patients are enrolled into comprehensive care programs resulting in better outcomes than in lower resource countries without comprehensive screening programs (Tshilolo et al., 2008). In 2003, Rahimy and colleagues suggested that the introduction of newborn screening in the developed world 20 years ago has cut down the mortality rate for SCD from 16% to >1% (Rahimy et al., 2003). Early neonatal screening for SCD enables the implementation of a comprehensive care approach including prophylactic treatment, parental education, and initiation of a tracking and follow-up program for identified patients (Grosse et al., 2011; Ohene-Frempong, Bonney, Tetteh, & Nkrumah, 2005; Ohene-Frempong, Oduro, Tetteh, & Nkrumah, 2008).

In low resource countries, access to newborn screening for SCD or SCT is limited because of economic constraints. In 2008, Odunvbun, Okolo, and Rahimy (2008) reported that despite the huge SCD burden in Africa and the advantages associated with newborn screening in the management of SCD, Benin and Ghana are the only two countries in Africa that have comprehensive newborn screening programs. The program in Benin is however targeted at mothers with the SCT (Odunvbun et al., 2008).

A number of studies have been conducted to assess the efficacy of newborn screening in Africa including studies in Nigeria (Odunvbun et al., 2008); the Democratic Republic of Congo (Tshilolo et al., 2009), and Ghana (Bosu, 2012). In 2008, Odunvbun, Okolo and Rahimy suggested that newborn screening would be widely accepted by parents in Nigeria (Odunvbun et al., 2008). Better management protocols including early screening and comprehensive care may reduce mortality rate among children with SCD in Africa. In 2012, Piel and colleagues recommended utilization of global mapping to track the findings from neonatal screening programs may provide important data on the incidence and prevalence of the disease in low-resource settings, thus promoting targeted interventions and services and more effective use of scarce resources (Piel et al., 2012).

8. Prophylaxis treatments

In 2009, Obaro noted that the high rate of child mortality due to invasive bacteria in SCD children in Sub-Saharan Africa has not received global international attention, however use of childhood immunizations could reduce the incidence of this problem (Obaro, 2009). Children with SCD need to receive routine immunizations based on the country-specific guidelines. In 2007, Makani, Williams and Marsh noted that pneumococcal vaccinations and prophylaxis using penicillin has increased survival rates among children in the developed world (Makani et al., 2007). In 2012, Aygun and Odame (2012) noted that improved immunization and better nutrition programs in many countries has improved survival among children with SCD. In 2010, Obaro suggested that development of vaccines against *non-Typhi Salmonellae* may reduce childhood mortality in SCD (Obaro, 2010).

Cox and colleagues (in 2011) reported that introduction of targeted interventions like penicillin prophylaxis and *Pneumococcal*

vaccinations in the developed world has increased survival to 18 years of age to 94% in the U.S. and 99% in the United Kingdom (Cox et al., 2011). There is disagreement among experts, however, as to whether penicillin prophylaxis and pneumococcal vaccination are effective in Africa since some studies have shown that bacteremia in most African countries is not caused by *S. pneumonia*. In 2005, Serjeant (2005) described results from studies conducted in Nigeria and Uganda, which indicated that *S. pneumonia* was responsible for only 10% of all septicemias, with *Staphylococci*, *E. coli* and *Klebsiella* responsible for the majority of septicemias. Children with SCD below 2 years are 600 times more susceptible to invasive *Pneumococcal* disease than children without SCD. In 2009, Battersby and colleagues reported that bacteria-related septicemia is responsible for many SCD-related deaths. *Pneumococcal* vaccine and antibiotic prophylaxis forms the backbone of septicemia prevention (Battersby et al., 2010). These authors suggested that febrile SCD patients suspected of bacteremia should have blood cultures to identify the causative organism, and prompt initiation of appropriate antibiotic therapy (Battersby et al., 2010).

9. Malaria prophylaxis

In 2007, Makani et al. (2007) noted that although it was widely believed that malaria was a major cause of hospital admission and mortality among SCD patients in sub-Saharan Africa, there was a need to review the evidence about which drugs should be recommended for long-term prophylaxis among SCD patients. In 2012, Aygun and Odame acknowledged that further research is needed to clarify the role of malaria as a cause of morbidity and mortality in SCD patients, but advised that the use of insecticide-treated bednets along with anti-malarial prophylaxis during high risk seasons may be useful (Aygun & Odame, 2012).

10. Hydroxyurea treatment

Aygun and Odame reported in 2012 that Hydroxyurea therapy has been used for the treatment of SCD in the United States and Europe for over 25 years; with proven effectiveness in the reduction of acute painful episodes (Aygun & Odame, 2012). Hydroxyurea works by increasing fetal hemoglobin, and increasing water content of red blood cells resulting in less cell deformity and adhesion to the endothelium. It is also believed to have anti-hemolytic properties (Aliyu et al., 2008; Aneni, Hamer, & Gill, 2013; Stuart & Nagel, 2004). Hydroxyurea also reduces hepatic sequestration and priapism reducing the need for blood transfusion; and lowers mortality from SCD related complications by 40% (Aliyu et al., 2008). In 2013, Aneni, Hamer, and Gill published a systematic review of strategies for reducing morbidity from malaria in SCD, including the use of hydroxyurea to reduce malaria-associated morbidity and mortality in SCD patients. These authors noted that most studies of hydroxyurea have been conducted in non-malarious regions, and there is little information on its use in malaria endemic areas. These authors noted that hydroxyurea actually upregulates the intercellular molecule receptor for adhesion of malarial-infected red blood cells and thus theoretically its use could enhance replication of malaria cells. However hydroxyurea also increases fetal hemoglobin levels which protect against malaria. In 2004, Stuart and Nagel (2004) suggested that infants and children with SCD who are at greatest risk for negative outcomes (e.g. those with hand and foot syndrome, severe anemia, or a history of a stroke) should be considered for hydroxyurea therapy. In 2015, Chakravoty and Williams reported that although hydroxyurea is the only agent that has been found to reduce the number of painful sickle cell crises in infants, children, and adults with SCD, it is not widely used due to patient and provider uncertainties about its risks and benefits (Chakravorty & Williams, 2015). There is clearly a need for further research to evaluate the use of hydroxyurea for children in Africa, particularly those who live in areas with a high prevalence of malaria.

11. Traditional Herbal Remedies

In 2005, Akinyanju, Otaigbe and Ibidapo reported that the use of traditional herbal remedies in the management of SCD is common practice in poor resourced countries such as Nigeria, where access to care is limited and the population is predominantly rural (Akinyanju, Otaigbe, & Ibidapo, 2005). In 2008, Okpuzor, Adebesin, Ogbunugafor, and Amadi (2008) reviewed medicinal plants with potential anti-sickling properties that have been used in low resource countries and described research that has been conducted to identify their beneficial effects. There is a need for further studies on efficacy and effectiveness of these remedies (Akinyanju et al., 2005). Such studies can be facilitated through partnerships between healers with knowledge of herbal remedies, and research organizations. One example of such a partnership is the development of NIPRISAN by collaboration between the National Institute for Pharmaceutical Research and Development (NIPRD) in Nigeria and members of the local communities with knowledge of herbal remedies. NIPRISAN is a phytomedicine that was developed to manage SCD by NIPRD from local plants including Piper Guineese and Eugenia Caryophllate that have been used by the Yoruba people to treat SCD. In a 2001 report of a double blind, placebo controlled, randomized cross over clinical and laboratory study, NIPRISAN was found to be safe and effective in lessening the frequency of severely painful episodes (Wambebe et al., 2001). In 2012, Ameh, Tarfa and Ebeshi reported that other medicines were under development at NIPRD (Ameh, Tarfa, & Ebeshi, 2012).

12. Treatment of anemia

Anemia is a major cause of morbidity and mortality in SCD, and many patients die in hospital emergency rooms and wards before blood transfusions can be initiated. In 2007 Ikefuna and Emodi reported results from a study of 71 children hospitalized for SCD in Nigeria (Ikefuna & Emodi, 2007). Findings indicated that 39.4% had severe anemia, and that most cases were related to aplastic, acute sequestration, hyper-hemolytic and vasculo-occlusive crises. The authors suggested, however, that it was important to assess for other causes of anemia in SCD patients including malaria parasitemia and septicemia.

In 2004, Stewart and Nagel reported that blood transfusions in SCD are routinely done either as an interim intervention to correct anemia or hypovolemia, or as a chronic therapy to prevent stroke (Stuart & Nagel, 2004). Indications for transfusion therapy include: chronic splenic sequestration; severe or lasting aplastic crises; acute stroke; acute chest syndrome; and hemolytic episodes associated with malaria. Indications for chronic transfusions are stroke prevention and chronic pulmonary hypertension (Aliyu et al., 2008; Kolapo & Vento, 2011; Stuart & Nagel, 2004). In order to prevent iron overload due to chronic transfusions, chelation may be indicated. In 2007, Makani, Williams and Marsh noted that the use of blood transfusions in Sub-Saharan Africa is restricted due to the limited supply of blood, and potential HIV infection due to poor blood screening (Makani et al., 2007). Sergeant cautioned that limited human and diagnostic resources in many African settings result in failure to properly investigate the causes of anemia, and use of tansfusions when these may not be indicated. Sergeant further suggested that reticulocyte counts and red blood cell indices

can help to diagnose iron or folate deficiency which can be treated more appropriately by iron or folic acid, instead of by blood transfusion (G. Sergeant, Personal Communication, December 1, 2014).

13. Treatment of vaso-occlusive crises

Vaso-occlusive crises are also known as pain crises, and these crises are the major reason for visits to the emergency rooms by children with SCD. These painful episodes arise as a result of microvascular occlusions in bone marrow leading to necrosis (Stuart & Nagel, 2004). Common sites of pain include long bones, ribs, sternum spine and pelvis (Sadarangani et al., 2009; Stuart & Nagel, 2004). In children younger than 3 years, acute hand-foot syndrome which involves painful swelling of the hands and feet is common. There are also abdominal painful episodes due to the micro-vascular occlusion in the mesenteric vessels coupled with decreased intestinal motility (Stuart & Nagel, 2004). Mild to moderate painful episodes may be treated at home using nonsteroidal anti-inflammatory drugs (NSAIDs), or opioids. Severe pain episodes requiring hospitalization are treated with continuous parental opioids. In 2004, Stewart and Nagel cautioned that although hydroxyurea therapy has been found to be effective in patients with frequent severe occlusive episodes, further research was needed and that the drug should only be given in an environment where medical care was available and compliance could be monitored (Stuart & Nagel, 2004).

14. Prevention of stroke

Stroke is the occlusion in the cerebral microvasculation and is another common cause of morbidity among SCD patients. In 2011, Kolapo and Vento reported that stroke is an increasing problem in sub-Saharan Africa in both adults and children, and noted that one of the factors contributing to this problem is SCD (Kolapo & Vento, 2011). In 2011, Weather all reported that prevention strategies of using regular screening and blood transfusion have brought down complications related to stroke (Weatherall, 2011). In 2004, Stewart and Nagel suggested the use of transcranial Doppler screening every year for children from 2 to 16 years of age who have SCD as a strategy to identify those at risk for stroke (Stuart & Nagel, 2004).

15. Treatment of infection

In a 2010 review of studies related to bacterial infections in children with SCD, Battersby, Knox-Macaulay and Carrol noted that a major reason for the increased susceptibility is due to splenic dysfunction (Battersby et al., 2010). These authors acknowledged the need for further research to study the benefits of treatments such as penicillin prophylaxis and pneumococcal vaccines in Africa. Nevertheless, these authors recommended that when children with SCD present to the emergency room with a fever, a broad spectrum antibiotic should be started as soon as blood and urine specimen have been obtained for culture purposes.

16. Management of spleen dysfunction

Battersby and colleagues (2010) noted that functional asplenia is present in about 50% of SCD children below the age of 2 years, and is due to sluggish splenic blood flow which leads to shunting of the splenic blood flow, bypassing the spleen's normal filtration function. In older children, asplenia is usually caused by repeated splenic infarction (Battersby et al., 2010). Hypovolemia caused by spleen sequestration requires prompt blood transfusion. In 2004, Stewart and Nagel recommended splenectomy following the first episode of acute spleen sequestration for children over the ages of 2–3 years (Stuart & Nagel, 2004). In 2008, Hankins and colleagues reported findings from a study of 43 children with SCA who were treated with hydroxyurea. The study was conducted in the U.S., and the authors concluded that use of hydroxyurea at the maximum tolerated dose may preserve spleen and brain function in children with SCA.

17. Recommendations for comprehensive SCD treatment programs

The decrease in morbidity and mortality among SCD children in low-resource countries is partly attributed to the presence of comprehensive care programs that include immunizations and vaccinations, prophylaxis therapy, vitamin supplements and patient and caregiver empowerment through education (Rahimy et al., 2003). In 2011, Cox and colleagues suggested that because SCD is associated with a high prevalence of malnutrition and stunting particularly among adolescents (Cox et al., 2011), comprehensive programs should also include nutrition education.

In 2003, Rahimy et al. (2003) reported findings from an evaluation of a comprehensive program in Benin that included provision of parent education about the SCD disease process and factors that may lead to acute SCD events. The education addressed topics such as the importance of hydration, providing adequate nutrition, spleen palpation, and other strategies to identify symptoms of acute SCD complications. Other interventions included providing recommended vaccinations and anti-pneumococcal and antimalarial prophylaxis. Findings indicated a 78% reduction in the frequency and severity of SCD-related acute events, as well as improvement in general status and physical growth.

In 2005, Akinyanju and colleagues reported findings from evaluation of a holistic program provided to 1223 SCD patients in Nigeria that included malaria prophylaxis, health and nutrition education, provision of folic acid and vitamin C, prompt attention for acute illnesses, and a support club for patients and their families. These authors reported a decrease in hospital admissions, mortality rate, and number of patients requiring blood transfusions over a 7 year period (Akinyanju et al., 2005).

18. Practice, policy, and research recommendation

In 2009, the members of the United Nations General Assembly passed a resolution declaring SCD as a major public health concern (United Nations General Assembly, 2009). In 2012, Bosu (2012) suggested the need for governmental policies and standards to address SCD that focus on health system strengthening. The WHO Regional Office for Africa has recommended the need for developing national SCD control programs that include advocacy, prevention and counseling, early detection, treatment, surveillance, research, and community education and partnerships (World Health Organization Regional Office for Africa, 2015). Others have suggested that policies should also provide for screening and genetic counseling for hemoglobin disorders (Modell & Darlison, 2008; Ohene-Frempong et al., 2005; Tshilolo et al., 2008). In 2008, Modell and Darlison recommended that policies should address strategies to ensure that members of the public and healthcare workers in Africa are informed about the importance of genetic testing, newborn screening, and management of children SCD (Modell & Darlison, 2008).

In 2010, Odame reported that participants at an international symposium and workshop on SCD in Benin noted that Hydroxyurea therapy is provided infrequently in Africa, yet its effectiveness in the management of SCD has been demonstrated in high resource countries (Odame, 2010). Odame also noted that other

interventions such as bone marrow transplantation and chronic blood transfusion are either limited or not used at all, leaving hydroxyurea to be a more viable option. For this therapy to succeed however, certain barriers may have to be addressed including adequate funding, and training of healthcare staff (Odame, 2010).

In 2015, Chakravorty and Williams (2014) recommended advocacy by influential groups such as celebrities and politicians, and the development of inexpensive and reliable point of care diagnostic methods. In addition, these authors recommended increased education about SCD in schools and colleges.

19. Recommendations for future research

There is a need for ongoing research related to SCD among children in Africa. Primary research priorities that have been identified in the literature include research to identify strategies to provide SCD education and screening (Abioye-Kuteyi et al., 2009), provide reliable data on SCD prevalence in Africa (Odame, 2010), identify the relationship between malaria and SCD mortality, and evaluate the use of antimalarial prophylaxis (Makani et al., 2007), pneumococcal vaccines, and penicillin prophylaxis (Komba et al., 2009). Although these vaccines have improved outcomes in developed countries where *S. pneumonia* is the major causative agent for bacterial infection, there is conflicting data in Sub-Saharan Africa about the organisms responsible for bacterial infections (Williams et al., 2009).

20. Developing partnerships to address SCD in Africa

In 2012, Aygun and Odame (2012) identified the need for greater international cooperation and partnerships to facilitate access to education, management, surveillance and treatment of SCD. These authors identified the potential role of partnerships between industry and academic health centers, and acknowledged that each country should develop their own programs based on their unique needs. Participants in the 2009 Sickle Cell Symposium in Benin agreed that global partnerships were essential for better clinical care and study of the disease, and recommended establishment of a global SCD network to foster global community and advance the clinical care and study of patients with SCD (Odame, 2010).

21. Summary and conclusions

It has been over a hundred years since the first SCD formal diagnosis from a dental student from Granada was made by Dr. James Herrick in Chicago (Serjeant, 2010). SCD has since ravaged the world in particular amongst people of African and Mediterranean heritage. The management and treatment of SCD in high resource countries has greatly improved. Life expectancy for people with SCD in Jamaica was reported at 53 years for men and slightly over 58 for women back in 2001 (Aygun & Odame, 2012). In 2012, Aygun and Odame reported that mortality from SCD among children in the U.S. has also greatly decreased with reports of patients reaching 18 years of age at 93.9% (Aygun & Odame, 2012). These results have been realized due to a number of advances in the management and treatment of SCD including early diagnosis through newborn screening programs, prophylactic therapy for encapsulated bacteria, comprehensive care programs including education to caregivers, hydroxyurea therapy, and bone marrow transplant.

Although it is important to be careful in transplanting wholly some of the interventions that have worked in high resource countries, many of these interventions can confer the same benefits to SCD patients in Africa. Newborn screening for SCD, developing partnerships between high resource countries and countries in Africa to support training of healthcare workers, research, and sharing of knowledge can help to reduce the SCD burden in Africa. Improvements in health policies are also needed, including increased funding for SCD programs, and establishment of comprehensive care programs encompassing nutrition, caregiver education, prevention and management of complications, use of hydroxyurea, and eventually, availability of bone marrow transplantation will assist in reducing morbidity and mortality related to SCD among children in Africa. As noted by Serjeant in 2005 "We cannot yet cure sickle cell disease, but we have learnt that simple interventions significantly improve morbidity and mortality. We need to extend these benefits to African patients urgently" (Serjeant, 2005).

Conflict of interest

None declared.

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