Chapter 2

A Global Perspective on Milestones of Care for Children with Sickle Cell Disease

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Additional information is available at the end of the chapter

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Abstract

Sickle cell disease (SCD) is one of the most common severe and monogenic disorders worldwide. Acute and chronic complications deeply impact the health of children with SCD. Milestones of treatment include newborn screening, comprehensive care and prevention of cerebrovascular complications.

Keywords: sickle cell disease, children, newborn screening, comprehensive care, stroke

1. Introduction

Sickle cell disease (SCD) is one of the most common severe and monogenic disorders worldwide with an average of 300,000 children born annually with sickle syndromes, the majority in Africa [1, 2]. SCD was initially endemic in areas of malaria disease (Africa, Southern India, Mediterranean countries, Southern Asia), but various waves of migration brought populations from areas of high prevalence of the HbS gene to the Americas and Europe (**Figure 1**). Moreover, the recent migration movements of the past decade have further increased the frequency of SCD in areas where it was generally uncommon. In Europe, SCD has become the paradigm of immigration hematology [3] and is now the most prevalent genetic disease in France [4] and the United Kingdom [5]; its frequency is steadily rising in many other countries of northern, central and southern Europe [6–10] posing a challenge to health systems. In addition, awareness regarding SCD is increasing in India [11] and in many African countries [12] where the prevalence of the disease is high. Although in low-resource

settings a great effort in terms of funding, care and research is still mainly destined to infectious diseases, the burden SCD poses on mortality and health systems in Africa is finally starting to be recognized [13–16]. Several African countries have developed dedicated services for children with SCD [17–20], including newborn screening [21–26]. Patients with SCD in many centers are being evaluated in a standardized comprehensive manner both in prospective observational cohorts [17, 19, 27] and randomized clinical trials [28, 29]. Although some experiences are still conceived as pilot programs and have yet to be scaled up at a national level, their results are promising and demonstrate increased commitment to tackle SCD at a global level.

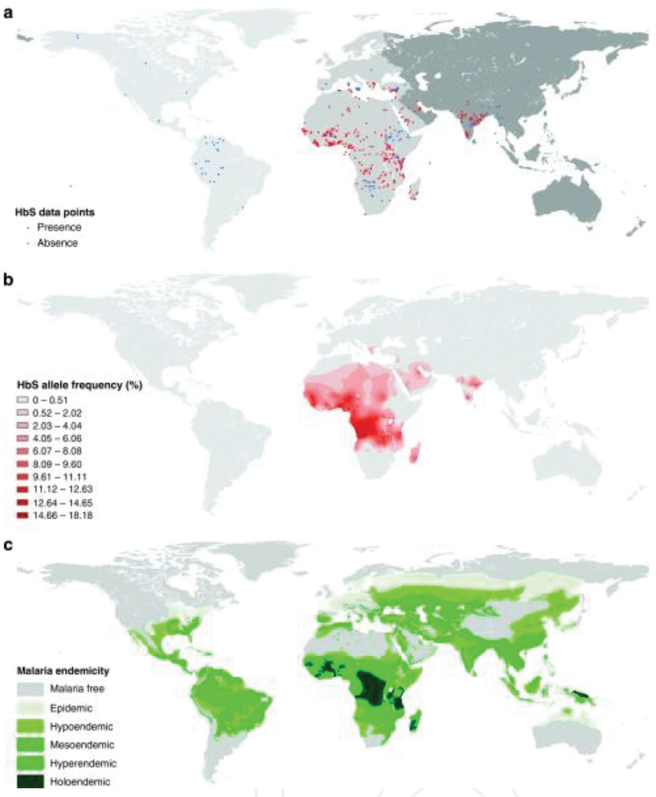

Figure 1. Global distribution of the sickle cell gene. (a) Distribution of the data points. Red dots represent the presence and blue dots the absence of the *HbS* gene. The regional subdivisions were informed by Weatherall and Clegg and are as follows: the Americas (light gray), Africa, including the western part of Saudi Arabia, and Europe (medium gray) and Asia (dark gray); (b) Raster map of HbS allele frequency (posterior median) generated by a Bayesian model-based geostatistical framework. The Jenks optimized classification method was used to define the classes; (c) the historical map of malaria endemicity was digitized from its source using the method outlined in Hay *et al*. The classes are defined by parasite rates ($PR_{2–10}$, the proportion of 2- up to 10-year-olds with the parasite in their peripheral blood): malaria-free, $PR_{2–10}=0$; epidemic, $PR_{2–10}=0$; hypoendemic, $PR_{2–10}<0.10$; mesoendemic, $PR_{2–10}\geq0.10$ and <0.50; hyperendemic, $PR_{2–10}\geq0.50$ and <0.75; holoendemic, $PR_{0–1}\geq0.75$ (this class was measured in 0- up to 1-year-olds). From Piel et al. Global distribution of the sickle cell gene and geographical confirmation of the malaria hypothesis. Nat Commun. 2010 Nov 2; 1: 104. Published online 2010 Nov 2. doi: 10.1038/ncomms1104. Copyright © 2010, Nature Publishing Group, a division of Macmillan Publishers Limited. All Rights Reserved.

SCD can be defined as a globalized disease, and its presence in so ethnically diverse populations, living in extremely variable environments and in very different socio-cultural societies,

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is a factor that must be taken into consideration when addressing its management. In fact, although SCD is a monogenic disorder, its phenotype can be highly variable, not only among individuals, but also among ethnic groups and populations [30, 31].

In this chapter, we will review the management of children with SCD from a global perspective focusing on the three milestones of care: newborn screening, comprehensive *prix-en-charge* and cerebrovascular complications.

2. Neonatal screening programs

Newborn screening programs for SCD allow the early identification of patients, with the advantage of starting prophylaxis with penicillin at two months of age, significantly reducing mortality from infections. Moreover, newborn screening allows the early enrollment of patients in specialized programs of care in reference centers, thereby reducing morbidity and subsequent mortality from acute and chronic complications and improving quality of life.

The first screening program for SCD has been introduced in the USA since 1975 [32] and in the UK in 1993 [33].

In 1987, an NIH Consensus Conference stated that every child should be subjected at birth to screening for HbS to prevent the severe childhood complications of SCD, mainly infections and splenic sequestration, both potentially fatal [34]. Subsequently, a randomized study demonstrated the effectiveness of neonatal screening in dramatically reducing infant mortality from infection, allowing early initiation of prophylaxis with penicillin [35].

International Guidelines on the treatment of SCD recommend universal newborn screening on a national basis, best if integrated with existing neonatal screening programs and programs of *prix-en-charge* in specialized hematology reference centers [5, 36].

The recommendation is that newborn screening for identification of SCD is performed to all newborns. All patients must be identified promptly and taken in charge by dedicated and specialized services in order to begin penicillin prophylaxis within two months of age (Strength of Recommendation A).

Since the late 1980s numerous are the experiences of newborn screening programs, many organized by national health systems other confined to single-center experiences or supported by private funding.

2.1. Neonatal screening for SCD: major international experiences

United States—In the United States, the first neonatal screening program for SCD dates back to the 1970s (State of New York and Columbia), but after the publication of the NIH recommendations, all the states have organized a universal neonatal screening program for the S gene, associated with neonatal screening for other diseases. The analysis is performed at the birth from capillary blood taken by pricking the heel and using Guthrie paper. The analysis is done in most cases by Hygh performance liquid chromatography (HPLC).

The results of 20 years of the program (1989–2012) show an average incidence of the S gene in the general population of 1:64 (1.5%) and an average incidence of SCD of 1: 2000 (0.05%) [37]. The program in the United States was effective in significantly reducing the mortality of children with SCD [38].

Canada—In 1988 a targeted screening pilot program was started at the University of Montreal on babies with at least one African parent. The test, performed by HPLC, identified a proportion of 10% with trait and 0.8% of the affected. A significant number of non-enrolled patients was reported by the program, as many as 11 patients born in the reporting period: 5 of 72 of infants escaped enrollment in a care program, six infants were not identified as affected, and three false negatives and three inadequate samples were identified, stressing the importance of an absolute rigor in the organization of a screening program [39].

In 2006 a universal neonatal screening program for SCD, on a national basis, was initiated in Ontario and subsequently implemented in eight other Canadian provinces, comprising 10 provinces and three territories. The survey is performed on the cord blood or capillary blood on tissue paper by HPLC, using Iso-Electric-Focusing (IEF) or hemoglobin electrophoresis as a confirmatory test. A debate is ongoing on whether to inform parents of the carriers subject [36].

In *Brazil*, many states organized a neonatal screening program for the identification of patients with SCD. Since 2001 in the State of Janeiro Rio a universal neonatal screening program is active, funded by the National Health System, which includes the analysis by HPLC of the sample from the Guthrie test, performed on the baby after discharge in association with the first vaccine administration; the program provides for the subsequent taking charge of patients with SCD at the Reference Center.

The results of the first 10 years of experience (2001–2011) showed a SCD incidence of 1:1335 births and incidence of the trait by about 5% of births [40, 41]. The mortality was 3.7% significantly lower than the mortality of 25% of a cohort of Brazilian children not included in a screening program [42] but also significantly lower than that of a population of children undergoing neonatal screening, but not incorporated in a comprehensive program of follow-up. In fact, mortality in this population was found to be 5.6% [43]. The importance of integrating neonatal screening in an effective program of care of the patient at a specialized reference center has been more recently confirmed by another recent Brazilian study, which indicated in Minias Gerais State a mortality of 7.5% patients with SCD in the first 14 years of life, even though they were undergoing newborn screening, because of a non-effective care program [44].

In *Europe*, although there is strong evidence that hemoglobinopathies are an increasingly important public health problem [3], as a result of recent migration flows from the Mediterranean countries, Africa and Asia, there is very little data regarding the overall prevalence of SCD; the health policy of the governments, regarding the management of SCD, is uneven in the various nations. The European Network for Rare and Congenital Anemias (ENERCA) estimates that there are around 44,000 people in Europe suffering from hemoglobinopathises, 70% of which are SCD, and strongly recommends that the National Health Systems develop

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screening programs and specialized reference centers for the care of the patient and their family [6].

The United Kingdom (UK) was the first European country to organize, in 1993, a universal neonatal screening program for SCD. The initial pilot program, which began in England, was updated and since 2010 is extended to the whole of Britain. The program, supported by the National Health System (NHS), provides universal neonatal screening, performed with analysis of Guthrie test concurrently with other screenings. Samples are analyzed at 13 reference hematological laboratories by HPLC, each laboratory screening between 25,000 and 100,000 newborns a year. The organization provides for centralized analysis in reference laboratories, each with a minimum of 25,000 tests per year. The incidence of carriers in the UK is an average of 15/1000 (1.5%) and 1:1900 (0.05%) with significant variations by region and ethnicity [45].

A national program of universal newborn screening of Guthrie by HPLC [46] is active in the *Netherlands* since 2007. A debate on whether to notify the carrier state to avoid stigmatization is currently underway [10].

In *Belgium*, since 1994 in the city of Brussels and in 2004 in the city of Liege, all newborns are subjected to universal screening for SCD. The analysis of umbilical cord blood is performed by IEF and HPLC as a possible confirmatory test. The affected frequency is determined to be 1:1559 [47].

In *Spain*, since 2000 universal neonatal screening programs have been initiated in Extremadura, Basque Country, Madrid, Valencia and Catalonia with plans of extending it from 2016 to the whole country. The prevalence of the affected varies from 1:3900 in Catalonia to 1:5900 in the region of Madrid [8, 48, 49].

In *Germany*, pilot programs of universal newborn screening were organized since 2011, first in Berlin, then in Heidelberg and in the Southeast Region of Germany and then in Hamburg. The tests were offered to all newborns although the original population was not at risk of hemoglobinopathy. The goal was to provide information about the global prevalence in Germany of a disease that has high prevalence in immigrant populations, coming mainly from areas at risk. The test was carried out by PCR for S chain from Guthrie paper in Hamburg, and by HPLC in the other experiences; the incidence of the affected ranged from 1:2385 to 1:8348 [9].

The results of the pilot studies were considered adequate to justify a universal neonatal screening program on a national basis, extended to the entire Germany. The activation of the project is planned for 2016. The carrier status is not communicated for fear of stigma.

Since 1985, *France* has organized a universal neonatal screening program for SCD in Guadeloupe: in the following years, many pilots studies were initiated in France; since 2000 a national screening program targeted at infants at risk of hemoglobinopathy was extended to the entire country; the selection is based on ethnic belonging. Although the program is not universal, it appears to be effective in intercepting almost all affected infants, ensuring their ultimate takeover by the Reference Centres [50].

In *Italy*, some experiences of neonatal screening for SCD have been reported.

From 2010 to 2012 in Ferrara, 1992 newborns have been tested and 24 carriers identified (1.2%). Screening was universal, run on Guthrie by HPLC. The experience was suspended for lack of funding [51].

In 2013 in Novara a project of newborn screening targeted to babies with a parent coming from areas at risk of hemoglobinopathy was implemented. A total of 337 of 2447 were tested and 20 carriers identified (6%) [52].

In Modena, since 2011 an antenatal screening program targeted at at-risk women by ethnicity was developed. The pilot study showed the presence of hemoglobinopathy in 27% of the 330 women tested (coverage of 70% of the program). Successively, the screening of infants of carrier mothers, run on cordon and analyzed by HPLC, has identified 48 carriers and 9 HbSS [53]. The universal antenatal screening program, extended to all pregnant women and including infants at risk of maternal positivity, is currently ongoing and supported with funding from the Province of Ferrara.

Since 2010, a centralized program of targeted neonatal screening (at least one parent from outside the region) is active in Friuli Venezia Giulia, financed by the region. The figures, as yet unpublished, report 6018 infants tested from 2010 to 2015, a percentage of carriers between 1.74 and 4.7% depending on the provinces (F Zanolli, personal communication).

A pilot program of universal newborn screening has been running since May 2, 2016, in Padua and is currently being activated in Monza.

Africa bears the highest burden of SCD. In the past years, several pilot newborn screening programs have been implemented in Central Africa [21], Ghana [20, 22], Congo [24], Benin [25], Angola [26], Nigeria [23, 54, 55] and Uganda [56] and are underway in Tanzania [19]. Some of the most significant experiences are described in detail below.

The first program started in *Ghana* in 1995 [22], and after 10 years, a total of 202,244 infants were screened through public and private clinics in Kumasi, Tikrom and a nearby rural community. 3745 (1.9%) infants were identified as having possible SCD with IEF: 2047 (1.04%) SS, 1684 (0.83%) SC.

In *Central Africa*, between July 2004 and July 2006, 1825 newborn dried blood samples were collected onto filter papers in four maternity units from Burundi, Rwanda and the East of the Democratic Republic of Congo. The presence of hemoglobin C and S was tested in the eluted blood by an enzyme-linked immunosorbent assay (ELISA) test using a monoclonal antibody. All positive samples were confirmed by DNA analysis. Of the 1825 samples screened, 97 (5.32%) were positive. Of these, 60 (3.28%) samples were heterozygous for Hb S, and four (0.22%) for Hb C; two (0.11%) newborns were Hb SS homozygotes.

In *Uganda* [56], punch samples were obtained from dried blood spots routinely collected from HIV-exposed infants for the national Early Infant Diagnosis program. Between February 2014, and March 2015, 99,243 dried blood spots were analyzed through IEF, and results were available for 97,631. The overall number of children with sickle cell trait was 12,979 (13.3%) and with disease was 716 (0.7%), with extreme variability across regions.

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Two pilot screenings from *Nigeria* are reported. Obaro et al. (54) screened HPLC children aged less than 5 years. Overall, 272 (2.76%) new cases from 9963 children who had not been previously tested were identified. The authors reported also the screening of 163 (1.6%) children whose parents indicated that their offspring had been previously tested. 31.2% of parents (51/163) did not know the result of their offspring's test.

Inusa et al. [55] from January 2010 to December 2011 screened children aged 0–60 months in 29 randomly selected local communities of three adjoining northern Nigerian states in a community-based study: Abuja, Kaduna and Katsina. For infants of 0–6 months, blood spots were used, and for infants of 7–60 months, EDTA blood samples were analyzed using HPLC. Thirty-one selected samples with high Hb A2 (3.5–7.4%) were further analyzed using molecular diagnosis to ascertain the presence of the Beta Thalassemia gene. Of the 10,001 infants and children screened, 269 (2.69%) had a SCD diagnosis, 90% of which were HbSS (n = 243), 5% HbSC (n = 13), 3% with high A2>6% (possible S with existence β thalassaemia (n = 9) and 1% HbSD (n = 2). A total of 74% of infants screened were HbAA (n = 7391). 2341 (23%) were carriers, 96% HbAS (n = 2236), 2% HbAC (n = 51), 1% HbAD (n = 25), and 1% HbABeta-thal (n = 22). HbSβo was confirmed by molecular analysis from the 31 selected samples.

3. Management of sickle cell disease in childhood

SCD is a chronic and complex multisystem disorder requiring comprehensive care that includes screening, prevention, health education, management of acute and chronic complications [5, 57]. Poor service organization and episodic health care cause higher rates of acute events and chronic complications, with subsequent increased burden on hospital structures and higher costs for health systems [58].

Neonatal screening program for SCD is not successful without a comprehensive care program at a specialized reference center for the treatment of the disease.

The organization of the Comprehensive Sickle Cell Centers proved crucial integration of screening programs, providing health education, preventive treatment (prophylaxis of infections, up-to-date vaccinations, stroke prevention), appropriate diagnostic therapeutic pathways for the treatment of acute and chronic complications, planning of blood transfusion and administration of HU, accompanying the transition to adult care for adolescents and young adults through structured transition programs. The care delivered by a specialized and multidisciplinary team in referral centers is effective in reducing mortality and improving the quality of life [38, 59]. Where these facilities were lacking, the effectiveness of neonatal screening program was reduced [60].

A recommended examinations schedule for yearly follow-up of children with SCD is shown in **Table 1** [61], while the services that a reference center should offer are displayed in **Table 2** [5].

	0 – 1 Year	2 years	3 - 5 years	6 - 9 years	10 – 15 years	16 -18 years
Physical examination	■	■	■	■	■	■
Transcutaneous O_2 saturation	■	■	■	■	■	■
Biological tests*	■	■	■	■	■	■
Adherence (treatments, appointments)	■	■	■	■	■	■
TCD		■	■	■	■	
Hepatic US			■	■	■	■
School success			■	■	■	■
Pulmonary function tests			■	■	■	■
Hip X-Ray				■	■	■
Electrocardiography				■	■	■
Ophtalmologic evaluation				**	■	■

* Complete blood count, liver profile, electrolytes, BUN, creatinine, γalbuminuria, ferritin if transfused, calcium metabolism including vitamin D and PTH, Parvovirus B19 serology until positive.

** Since the age of 6 y.o. if Hb SC disease

Table 1. Recommended examinations to be performed annually in children with SCD [60].

◦ Pediatrician or hematologist with hemoglobinopathies skills
◦ Dedicated outpatient clinic
◦ Network with the territory and the peripheral hospitals
◦ Diagnostic laboratory
◦ Newborn screening program
◦ Transcranial Doppler service
◦ Pediatric intensive care
◦ Transfusion service
◦ Pediatric specialist services (cardiology, urology, nephrology, pulmonology, endocrinology, orthopedics, surgery, anesthesia, ophthalmology, dentistry)
◦ Psychology service with availability of psychometric assessments
◦ Radiology and neuroradiology
◦ Bone marrow transplant unit
◦ Adult-specialist team for the transition program

Table 2. Characteristics of a specialized reference center [5] and services that it should be able to offer directly or in agreement with nearby centers.

A comprehensive approach to the care of children with SCD should include the following goals: to improve quality of life, by preventing and treating infections, adequate pain man-

agement and anemia control; to prevent organ damage, mainly stroke, renal and lung; to prevent SCD related mortality [61].

3.1. Management of sickle cell disease in childhood: open issues at a global level

In spite of the strong evidence to perform newborn screening and comprehensive care, these services are far from optimally delivered to patients with SCD not only in Europe and the USA, but mainly in areas of Africa and India where the majority of the children with SCD live. Many pilot programs were initiated in the last decade in many countries of Latin America, Middle East, Asia, and Africa; some were integrated with other screening programs. These data are encouraging but such programs need to be further enhanced.

Increased North-South, South-South and East-West collaboration could be an important way to increase service delivery to all affected children.

4. Cerebrovascular complications of sickle cell disease: stroke and silent infarcts

In the most severe forms of SCD, the homozygous SS and the double etherozygous Sβ°, the brain is frequently affected (**Figure 2**). Overt ischemic stroke occurs in 11% of untreated children as a result of stenosis or occlusion in the large arteries of the Circle of Willis [62, 63]. Cerebral silent infarcts (CSI), affecting 40% of children by the age of 14, are caused by small vessel disease [64, 65] although recent evidence suggests that also a combination of chronic hypoperfusion or hypoxic events, favored by an underlying artheropathy of the large vessels, can lead to CSI [66]. In the past 15 years, improvements have been made in the management of stroke and CSI [66, 67]. In fact, algorithms for screening, prevention and management of stroke and CSI based on neuroimaging techniques such as transcranial Doppler (TCD) and

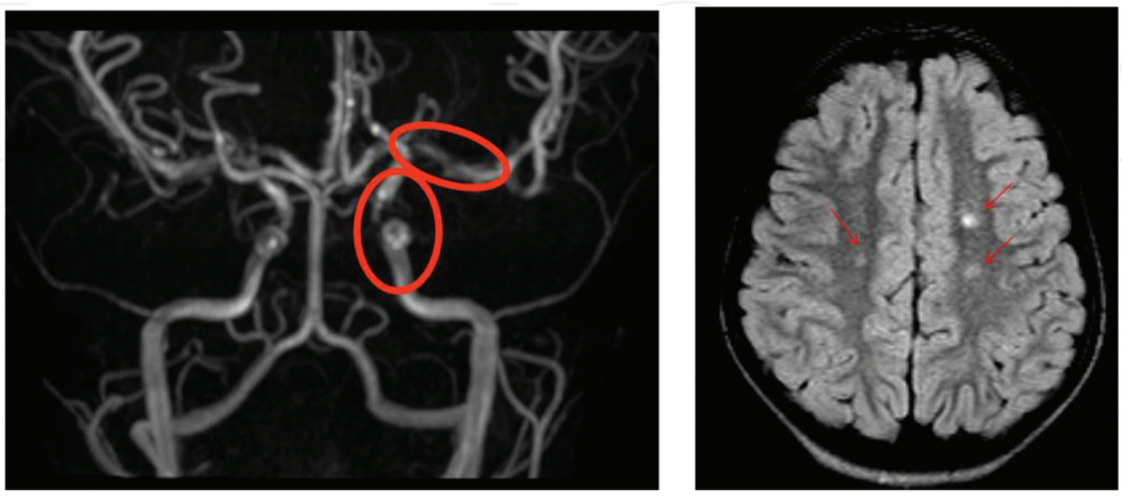

Figure 2. Stenosis on magnetic resonance angiography (left) and silent infarcts on magnetic resonance imaging (right).

magnetic resonance imaging/angiography (MRI/MRA) are routinely used in clinical practice [67–70].

TCD screening is recommended starting at age 2 years in children with HbSS and HbSβ°, and those identified at risk of stroke are offered chronic transfusion as stroke prevention [67]. Stroke can be virtually eliminated or dramatically reduced if a proper TCD screening program followed by chronic transfusion for at risk patients is established [59, 68]. Recently, a randomized study demonstrated that after one year of chronic transfusion, hydroxycarbamide (HU) can be safely offered to children with normal neuroimaging under strict surveillance [71]. While TCD allows identifying patients at risk of stroke and initiate appropriate treatment, it is not useful to screen for the other cerebrovascular complications of SCD such us CSI. Moreover, its usefulness in identifying risk of stroke in other genotypes of SCD such as HbSC and HbSβ+, in which stroke is less common, has yet to be evaluated.

Screening with MRI/MRA, although unable to indentify children at risk of developing CSI, is strongly recommended in many centers starting at age 5 years, when sedation is no longer necessary [66, 68, 72], to ensure diagnosis at young age and promptly start therapeutic or educational measures. In case of abnormal TCD, developmental delay or cognitive impairment or any other clinical reason, MRI is indicated even before 5 years of age. Both chronic transfusions and HU have been shown to stabilize CSI [66, 67, 73], but at present there is no general agreement on prevention strategies.

4.1. Stroke and silent infarcts: open issues at a global level

In spite of extensive research performed in the United States and Europe on the management of stroke and CSI in children with SCD in the past decades, the delivery of routine TCD screening to children with SCD has been quite low. Primary stroke prevention through TCD is recommended in all national and international guidelines, but less than 50% of children in the USA [74] and the United Kingdom benefit from this technique [75]. Data regarding the coverage of TCD screening are not available for other countries of Europe, South America or the Middle East at a national level, but only for single-center experiences [59, 66, 69, 72, 76], and this is a gap that should be filled.

TCD data are not yet available from many areas of the world like India, Northern and Sub-Saharian Africa. Nevertheless, personnel training on the correct protocol of TCD screening for SCD has been performed in Africa, and promising pilot studies are being conducted in Nigeria [77–79]. These studies demonstrate the feasibility of primary and secondary prevention programs in low-resource settings with huge numbers of patients. They also allow us to explore the efficacy of alternative protocols compared to those in use in the USA and Europe and to demonstrate the benefit of HU in reducing TCD velocities [80].

A challenge that a global approach to SCD can address is the reported variability of stroke and cerebrovascular complications in populations of different ethnic backgrounds. Stroke and CSI seem to occur with different frequencies across populations, although data are still poor and warrant further investigation [81–85]. Moreover, biological factors such as G6PD deficiency and alfa thalassemia co-inheritance as well as coagulation activation and single nucleotide

polymorphisms (SNPSs) do not seem to have the same role on the genesis of cerebrovascular complications in different populations [86–90].

In conclusion, more TCD and MRI/MRA data from SCD populations across the world could aid in designing wide population studies to explore genetic and biological modifying factors of cerebrovascular disease as currently performed in other pathologic conditions [91]. Coordinating cerebrovascular studies across countries and continents can be challenging [79, 92–95] but is now warranted to improve patients access to recommended screening tools and to better target treatment interventions according to biological disease-modifying factors, which may vary across ethnicities.

5. Future directions

The main objective would be to increase the access to the milestones of care:

- Expand universal newborn screening to all Countries with sufficient prevalence of disease
- Expand access to vaccinations, antibiotic prophylaxis and transcranial Doppler for stroke prevention, by increasing the number of skilled personnel and service availability
- Increase the use of disease-modifying treatments for the pediatric age, such as hydroxiurea, in formulations that are suitable for children (low dose tablets or syrups) in all countries

Strengthening collaboration at a global level and developing North-South, South-South and East-West partnerships could aid in reaching the above mentioned aims.

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