

EDITORIAL

Treatment of sickle cell disease in sub-Saharan Africa: we have come a long way, but still have far to go

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The first documented case of sickle cell disease (SCD) was in the United States of America (USA), published in 1910 by James B. Herrick (1861–1954), in the Archives of Internal Medicine [1]. The patient was a 20-year-old dental student from the Caribbean Island of Grenada – who had been admitted to a Chicago hospital with anaemia necessitating repeated admissions over a 3-year period [2]. It was Herrick who coined the term ‘sickle cell’, describing the unusual appearance of the patient’s red blood cells, which were shaped like the sickle, the ancient, C-shaped harvesting tool.

Although the first published case was in the USA, sickle cell disorder had been recognised much earlier in Africa as far back as in the 17th century [2] and Africans had names for the condition, such as ‘ogbanje’ in the Igbo region of South Eastern Nigeria (referencing ‘children who come and go’), ‘Abiku’ (meaning ‘born only to die’) amongst the Yorubas of Nigeria’s South West, and Woaye Ndwedwe Ndwedwe (speaking to the stunting characteristic of the condition) among the Akan people of Ghana’s south and Central regions [3]. The Igbo and Yoruba nomenclature for sickle cell speak to the high death rates among children with SCD. Historically, areas of high frequency of the sickle cell gene coincided with high levels of malaria [4], and prior to global migration, the world sickle cell map and the world malaria map closely approximated each other.

It must be emphasised that, unlike the widely-held belief that sickle cell is a ‘black man’s disease’, it is a condition that occurs globally. About 50 million people live with SCD globally. However, SCD occurs most commonly in sub-Saharan Africa (SSA), but it is also present in the Middle East, in the Mediterranean countries, in India and as far East as the Indonesian Archipelago [5]. Sickle cell is also found in the Americas and in the Caribbean Islands, where it is believed to have been introduced via the slave trade [6,7]. The top 3 countries in the world with the highest burden of SCD are Nigeria, India and the Democratic Republic of the Congo (DRC) – in that order – where the disease affects up to 2% of the population and, the carrier state prevalence is as high as

10–30%. Nearly 90% of the world’s SCD population lives in these three countries [8,9].

To put the African sickle cell problem in perspective, at least 240,000 children are born each year with SCD on the continent, which is more than 80 times the occurrence in the USA. With an estimated 150,000 babies born annually with SCD (75% of whom do not live to celebrate their 5th birthday), Nigeria has the highest burden of sickle cell of any country in Africa – and in the world; this is followed by the DRC – where up to 40,000 babies are born every year with the disorder and then Uganda ranks third with about 20,000–30,000 babies born annually. In Tanzania, approximately 11,000 babies are born with SCD each year, ranking 4th in Africa and 5th in the world.

There are still more dire statistics on SCD in Nigeria, including the following [10–12]:

- Nigeria accounts for 75% of all infant sickle cell cases in Africa
- 40 million people in Nigeria have the sickle cell trait/are carriers of the sickle cell gene
- 100,000 Nigerian children die every year from sickle cell
- The economic burden of SCD is very high for patients with SCD and their caregivers [13]

Turning attention to the continent of Europe, SCD used to be prevalent only in Greece and in Southern Italy, but due to migration, its prevalence has increased over time in parts of the continent where the disease was previously rare. Although, generally, sickle cell is still considered a rare disease in Europe, it remains the most prevalent genetic disorder in France and in the UK, and its frequency is on the rise in many other countries on the continent [14].

Considering the timeline of the evolution of sickle cell management over the years, the year 1972 in the USA remains a vital milestone; this was when President Richard Nixon signed the National Sickle Cell Control Act into law, establishing information, education, screening, testing, counselling, research and treatment programmes for

SCD, thus setting the ball rolling in ensuring the availability of treatment options for persons with SCD all over the world [15].

In 1994, research in America showed that long-term blood transfusions reduced frequency of hospitalisation and in 1998 the first drug treatment option for SCD (hydroxyurea) was approved by the US FDA. Fast-forward to 2017 and the FDA approved the amino acid L-Glutamine for the treatment of complications of sickle cell, continuing in 2019 with the approval of the haemoglobin modulator – voxelotor – as well as the monoclonal antibody – crizanlizumab [16].

The World Health Organization (WHO) and the United Nations (UN) also gave impetus to global mobilisation around SCD, with the former's recognition in 2006 of sickle cell as a Global Health Crisis and the latter's resolution in 2008, recognising SCD as a public health problem and as one of the world's foremost genetic disorders; the resolution also established World Sickle Cell Day – a day set aside to raise awareness about SCD locally and globally, urging governments and other stakeholders to deploy resources for its control and facilitating access to education and treatment [17].

Mindful of the pioneering status of the USA in the advances recorded in sickle cell research and treatment, it is not a surprise that in the USA, health outcomes for persons with SCD have improved greatly over the years. Generally, in high-income countries, the survival of persons with SCD has been improving over time, with many more affected persons living well into adulthood [18].

This is, however, not the case in SSA where childhood mortality could be as high as 90% [12]. Such alarming mortality has been attributed to a number of factors; for instance, a study in Nigeria which showed that the burden of child mortality from SCD was disproportionately higher than the burden of mortality of children without the disease, concluded that most of the deaths from sickle cell could be prevented with application of adequate resources and implementation of focused interventions [12].

These focused interventions have already been very clearly elucidated. In 2008, Ministers of Health from the WHO African region adopted a regional strategy to combat SCD and indeed some African countries have control programmes for SCD. The WHO AFRO Strategy for the control of SCD in the region focuses on the problem areas of cultural beliefs, cost of treatment and infrastructure limitations as barriers to accessing treatment for sickle cell in SSA, as well as inadequate facilities and diagnostic tools, insufficient treatments and paucity of trained personnel; the strategy also notes that mortality from SCD occurs mostly in children under five, in adolescents and in pregnant women and, therefore, also focuses on adequate management of these vulnerable groups and providing a

set of public health interventions to reduce the burden of SCD in the African region through improved awareness, disease prevention and early detection [19].

These interventions include improvements in health-care provision – i.e. effective clinical, laboratory, diagnostic and imaging facilities, adapted to different levels of the health system, newborn screening, training of health workers and development of protocols, genetic counselling and testing, accessibility to health care, establishment of patient support groups, advocacy and research.

Successful implementation of the strategy will depend on the commitment of WHO-member states to integrate SCD prevention and control into National Health Plans and provide an environment conducive for various stakeholders to contribute to the reduction of SCD prevalence, morbidity and mortality [19]. The WHO has also recommended that SCD should be managed at different levels of care through use of simple, cost-effective and affordable strategies and technologies that are accessible to all patients. The organisation has also shared a step-wise gold standard on multi-dimensional strategies for prevention, diagnosis, and treatment of SCD [20].

With respect to care providers, it has been found that knowledge and awareness gaps among clinicians are a challenge in Africa. A study in tertiary hospitals in Nigeria determined that half the doctors treating persons with SCD lacked training on the use of hydroxyurea, prescribing the drug 5 times less often than the other half [21]. Thus, the lack of expertise in the use of hydroxyurea is a major barrier to treatment.

Indeed, vital interventions for management of SCD recommended by experts have been consistent with the afore-mentioned WHO strategies – namely, early diagnosis through newborn screening, genetic counselling and accessible comprehensive care. Experts note that early diagnosis of SCD improves survival, but only a few centres in SSA have the capacity for screening newborns and delivering comprehensive health care at an early age – most persons with sickle cell being diagnosed on presentation with symptoms in childhood at a mean age of 2 years [8]. Such comprehensive health care includes education of families and care givers to recognise symptoms and signs of sickle cell, to appreciate the importance of prevention of bacterial infections with vaccinations and prophylactic penicillin and mosquito netting and prophylactic medicines to prevent malaria. In addition, seeking prompt treatment for infections and malaria as well as recognising symptoms of complications – such as acute chest syndrome and stroke is paramount.

Still on comprehensive health care for SCD, it is advised that in SSA:

- All patients and care givers should understand the importance of transcranial Doppler (TCD) screening

and it is imperative that children living with SCD aged 2–16 years are screened for stroke risk.

- Adult sickle cell patients should be counselled about the risk of chronic complications, such as renal, pulmonary and orthopaedic complications as well as interventions that are available. (Complications limit opportunities and worsen quality of life for many people with sickle cell.)
- Women with SCD who become pregnant should be counselled about the importance of appropriate prenatal care.
- Counselling should be provided to educate people about risks of having an affected child.
- Provision of well-organised, holistic care can significantly reduce morbidity and mortality and improve the quality of life for persons with SCD in developing countries [10].
- A multidisciplinary approach to care is recommended as best practice for the management of persons with SCD [8].

The role of not-for-profit non-governmental organisation (NGO) stakeholders in the sickle cell space, for example, Sickle Cell Foundation Nigeria, Sickle Cell Foundation of Ghana, the Putting Rare Diseases Patients First! (PRDPF!) – a US-registered charity – cannot be overemphasised. They have been in the forefront in the areas of raising awareness about sickle cell, advocating for political will, holding governments accountable for ensuring that sickle-cell-related international agreements are domesticated and also – through international partnerships – improving access to treatment for persons with SCD in Africa. PRDPF! has frequently brought countries in SSA together for webinars on newer drugs for sickle cell (e.g. voxelotor and crizanlizumab) and updates on relevant clinical trials [22].

Focusing on Nigeria, the country with the highest burden of sickle cell globally, we have certainly come a long way – from the early days when sickle cell was largely a neglected paediatric disease, when it was considered a spiritual illness, when it was widely thought to be caused by witchcraft and, when parents would often hide away their children with the condition – to the present time, when there is in fact, ‘name recognition’ for SCD in many communities. Today, people generally have heard the term ‘sickle cell’ and among the Yoruba of South West Nigeria, SCD is increasingly less referred to as ‘abiku’ (born to die), but rather, a more apt terminology for the disorder has evolved – ‘*Şe èjè di olè*’ (*şejedolè* for short) – meaning ‘a disease that renders the blood lazy’ – speaking to the anaemia of the condition.

Political will has also increased over the years, with a Sickle Cell Control Unit at the Federal (Central or National)

Ministry of Health that has produced Policies and Guidelines for the Management of SCD in the country; there are corresponding SCD units at the state/regional level and, with support of NGOs such as Sickle Cell Foundation Nigeria, training on Guidelines for Treatment of SCD has been stepped down to Primary Health Care level.

Furthermore, the Federal Government of Nigeria has also established 6 centres of Excellence – one in each of the country’s geo-political zones with capacity for newborn screening [12].

As an NGO in Nigeria, Sickle Cell Foundation Nigeria (SCFN) has done a great deal of the heavy-lifting in the sickle cell space – recording significant achievements including the following:

- (1) **The National Sickle Cell Centre:** The foundation established the National Sickle Cell Centre in Lagos to address the key problems of SCD. It is the first of its kind in all of Africa.
- (2) **Clinical Services:** The foundation runs dedicated Sickle Cell Clinics, providing free drugs and basic equipment in a number of states in the country.
- (3) **Genetic Counselling Service:** Genetic counselling – which is central to the management of SCD – is offered daily at the National Sickle Cell Centre.
- (4) **Prevention of Strokes:** The foundation has a Stroke Prevention Unit at the Sickle Cell Centre, where, with a Trans Cranial Doppler (TCD) Scan, children at high risk of developing stroke are identified and promptly receive stroke-prevention interventions.
- (5) **Prenatal Diagnosis:** This service is also provided at the centre, whereby a couple can determine the genotype of their unborn child in early pregnancy.
- (6) **Laboratory Services:** The foundation runs state-of-the-art Reference Haemoglobin and DNA Laboratories.
- (7) **Apheresis/Exchange Blood Transfusion Unit:** The foundation also provides this rare, life-saving procedure for persons with SCD at the Sickle Cell Centre.
- (8) **Welfare Services:** Welfare assistance is provided to affected persons for procurement of medicines and surgical procedures, for school fees and skills acquisition and job placements.
- (9) **Advocacy, Information, Education & Communication:** The foundation educates the public about SCD through community outreach programmes and via the media – mainstream and social media – raising awareness about SCD all over Nigeria and beyond – including in rural areas, in schools, churches and mosques, and among other groups.
- (10) **Stem Cell Transplantation/Bone Marrow Transplantation (BMT):** SCFN has established a

Comprehensive BMT Programme in partnership with Lagos University Teaching Hospital (LUTH). This cure for SCD is now locally available and accessible for Nigerians in Nigeria.

- (11) **Training & Capacity Building:** SCFN trains doctors and nurses and other health workers in the proper management of SCD.
- (12) **Arts in Medicine:** SCFN has blazed the trail in incorporating visual arts, music and dance into the management of SCD.
- (13) **Publication of Handbook on SCD for Doctors & Nurses:** SCFN has published a handbook (in collaboration with the WHO), for the management of SCD and distributed it across the country to help doctors and nurses have a handy reference as they care for persons with SCD.
- (14) **Development of a Strategic Plan for the Control of SCD in Nigeria:** A strategic plan for the control of SCD in Nigeria was developed by the foundation and presented to the Honourable Minister of Health – as a veritable means of supporting Nigeria in achieving Target 2 of Sustainable Development Goal #3 (SDG #3) – reducing under-five mortality by preventing childhood deaths from SCD.
- (15) **Engaging the Legislature:** SCFN continues to engage the legislature for appropriate laws on SCD that will give bite to policies developed; e.g. to ensure there is a law on newborn screening for SCD and free treatment for children under five.
- (16) **Research:** SCFN is in the forefront of research into various aspects of SCD – researching into more effective treatment protocols and better understanding of the disorder.
- (17) **Sickle Cell Registry:** This was established by the foundation with a comprehensive CRF to foster vital SCD research.
- (18) **Sickle Cell Clubs:** The foundation coordinates Sickle Cell Clubs in many states across the country. These are support groups for affected persons and other interested persons – including health workers.

Looking ahead, the future does appear bright for persons with SCD – with newer drugs which hold great promise as well as stem cell transplantation and of course cutting-edge gene therapy that targets the cause of the disease. Countries in SSA are slowly but surely playing catch-up – with support from international and regional organisations, as well as NGOs on the continent. So, although the burden of SCD in SSA is huge, there is hope – as progress is being made across the continent to improve the situation. Be that as it may, SSA governments need to put their money where their mouth is and ensure

investments in SCD control in order to move SCD up the priority ladder. To facilitate this though, research into the burden of the disease in SSA, as well as cost-benefit analysis studies are still required to help convince health authorities about the importance of prioritising SCD. There is also need for better understanding of peculiarities around the natural history of the disease in the African scenario, because lessons learned from research conducted in the USA and Europe may not always apply wholesale to the African situation [8].

Finally, in the SSA context, the importance of access to care – in terms of availability and costs – cannot be overemphasised. Reducing cost of treatment and ensuring implementation of Universal Health Coverage (UHC) – a strategic priority of the WHO's – will improve both quality of life and longevity of persons living with SCD in SSA [23].

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