Indian J Med Res 143, June 2016, pp 678-681
DOI:10.4103/0971-5916.191917

Editorial

World Sickle Cell Day 2016 : A time for appraisal

In 2006, sickle cell disease (SCD), a heritable blood disorder with devastating effects, was recognized as a global health problem by the World Health Organization. Two years later, the 63rd United Nations Assembly designated June 19 as the "World Sickle Cell Day", in an attempt to improve public awareness of the disease and to improve the prospects for patients. Now in 2016, do we detect any changes in public awareness and are the patients more research aware? Has research funding for SCD increased, and has advocacy for SCD improved?

Why is SCD a global health problem? From its origins in sub-Saharan Africa, the Arabian peninsula and the Indian subcontinent, population migration has increased SCD prevalence in areas not previously associated with the disorder, such as the USA, western and northern Europe[1]. In the USA, it affects close to 100,000 people with 3000 affected newborns each year, while in the United Kingdom, it is estimated that 12,500 individuals have SCD with an annual birth rate of 300 affected newborns[2]. SCD is said to be the fastest growing serious genetic disorder in the UK and Western Europe. These figures pale into insignificance when compared with Africa and India. It is estimated that more than 300,000 children are born each year with SCD, about two thirds of them in Africa; Nigeria, India and the Democratic Republic of Congo bear half the global burden of SCD[3]. Numbers are expected to climb projecting that by 2050, there will be about 400,000 babies born with SCD annually[4].

How is SCD a global health problem? In well-resourced countries (*e.g.* USA, UK and France) 94 to 99 per cent of newborns with sickle cell anaemia can now expect to survive into adulthood[5,6] but they face emerging complications and morbidity, as they grow older. The adolescent with HbSS also face a crucial period of transitional care to adult services. But while survival estimates have continued to improve from a median survival of 42-48 years in 1994, to 58 years in 2014, in the USA, the life expectancy of patients with SCD is still shortened by more than two decades compared to the general population[7-9]. The early mortality comes from several sickle-related complications affecting multiple organs from the damage inflicted by years of ongoing inflammation and vasculopathy. In well-resourced settings, adults with SCD are screened for potential complications including pulmonary hypertension, renal impairment, and retinopathy but we are still not clear as to the optimal frequency of screening, and when and how to intervene[10,11]. Further, there are very limited data on reproductive and mental health issues. Management of chronic pain, probably the most common chronic complication in SCD, remains an issue, and needs better evaluation and enhanced research. Similarly, management of acute clinical events, including acute pain, priapism, intra-hepatic cholestasis, multi-organ failure and delayed haemolytic transfusion reactions, need high quality evidence to direct more effective management[12].

The improved childhood survival in well-resourced countries can be attributed to expansion of newborn screening and early implementation of comprehensive care including vaccinations, penicillin prophylaxis and parental education. Screening for children at risk of developing stroke by transcranial Doppler (TCD), and prevention of stroke by blood transfusion in those at risk, has also impacted childhood mortality and morbidity[13]. Before the end of the Stroke Prevention Trial in Sickle Cell Anemia (STOP) in 1998, approximately

This editorial is published on the occasion of World Sickle Cell Day - June 19, 2016.

11 per cent of children with SCD in high-income countries developed a stroke[14]. Since implementation of TCD screening, overt stroke occurred in just one per cent of these children[15]. Thus, implementation of TCD screening and preventive blood transfusion has significantly reduced the incidence of first stroke in children from 0.67/100 person-years before 1998 to 0.06/100 person-years after the implementation of this practice in the United States[16].

Disease modifying treatment options are still limited to two strategies - hydroxyurea (HU) and blood transfusion. Despite evidence of its beneficial effects, hydroxyurea remains underutilized. Its long-term toxicity and effects on reproduction remain to be addressed in the SCD population. Hydroxyurea, which received FDA approval in 1998 for the treatment of sickle cell anaemia in adults in the USA, has now been investigated in children and infants as young as nine months, and shown to be equally effective as in adults[17,18]. HU therapy for children with SCD is now widely implemented in many centres in high-income countries. The main challenge of using hydroxyurea globally is to answer if it is safe to use in the settings where the risk of communicable diseases remains high. In years to come, the results from REACH (Realizing effectiveness cross continent with hydroxyurea) trial could help us answer an essential question of "How can we safely and effectively introduce the use of hydroxyurea in different regions of Africa?[19]"

Blood transfusion is an effective treatment for the prevention and management of many acute and chronic complications, contributing to its increasing usage and transfusion-related complications. Iron overload and alloimmunization are unavoidable with repeated transfusions. In countries with limited resources, the risk of transmission of blood borne diseases is a great concern. Bone marrow or stem cell transplant (Allogeneic Haematopoietic Stem Cell Transplant: HSCT) is currently the only established curative therapy available for SCD. However, there are some unique challenges that come with HSCT[20]. So far, it has been offered only to patients with severe SCD and only if a genetically matched sibling donor is available. The major challenge of this approach is the limitation of donor, as fewer than 14 per cent of SCD have a genetically matched-related sibling donor[20]. Another limitation is that everyone, particularly adults with organ damage may not be able to tolerate the toxicity of medications that are needed to prepare the body for new stem cells and to suppress immune rejection. Vigilant monitoring and timely intervention of transplant-related complications by a comprehensive team approach are essential in improving the outcomes of HSCT. Considering those limitations, HSCT is not widely available for all patients with SCD, even in the well-resourced countries.

The good news though, is that we are now awash with many competing clinical studies and emerging therapies, using genetic, genome-editing, cell-based and pharmacological approaches as potential disease-modifying treatment options in SCD[21,22]. New approaches have been explored to overcome the barriers of matched sibling related donor transplant, including using half matched HSCT (known as haploidentical) from a family member to overcome the barrier of donor limitations. Some have also explored the option of using umbilical cord and cells from placenta. Genetic therapeutic strategies include replacing or changing the defective sickle gene, or manipulating foetal haemoglobin switching[23]. Several pharmacological agents targeting different parts of the pathophysiological pathway are in the pipeline[24]. The most promising new drug is GBT440, which targets HbS polymerization; GBT440 has the potential to become the first mechanism-based or disease modifying drug for SCD[25]. Other notable new drugs in development include Selg1 targeting adhesion, NKTT 120 (humanized monoclonal antibody) targeting inflammation, Sanguinate targeting vasoconstriction and HDAC (histone deacetylase inhibitors) targeting gamma globin switching[26]. Considering the complexity of the sickle pathophysiology, the optimal therapeutic approach could well include combinations of drugs targeting multiple pathways.

How can we do better for people with SCD? In Africa with 75 per cent of the global sickle burden, more than 50 per cent of the affected children die before they reach their 5th birthday[3], due primarily to infections – pneumococcal and other bacteria, and malaria. Implementation of the roadmap for reducing childhood mortality from SCD (as shown in high-income countries) is fraught with challenges in low-income settings from a combination of lack of political will and government strategies, limited resources, and lack of research infrastructure. It will take a collaborative effort of researchers, clinicians, policy makers, investors and media to improve care and promote awareness of the disease. To improve the lives of patients with SCD globally, the creation of international networks of providers knowledgeable in

treating SCD is needed. This can facilitate the building of data repository to help us understand better about the disease outcomes and epidemiology in Africa, Asia and elsewhere.

An inequity of treatment exists not just between high and low income countries, but even within well-resourced countries. Screening for stroke with TCD in children with SCD is not universal in well-resourced countries. Patients who live in remote areas may not have an access to centres with specialized care for sickle cell disease. In a country like United States, without health insurance coverage, an access to those centres is hardly possible. There is a need to develop a network of experts who could serve as resources for community-based providers. To address this important issue, we will require more funding allocation, increased awareness, and enhanced education.

Prediction of disease severity remains an issue; we need more, and better bio-and genetic markers if precision medicine is to become a reality in SCD. This would allow us to focus the potentially toxic treatments (hydroxyurea, stem cell transplant, gene therapy) to those patients with high-risk disease. In parallel with the development of cutting-edge therapies, it is utmost important to realize that we still have a long way to go to close the gap between the haves and have nots. Research funding needs to be allocated to developing nations to implement simple measures such as newborn screening with low-cost diagnostic tools and infection prevention to save the lives of many children, and also to establish an infrastructure to facilitate local research. Only with improved awareness of the disease and collaborative efforts worldwide, we can offer simple life-saving measures to every child with SCD.

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