



## Cerebrovascular Complications and Cognition in Children with Sickle Cell Disease: A Global Perspective

Raffaella Colombatti\*, Maria Montanaro and Laura Sainati

Department of Child and Maternal Health, Azienda Ospedaliera-University of Padova, Italy

### Abstract

Sickle Cell Disease (SCD) is one of the most common severe monogenic disorders worldwide. Cerebrovascular complications, mainly stroke and silent infarcts deeply impact the health of children with SCD. Cognitive impairment and poor academic performances can also affect the quality of life. This chapter reviews the approach to cerebrovascular complication and cognition in different countries and populations.

**Keywords:** Sickle Cell Disease; Children; Cognition; Cerebral; Vasculopathy

### Introduction

MERGEFORMAT Sickle Cell Disease (SCD) is one of the most common severe 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 in 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]. 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 and increased commitment to tackle SCD at a global level.

SCD can be defined a globalized disease and its presence in so ethnically diverse populations, living in extremely variable environments and in very different socio-cultural societies, 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 cerebrovascular complications of SCD, focusing mainly on cognition, from a global perspective. Further, recent achievements in understanding the causes of altered cognition in SCD will be highlighted as well as future clinical and research directions.

### Cerebrovascular Complications of Sickle Cell Disease: Stroke and Silent Infarcts

In the most severe forms of SCD, the homozygous SS and the double heterozygous S $\beta$ <sup>0</sup>, the brain is frequently affected (Figure 2). Overt ischemic stroke occurs in 11% of untreated children as a result from stenosis or occlusion in the large arteries of the Circle of Willis [32,33]. Cerebral silent infarcts (CSI), affecting 40% of children by the age of 14, are caused by small vessel disease [34,35] although recent evidence suggests that also a combination of chronic hypoperfusion or hypoxic events, favored by an underlying arteriopathy of the large vessels can lead to CSI [36]. In the past 15 years improvements have been made in the management of stroke and CSI [36,37]. In fact,

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#### \*Correspondence:

Raffaella Colombatti, Department of Child and Maternal Health, Veneto Region Reference Center for Diagnosis and Treatment of Sickle Cell Disease in Childhood, Clinic of Pediatric Hematology-Oncology, Azienda Ospedaliera-University of Padova, Padova, Italy,  
E-mail: rcolombatti@gmail.com

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algorithms for screening, prevention and management of stroke and CSI based on neuroimaging techniques such as Transcranial Doppler (TCD) and Magnetic Resonance Imaging/Angiography (MRI/MRA) are routinely used in clinical practice [37-40].

TCD screening is recommended starting at age 2 years in children with HbSS and HbS $\beta^0$  and those identified at risk of stroke are offered chronic transfusion as stroke prevention [37]. 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 [41]. While TCD allows to identify patients at risk of stroke and initiate appropriate treatment, it is not useful to screen for the other cerebrovascular complications of SCD such as CSI. Moreover, its usefulness in identifying risk of stroke in other genotypes of SCD such as HbSC and HbS $\beta^+$ , in which stroke is less common, has yet to be evaluated.

Screening with MRI/MRA, although unable to identify children at risk of developing CSI, is strongly recommended in many centers starting at age 5 years, when sedation is no longer necessary [36,38,42], 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 [36,37,43], but there is no general agreement on prevention strategies.

### 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 [44] and the United Kingdom benefit from this technique [45]. Data regarding the coverage of TCD screening are not available for other countries of Europe, South America or the Middle East at national level, but only for single center experiences [36,39,42,46,47] 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-Saharan 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 [48-50]. These studies demonstrate the feasibility of primary and secondary prevention programs in low-resource settings with huge numbers of patients. They also allow 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 [51].

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 frequency across populations, although data are still poor and warrant further investigation [52-55]. Moreover, biological factors such as G6PD deficiency and alfa thalassemia co-inheritance as well as coagulation activation and Single Nucleotide Polymorphisms (SNPs) do not seem to have the same role on the genesis of cerebrovascular complications in different populations [56-61].

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 biologic modifying factors of cerebrovascular disease as currently performed in other pathologic conditions [62]. Coordinating cerebrovascular studies across countries and continents can be challenging [50,63-66] but is now warranted to improve patients access to recommended screening tools and better target treatment interventions according to biological disease modifying factors, which may vary across ethnicities.

### Cognition in Sickle Cell Disease

Impaired cognition and poor academic performances are a major morbidity among children and adults with SCD [33]. Children experience general cognitive deficits as assessed by Full Scale IQ (FSIQ), as well as deficiencies in specific domains of cognition (i.e. memory, attention...) [67].

Impairment of cognitive function is reasonable in children who experienced an overt stroke or present CSIs, even at young age, due to the anatomical damage to the brain [67-70]. A recent meta-analysis [71] including most of the published studies exploring cognition described a drop of FSIQ from controls to, patients without CSI, to patients with CSI to patients with stroke (96.68 vs. 89.18 vs. 83.81 vs. 71.08 respectively). Nevertheless, there was a mean difference of -6.90 IQ points in patients without cerebrovascular damage compared to controls.

The pathophysiology of cognitive impairment in children with SCD and normal neuroimaging studies is less clear. In fact, patients with normal TCD and normal MRI/MRA still display cognitive deficits not only on FSIQ, but also in attention, memory and executive functions [32,67,72,73], with profound adverse impact on health, education and quality of life. Recent evidence suggests that both biological and clinical parameters as well as socio-economical and environmental factors can be involved [71].

In fact, anemia severity or hematocrit, oxygen saturation, sleep disturbances, nutritional deficiencies (biological factors) and parent's level of education, household income, immigration status, languages spoken at home, pollution (socio-economical and environmental factors) are all considered to have an effect on cognition in SCD [72-76].

### Cognition: open issues at a global level

The majority of studies exploring cognition and reported in the above paragraph have been conducted in the USA, some in Europe (UK, France, The Netherlands, Italy) and very few in the Middle East or Africa (Kuwait, Cameroon, Nigeria) [77-80]. More has to be done in order to define the role of socio-economic and environmental factors. The latter may be extremely different among populations, similarly to the genetic determinants of phenotype variability and therefore the need to target each one of them in a comprehensive therapeutic approach could vary according to the population or the country. Studies in Africa, South America and India are warranted.

Moreover the more appropriate battery of intellectual function test has not yet been defined, and in many centers cognitive evaluation and educational support are not included as part of comprehensive care, although recommended. Migration movements and multiple languages make even culture free tests difficult and time consuming to administrate, with lack of standardized values for comparison. This could be overcome by technologies that can simplify and standardize cognitive evaluation [81].

## Recent Highlights and Future Directions

The above reported difficulties highlight the need for biomarkers that bridge the gap between early pathophysiological alterations occurring in the brain (micro-vaso-occlusion, small vessel vasculopathy, endothelial dysfunction-intimal proliferation, vascular tone dysregulation), and clinically evident impaired cognition, which seems to be a later manifestation of cerebral damage. Some cerebral abnormalities might be undetectable with conventional imaging studies and the development of more sophisticated imaging techniques [82] might reveal that MRIs which are considered normal with the currently available equipments, present subtle brain parenchymal lesions. In addition, patients with SCD seem to present functional brain abnormalities not evaluable by conventional studies. Functional imaging studies, whether EEG based or MRI based, have recently been applied in SCD and have shown promising insights in exploring clinical manifestations and cognitive abnormalities in this disease [83,84]. Cognitive evoked potentials and EEG analyses revealed abnormal neural networks even without severe anemia, pain or silent infarcts. Altered brain connectivity detected by functional magnetic resonance imaging (fMRI) is associated with increased pain. Functional technologies are promising approaches to explore biological basis of cognition and to be used in prospective interventional trials.

Rehabilitation cognitive programs and tutoring, involving the private and volunteer sectors are useful to improve cognition and academic performances in children with SCD [85].

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