

Sickle Cell Disease: Current Challenges

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Abstract

Sickle cell disease (SCD) is one of the most common monogenic diseases worldwide. Although there have been some advances in the management of SCD, much remains to be learned about the mechanisms underlying the wide phenotypic diversity of the disease. In resource poor countries, basic facilities for diagnosis and management are lacking, systematic screening is not common practice, and diagnosis is made late. Common and important morbidities associated with SCD are vaso-occlusive episodes, infections, acute chest syndrome, stroke and hip necrosis. These morbidities are often not managed effectively due to lack of proper infrastructure, expertise, and economical burden. Inadequate laboratory facilities and prenatal diagnostic services hamper proper management of disease complications as well as prevention. Newborn screening is yet to be implemented at national level in countries like India. Population screening programs are not universally undertaken, and some of the diagnostic strategies used have limitations. Advanced therapeutics like bone marrow transplantation are expensive, and gene therapy and stem cell therapy are still at an experimental stage. Emphasis should be placed on early counseling, newborn screening, anti-microbial prophylaxis, vaccination against infections and training of healthcare workers, patients and caregivers. Natural history of sickle cell disease in specific geographic areas like Africa and India is still unknown, where infections, malaria and malnutrition are key factors affecting the outcome. Further, in these countries, management guidelines used have been largely extrapolated from resourceful countries where most of the research has been done. There is need to develop tailor made guidelines for specific countries and areas. Global burden of SCD is rising, highlighting the need to develop specific prevention and management related national policies for appropriate public health planning. In resource poor countries where SCD is a major public health concern, basic facilities for management are usually not available, systematic screening is not common practice and diagnosis is usually made late, when patients present with severe complications. This article highlights the challenges faced at all levels including patients, relatives, health care personnel, international health organizations, and government health policy makers.

Keywords: Sickle cell disease; Resource poor countries; Clinical heterogeneity; Challenges in diagnosis; Prevention

Introduction

Sickle cell disease (SCD) affects millions throughout the world. It is particularly common among people whose ancestors come from Sub-Saharan Africa, South America, Cuba, Central America, Saudi Arabia, India, and Mediterranean countries such as Turkey, Greece, and Italy [1,2]. Prevalence of sickle cell trait varies markedly between different regions but reaches levels as high as 40% in some areas of sub-Saharan Africa, eastern Saudi Arabia, and central India [3,4]. Population migrations to North America, Brazil, Caribbean, Central America, and Europe account for the variable frequencies of SCD in these regions. Although WHO has estimated that each year 220,000 babies (this may be an underestimate) are born with SCD in Africa, and that SCD accounts for up to 16% of deaths of children aged <5 years in some African countries, very little is known about the overall global burden of SCD [5,6]. The magnitude of the problem is set to rise as a consequence of improved survival in high-prevalence low- and middle-income countries and population migration to low prevalence higher-income countries [2]. In some European countries, SCD has now overtaken more familiar genetic conditions such as haemophilia and cystic fibrosis. In 2013 it resulted in 176,000 deaths, a figure much

higher than 113,000 deaths in 1990. Despite being a major health problem of massive public health significance, it has not been studied extensively at the global level especially in Africa and India, which are the epicenters of SCD burden [7]. The host of quantitative evidence documenting other changes like migration, population epidemiology, and exact prevalence has not been assembled. It's been amply clear that life expectancy of SCD patients in developed countries could approach that of those without SCD, when managed appropriately. Between 2005 and 2008, SCD was declared as a public health priority issue worldwide [7]. In 2006, WHO recommended that African states should include the fight against SCD in their health policies. Nevertheless, there are yet no data on effective strategies to implement SCD control programs in these countries. Although there are multiple constraints, there is a need for an organized network of health professionals working in sickle cell referral centers with specific missions of research, communication, and teaching, establishment of guidelines for diagnosis, treatment, and prevention. These centres of competence should focus primarily on screening, diagnosis, and management of SCD patients favoring equality in access to care.

Currently there are multiple challenges being faced by patients and their family members, health care providers, public health planning experts, international collaboration agencies. This commentary focuses on the many such burning issues with respect to diagnosis, management, counseling and socio-behavioral aspects, and solutions

available to health care professionals in both resourceful and low resource countries in caring for patients with SCD. Identifying the challenges in each arena and specifically targeting to formulate strategies to circumvent the challenges could go a long way in dealing with SCD burden at global level and reducing the heavy load of mortality and morbidity due to SCD. The challenges can be further classified into different domains for better understanding and to lay special emphasis.

Clinical Heterogeneity and Challenges

About 7% of the world's population are carriers of some form of a hemoglobin disorder. There are about 270 million carriers of sickle cell anemia and/or thalassemia [4,8]. There is considerable diversity in phenotypic expression even though the genotype is same. Reflecting both genetic and environmental factors is variability of SS disease in different geographic areas [3,7]. In eastern province of Saudi Arabia and central India, the Asian haplotype appears to be associated with less hemolysis, greater persistence of splenomegaly, generally more mild clinical features, and probably longer survival although the extent to which this is due to haplotype or to the commonly co inherited genes for α -thalassemia and persistence of HbF production remains unclear [3,4]. Although the same sickle mutation in the β -globin gene is responsible for the diverse spectrum of pathophysiology of the sickling disorders, clinical manifestations of the disease are extremely heterogeneous. Many factors that contribute to this heterogeneity, such as an interaction with β C gene and β -thalassemia gene, are well known [9]. Other factors such as Hb F levels and coinheritation of α -thalassemia have also been known to modulate clinical severity of sickling disorders for many years. Although sickle cell anemia is believed to be milder in India due to presence of the Arab-Indian haplotype, retrospective analysis of long follow-up of 316 children with sickle cell anemia in central India has shown that the clinical presentation in significant proportion of patients is severe and in some patients similar to African patients [10]. As is the case with coinheritation of α -thalassemia, various geographical, environmental, community, racial and few genetic determinants might increase the risk of some complications and decrease the risk of others [9]. Local bacteriological flora differs significantly in resourceful and resource poor countries, hence pattern of infections is different. Such clinical heterogeneity makes it difficult to make universal therapeutic guidelines at global platform such as indications for hydroxyurea, special vaccinations, chelation therapy, and penicillin prophylaxis. Pain management too differs as clinical pain episodes may differ in terms of severity, societal perception, and local non pharmacologic customs of pain control [11]. Barriers exist in measuring pain objectively and hence its management [5]. Also, clinical presentation of SCD is quite variable with no fixed pattern of symptoms and signs. There are no pointers towards diagnosis of SCD with respect to specific community, geographic region, race, or age. Unlike many other disease patterns, varied clinical spectrum of SCD can't be related to specific age groups. This poses difficulty for peripheral health workers while identifying probable suspected SCD children in community.

Diagnostic Challenges

Weak laboratory support and infrastructure in resource poor countries does not allow clinicians to make complete and confirmatory diagnosis of causes of anemia. It is important to always evaluate reticulocyte count, full blood counts, peripheral blood smear and electrophoresis or high performance liquid chromatography (HPLC)

findings along with parental studies for arriving at a diagnosis of SCD in patients. Diagnosis of the cause of severe anemia in SCD is based on history, physical examination and limited laboratory results in most hospital settings in sub-saharan Africa and India [12]. In most laboratories, reticulocyte counts are never done or the results are unduly delayed and this puts clinicians in a dilemma with regards to management. There is a lack of universal population screening program strategies, or worse, poor implementation of screening methods where they exist. However, in some states in India screening for sickle cell disorders is now being done extensively. Lack of initiative on the part of the government or poor collaboration with health agencies hampers prospects of good implementation. Generally, solubility test is used as a first line screening test. It has some limitations in terms of sensitivity, predictive value, differentiating power between sickle heterozygotes and homozygotes, and also it is not suitable for infants. This calls for a better alternative. Diagnostic tests based on electrophoresis or HPLC also have certain limitations. These tests can't be performed in recently transfused children, and also may not correctly differentiate between sickle cell anemia and sickle-beta thalassemia. Hence molecular diagnosis is often required for accurate diagnosis of such cases particularly when parental studies are not available. Lack of well calibrated automated hematology cell counters and HPLC analyzers in laboratories is a major concern. Effective management of infections obviously depends on availability of functional microbiology laboratories. Lack of this facility in most health institutions in poor resourced countries is a major challenge for the care of patients as infections are major determinants of mortality. Radiological facilities like neuroimaging, trans cranial doppler or even X ray machines in health care institutions to support diagnosis of stroke or acute chest syndrome or screening for stroke are usually lacking in resource limited countries at peripheral levels. Although stroke can be diagnosed clinically, brain imaging studies are necessary to distinguish infarctive from hemorrhagic stroke in order to offer appropriate intervention. Genetic approaches that consist of analysis of polymorphic variations in different genes that may increase the risk of a particular complication may help in implementing therapeutic interventions before the complications develop. But this strategy is still experimental even in resourceful countries and needs further elaborative research [1].

Prenatal Diagnosis

Prenatal diagnosis is another area with limited impact in SCD management. In spite of the fact that DNA analysis has made it possible to identify an affected fetus much earlier during pregnancy, impact of these advances on number of new births with SCD has been extremely small, even in resourceful countries. In contrast, the same technology has had great impact on number of new births with β -thalassemia in Mediterranean regions including Greece, Cyprus, and Sardinia. Although the reasons for differences in impact of the same technology in these closely related disorders have not been investigated, it is conceivable that they are a reflection of the fact that a majority of patients with β -thalassemia die from iron overload before the third decade of life, while survival of patients with SCD into the fifth, sixth, and even seventh decades is not unusual [1]. There is thus a dilemma whether fetal diagnosis and termination of affected pregnancies is needed for every couple at risk of having a child with SCD. With the advent of DNA diagnostics, it has become possible to make definitive diagnosis of different sickling disorders during first trimester of pregnancy by analyzing fetal DNA obtained from chorionic villus tissue using PCR based approaches using allele specific

priming, reverse dot blot hybridization or restriction enzyme analysis. In India, however, there is a demand for prenatal diagnosis for sickle cell disorders with around 30% of couples at risk seeking prenatal diagnosis prospectively. Major barriers for effective implementation are scarcity of trained gynecologists and sonologists for fetal tissue and fetal blood sampling as well as adequate number of centers with expertise in prenatal diagnosis in periphery. It is thus difficult for couples to travel long distances to reach to a center [13]. Molecular diagnostic technology is being pushed further to allow diagnosis to be made from small number of fetal cells or cell free fetal DNA that can be harvested from the maternal circulation [1,9,13,14]. Currently, chorionic villus sampling (CVS) in the first trimester of pregnancy or amniocentesis and fetal blood sampling in the second trimester are used to obtain fetal tissue or fetal cells for genetic diagnosis. These invasive procedures pose a small but not negligible risk to the fetus. Efforts have been directed towards enrichment of fetal cells, such as erythroblasts, from maternal blood and progress has been made in diagnosis of some chromosomal disorders and in sex determination [13,14]. However, for single gene disorders like SCD and the thalassemias, non-invasive fetal diagnosis is still a challenge even in developed countries. Pre-implantation genetic diagnosis (PGD) is another option but not a replacement for prenatal diagnosis. It is mainly applicable to those couples where termination of an affected pregnancy is not acceptable or when couples have repeatedly had sickle homozygous children. PGD requires collaboration between a good in-vitro fertilization centre and a competent molecular biology laboratory capable of doing single cell analysis. This option is really not a choice for majority of couples at risk of having a child with SCD. It is also beyond the reach of most of the families in resource poor countries.

Newborn Screening

There are well-established criteria for development of neonatal screening programs for SCD in sub-Saharan African and some Asian countries. In particular, in regions where incidence of disease is 0.5 per 1000 or higher, sickle cell screening program can be proposed that includes systematic screening of all newborns, or targeted screening newborns of mothers with sickle cell or hemoglobin C trait [2,11]. Currently very few countries have adopted nationwide newborn screening programs and there is lack of facilities to undertake these programs in many resource limited countries [14]. In few regions in India, newborn screening programs have been well established both for tribal and non-tribal populations having a high prevalence of sickle cell disorders and these cohorts are being monitored to understand the natural history of SCD [15,16]. As in high-income countries, biggest challenge in newborn screening programs is follow-up component [5].

Management Challenges

Vaso-occlusive crises

Long-term use of analgesics poses major challenges and complications. Patients develop gastric erosion and ulcers or even analgesic nephropathy with NSAIDs [17]. Clinicians are also confronted with side effect of the long-term use of opioids like pethidine, codeine and morphine in management of pain without significantly causing respiratory depression with parenteral use and tolerance with long term use [11,12]. Hence opioids should be used with caution for the fear of respiratory depression as well as development of tolerance. Option of hydroxyurea to ameliorate vaso-occlusive episodes should be exercised judiciously. However, benefits of

low dose hydroxyurea have been demonstrated in different regions in India in SCD patients having the Arab-Indian haplotype [18]. There are several other behavioral and non-medicinal therapies that are also available for the management of pain.

Infections

Availability of proper antibiotics plays an important role in making an appropriate choice. Physicians in resource poor countries are sometimes limited in their choices [17]. Delays in treatment for bacterial infections and for malaria in children in endemic areas could lead to fatal consequences. Important interventions in preventing infections could be provision of basic amenities like clean water, adequate sanitation facilities and appropriate nutritional education and counseling, which could be a useful preventive step to avoid acquiring infections. Penicillin prophylaxis, and anti-Pneumococcal, *H. influenzae*, Typhoid vaccinations are among the most significant life-saving preventive interventions. Local bacteriologic spectrum is vastly different in Africa and India from developed countries, hence antibiotic policy needs to be developed separately and guidelines from other countries can't be followed blindly.

Acute Severe Anemia

Safety and availability of blood products are major challenges for clinicians. Very few institutions provide specialized blood-banking services like leucodepleted RBCs, triple saline washed RBCs for chronically transfused SCD children. Regimes of complete or partial exchange transfusion have not been evaluated adequately in various episodes of SCD [12,17]. Parental education for regular measurement of spleen size and detection of sudden pallor or jaundice as well as observing urine color for evidence of hemolysis is important and is an inexpensive way to detect severe anemia.

Acute Chest Syndrome

Facility for exchange transfusion if needed is mostly lacking at outreach facilities.

Stroke

Diagnosis and management of stroke remains one of the biggest challenges in resource poor countries. Once stroke is diagnosed, long-term management to prevent recurrence is matter of concern as child requires chronic transfusion therapy. Facilities for Trans-Cranial Doppler, followed by preventive chronic transfusion therapy, are non-existent in peripheral parts of most developing countries. As many as 20% of children with no history of overt stroke, have been found on brain Magnetic Resonance Imaging to have "silent" cerebral infarcts. These infarcts predispose to higher risk for completed stroke and neuro-cognitive defects. Screening of children with SCD with brain MRI is not routinely available in developing countries [12,17].

Hip Necrosis

The best options are physical therapy in milder cases or palliative surgical interventions, and ultimately hip replacement for advanced cases [17]. However, very few hospitals have the capabilities to perform hip replacement surgery or core decompression due to several reasons including cost, required expertise and equipments. There are currently no preventive measures in place to prevent avascular necrosis of the femoral head; however the use of crutches is encouraged to delay the

need for replacement and also use of hydroxyurea has been associated with a reduction in incidence and progression.

Malnutrition

Deficiency of essential components in the diet leading to malnutrition, protein calorie malnutrition and micronutrient deficiencies (vitamin A, iron and iodine) are common in children with SCD and aggravate the magnitude of anemia and poor general health. Iron deficiency complicates the picture of existent sickle cell anemia and these patients may need iron therapy. A significant number of sickle cell anemia patients among different primitive tribes in India were shown to be iron deficient [19]. Goiter of various grades is also endemic in some of the tribal areas. Malnutrition is a risk factor for infection. Infections and the existence of malnutrition in Africa is a major concern. A study in Ghana revealed that the prevalence of malnutrition was 61.3% among SCD subjects and 28.6% among controls [12].

Pharmacotherapy

In spite of the fact that hydroxyurea has been shown to improve both survival and the quality of life in patients with SCD, only a small fraction of eligible patients with SCD even in developed country like the United States of America are currently receiving hydroxyurea [1,14]. Although the reasons for the reluctance are not entirely clear, there are many potential contributing factors. These include patient concerns about a drug that is used primarily to treat cancer, physician concerns about potential long-term mutagenic effects, lack of familiarity of primary care providers with the use of a chemotherapeutic agent, and resistance among patients with SCD to use therapies that are perceived to be experimental in nature. Careful investigation into the impediments to the use of hydroxyurea is necessary in order to realize the full potential of this important therapeutic advance [1]. Similarly, in case of chronically transfused SCD children with iron overload, there is little clarity on the choice of the chelation regime and the drugs to be used among the many oral or parenteral drugs available. Also lack of patient awareness, ferritin monitoring, liver and cardiac MRI makes it difficult to maintain proper chelation therapy. As bacteriologic flora and the pattern of prevalent infections differs in low resource countries, further studies are warranted to evaluate efficacy of routine and special vaccinations for SCD. Also availability of expensive vaccines remains a major issue of concern in developing countries.

Bone Marrow Transplant

Stem cell transplants offer a potential cure; however, the high cost, lack of suitable donors (ideally the donor is a sibling), and the risk of complications make these transplants relatively infrequent [20]. In an effort to increase the availability of sources of hematopoietic stem cells for transplantation, clinical trials are being conducted to evaluate cord blood transplantation in the treatment of SCD. The use of nonmyeloablative BMT to reduce peritransplant morbidity and mortality has been associated with a very high graft rejection rate. BMT is the only curative therapy for SCD, and the major challenge is to make it more widely available to patients with a severe disease phenotype [1,9,20].

Burden in Tribal Populations

It is amply clear that vast majority of SCD cases occur in tribal populations of Africa and different regions in India. With a large population, burgeoning birth rate, and consanguineous marriage practices, there is dangerously high prevalence of genetic disorders among tribal populations [4,8]. Relatively few primary and specialty healthcare health facilities exist in tribal areas, and gaping disparities in health status of tribal population, as compared to those in metropolitan areas, are evident [8].

Counseling

There is no robust program of genotype identification with education and counseling on its significance which would allow persons to make informed decisions on their choice of partner and should they wish, avoid the risk of having a child with SCD [3]. The ethnic groups (mainly the tribal population of various states) harboring the sickle gene are in urgent need of good health education and premarital as well post marital counseling explaining detrimental effects of consanguineous marriages.

Research

Research in various clinical and pharmacological domains of SCD is the need of the hour to make universal global guidelines for effective and rational management of SCD [14]. It has been observed that most of the studies reported in the literature involve case studies and reports from hospital based studies, which cannot be regarded to represent population surveys, as samples studied are heterogeneous. Further, most of the studies have not given any details about the ethnic groups, social and environmental factors etc. Carefully designed studies should therefore be planned in the future. There is paucity of data for SCD in tribal populations. With many of the basic molecular issues in SCD being better understood, major research efforts now focus primarily on clinical issues such as treatment for the disease.

Gene therapy

Gene therapy offers enormous promise as a potential curative therapy for SCD, but concerns over the safety of random genomic insertion must first be resolved. Preclinical studies in mice have provided the proof of principle that transduction of bone marrow stem cells with lentiviral vectors that express a β -globin gene can prevent Hb S polymerization *in vivo* [21]. However, far more extensive experimentation followed by clinical trials would be required before gene therapy can reach from the bench to the bedside.

Patient Education

Education, awareness and access to care emerged as topics of high priority for people with SCD and their families. There are no credible educational resources for patients with SCD and their families on the benefits and side effects of hydroxyurea therapy, resources on education of heterozygotes, and reproductive issues, resources on attaining education and vocational training, material on navigating developmental transitions, on what families need to know as children get older, and decision support tools for people living with SCD (e.g., helping people living with SCD to become more active participants in their care, recognizing that every health event is not related to SCD, identification of appropriate providers).

Medical Care Providers Education

SCD specific training emerged as a priority area for health care providers. Generally, many are ill-equipped to care for the SCD patient over their life span especially at the periphery. There are gaps in provider knowledge around management of pain in SCD (especially among emergency room clinicians), cultural sensitivity (e.g. assumption that all people living with SCD are drug seeking), and understanding that every medical encounter is not necessarily related to SCD.

Partnerships and Collaboration

There is a need for integration and collaboration between the Department of Education, school-based health clinics, medical colleges, medical associations, nurse practitioners, mental health provider networks, international physician networks, various cultural alliances and most importantly between governmental and international organizations at the global level. There is a greater need to develop long-term partnerships between SCD clinicians and researchers in high- and low-income countries in order to further research and improve clinical care globally [5].

Innovations for Resource Poor Countries

In resource poor countries like India, general people do not understand the terms like AS, AA, SS patterns and their implications. To circumvent this, colour coding system was devised to each category, notably, blue for AS, pink for SS and white for AA patterns in some part of central India. This helped to a great extent to make common people understand these terms, clinical implications, and also premarital counseling so that only blue and white coded individuals can marry and alliances between blue and pink could be detrimental [22]. Significant obstacles exist with regards to hydroxyurea therapy like compliance, availability of drugs and adverse effects profile and poor follow up for monitoring. As a remedial measure, low fixed dose hydroxyurea was started in severely affected Indian children in low dose of 10 mg/kg/day and was continued same dose. Therapeutic response was comparable with that of standard therapy even with issues of lack of proper monitoring, compliance and toxicity profile monitoring [10]. Universal Newborn screening program for SCD is not feasible due to resource limitations. So guided targeted neonatal screening strategy was devised, wherein all postnatal mothers underwent solubility test. Only those newborns of positive mothers had newborn screening tests done. Primary objective was to detect Sickle SS patterns at the earliest, though other patterns could have been missed. Guided and targeted neonatal screening can help in resource poor countries [23].

Conclusions

Currently health care providers and international health agencies face multiple challenges in managing the SCD burden in children worldwide. Nature of challenges across resourceful and resource poor countries may differ significantly but similar set of problems are deterrents to the effective management of SCD in children. Emphasis should be placed on newborn screening, anti-microbial prophylaxis, vaccination against infections, and training of healthcare workers, patients and caregivers. These are affordable in resource poor countries. Efforts should be made to develop scientific research that would focus on solutions to improve morbidity and mortality as well as quality of life. Great advances have been made in the management of

SCD but many of these are expensive and dependent on medical infrastructure, which may take a long time to developing resource poor high-risk societies. Only very few SCD patients have been successfully treated with hematopoietic stem cell transplantation and, gene therapy has not been successful yet in curing SCD. Several categories of resources are needed including the training of health workers through North-South and South-South partnerships, commitment by countries to acquire equipment and supplies for laboratories, clinical care, and data management, to organize sustained educational programs for health workers as well as the general public. Above all, political willpower is needed and the help of patient/parent support groups, advocacy organizations, and national spokespersons to draw government's attention to SCD as a public health priority. There is greater need for proactive measures and collaboration on the part of the government and international health agencies to effectively implement population screening and counseling programs as a prevention strategy is much more economical than spending on managing the burden of SCD children. This holds true more in context of Africa and India which harbor more than two thirds of the SCD burden. Further empirical collaborative epidemiological studies are vital to assess current and future health care needs, especially in Africa (specifically Nigeria and the Democratic Republic of the Congo), and India. It is the need of the hour to establish the Global SCD Network to foster a global community to advance the clinical care and study of patients with SCD.

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