Silent Strokes May Be Involved in Neurocognitive Impairment in Children With Sickle Cell Disease

Bruno Silva

UFPA: Universidade Federal do Para <https://orcid.org/0000-0002-7860-2170>

Ândrea Ribeiro dos-Santos

UFPA: Universidade Federal do Para

Diana Oliveira Ribeiro

USP Ribeirao Preto: Universidade de Sao Paulo Campus de Ribeirao Preto

Tamara Tavares da Cruz

CESUPA: Centro Universitario do Estado do Para

Ana Emília Vita Carvalho

CESUPA: Centro Universitario do Estado do Para

Larissa Nobre Lopes

UFPA: Universidade Federal do Para

Alessandro Cardoso Rodrigues

UFPA: Universidade Federal do Para

Fernando Mendes Paschoal-Junior (✉ tenpaschoal@gmail.com)

UFPA: Universidade Federal do Para

Short Report

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Abstract

Neurological complications are frequent occurrences in children and adolescents with sickle cell disease (SCD). This research has investigated the prevalence of neurovascular and neurocognitive impairments in 17 patients with SCD from Northern Brazil, with aged 6-16 years. Transcranial Doppler Ultrasound (TDU) examinations were performed on patients employing the STOP protocol as a risk score to predict stroke. Neuropsychological assessments were also performed: the Wechsler Intelligence Scale for Children - 4th Edition (WISC-IV). Fisher's Exact Test was used for statistical analyses ($p \leq 0.05$) of the collected dataset. Frequent headaches were a common clinical finding, occurring in over 75% of the children. There were no alterations in cerebral hemodynamics on TDU for over 70% of the patients. In general, patients had below-average scores on most cognitive domains. There was a tendency for correlation between transcranial Doppler results and the WISC-IV indices of total Intelligence Quotient ($p = 0.069$) and Processing Speed Index ($p = 0.082$). *Conclusion:* Most SCD patients showed impairments on cognitive tests, but there was no statistically significant correlation between the presence of neurovascular damage and worse performance on the tests.

What Is Known

- Neuropsychomotor developmental delays are common in children with SCD and are widely reported in the literature. In general, they are associated with cognitive deficits and delay in psychomotor development, hindering school progress and social integration.

What is New:

- In this research, we found that neuropsychomotor impairment was a rare finding, reported in 11% of the patients, but the patients showed worse cognitive performance and we found a trend towards a correlation between TDU with QI and PSI.

Introduction

Sickle cell disease (SCD) is a group of hereditary hemolytic anemias caused by the presence of hemoglobin S that affects about 3.2 million people worldwide, mainly affecting patients of African ancestry[1].

Some of the most severe complications of this disease are neurological. Neurocognitive impairments resulting from this disease are common and probably have a multifactorial etiology. Injury to the brain tissue during childhood and adolescence are associated with cognitive deficits and delay in psychomotor development, hindering school progress and social integration[1]. Moreover, SCD has different forms of expression and severity levels, requiring individualized clinical follow-up and treatment for patients[2].

SCD is the main cause of ischemic stroke during childhood[3], rendering neurological investigations crucial during patient follow-ups to determine prognosis and to identify complications. Transcranial

Doppler ultrasound (TDU) is a technique for detecting neurovascular disorders resulting from this pathology[3]. The TDU measures cerebral blood flow through the insonation of arterial segments, determining the time-averaged mean maximum velocity in the brain vessel. TDU is an economically accessible, safe, and reliable technique compared to other procedures, and due to its reproducibility, is also suitable for monitoring[4].

Thus, this study investigates the prevalence of neurovascular and neurocognitive impairments in children and adolescents with SCD using TDU to determine the correlation between cerebral circulation and neurocognitive performance.

Materials And Methods

The studied population consisted of 17 patients between 6 and 16 years old with SCD. Investigations were conducted between March 2018 and January 2020 in João de Barros Barreto University Hospital and Pará State Blood Center. Those who had any cardiovascular, metabolic, or immunological comorbidities or that refused to participate in the research were excluded from the study.

A questionnaire developed by the researchers was applied to patients during medical visits. The instrument collected sociodemographic information, education status, household income, as well as medications in use, history of blood transfusions, and neurological symptoms. Additional information was obtained from patient medical records held in Pará State Blood Center and from neuropsychological assessment sessions performed by an expert in pediatric neuropsychology. Neurocognitive assessments were performed using the Wechsler Intelligence Scale for Children – 4th Edition (WISC-IV) for assessing the intellectual capacity of children and the problem-solving process, comprising the Verbal Comprehension Index (VCI), Perceptual Reasoning Index (PRI), Working Memory Index (WMI) and Processing Speed Index (PSI), in addition to the Total Intelligence Quotient (IQ). For neurovascular evaluations, TDU was performed by a neurologist with extensive experience in neurovascular imaging to analyze the brain hemodynamics, measuring the blood flow velocity of the M1 segment of the middle cerebral arterial and the internal carotid bifurcation employing the Stroke Prevention Trial in Sickle Cell Anemia (STOP) protocol in risk stratification for stroke. Patients with values below 170 cm/s are considered normal, those with values between 170 to 199 cm/s are grouped into conditional, and finally, those who exhibit 200 cm/s or higher are defined as abnormal[5].

Fisher's exact test was performed to analyze the correlation between TDU, clinical variables, neuropsychological variables, and neuropsychological domains. These tests were performed using the GraphPad Prism® 5.01 software ($p \leq 0,05$).

Results

We obtained data from 17 patients with SCD with a mean age of 12.05 (± 3.09) years. In the overall sample, 16 out of the 17 patients carried the homozygous *HB*SS* genotype (sickle cell anemia) and one

individual was a heterozygous carrier, with the *HB*SC* genotype. The racial profile of the patients showed that our sample consisted of 35.29% White and 64.71% Black or Admixed, with a similar proportion of men and women. The majority of participants had low socioeconomic status and an average of 4-6 years of formal education (Table 1).

Table 1
– Sociodemographic and clinical characterization of the patients.

Sociodemographic characteristics	N	%
Female	9	52.94
Male	8	47.05
Ethnicity		
White	6	35.29
Black	1	5.88
Admixed	10	58.82
Household income		
\$1.52 – 3.04 per day	15	88.23
≥ \$4.57 per day	2	17.76
Years of formal education		
1-3 years	2	11.76
4-6 years	10	58.82
7-10 years	5	29.41
Clinical features	N	%
Headache		
Episodic	9	52.94
Frequent	4	23.52
Absent	4	23.52
Epilepsy		
Yes	2	11.76
No	15	88.23
Neuropsychomotor developmental delay		
Yes	2	11.76
No	15	88.23
History of the previous stroke		
Yes	4	23.52

Sociodemographic characteristics	N	%
No	13	76.47

Regarding the TDU exam conducted in the 17 study participants, two had established cerebral vasculopathy, while two patients showed changes in blood flow, indicating a higher risk of having a stroke. Moreover, frequent headache was the most common clinical finding in our sample. Otherwise, seizures and neuropsychomotor developmental delay were rare findings, reported in 11% of the assessed patients.

In general, patients scored below the expected mean for age on most of the cognitive domains assessed by the WISC-IV. Furthermore, there was a trend towards a correlation between transcranial Doppler and some sub-items of the WISC-IV: TDU with total IQ (p -value = 0.069) and TDU with PSI (p -value = 0.08) (Figure 1).

The data that support the findings of this study are available from the corresponding author upon request.

Discussion

The Brazilian population exhibits a great ethnic mixture in its genetic composition, with a strong African contribution [6]. In our study, this pattern was corroborated through the sociodemographic profile of the participants, with most participants being Black or Admixed.

It is interesting to note that the majority of patients have low socioeconomic status and substantial age-grade distortion. It had been shown that SCD is a disease that causes recurrent infections, pain crises, need for blood transfusions, and frequent hospitalizations, directly affecting the quality of life of patients in terms of school performance, social adjustment, and adequate nutrition, factors associated with worse disease prognosis[7].

In our dataset were shown that approximately 25% of the participants had a previous documented episode of cerebral ischemic, despite having received treatment for the disease. However, these rates may differ from those in the literature, depending on which study is been compared[8, 9]. Frequent headache was a common clinical finding in our samples (76.46%), exceeding rates reported in studies involving larger samples[10]. Moreover, seizures and neuropsychomotor developmental delay were rare findings (11.76%). This is interesting data since neuropsychomotor developmental delays in children with SCD are widely reported in the literature[10, 11].

Towards the cognitive tests, the patients scored below the expected mean for age on most of the assessed domains. In addition to presenting deficits in cognitive domains, these patients exhibited a progressive neurological decline characterized by an increased incidence of cognitive deficits with advancing age, possibly due to greater exposure to ischemic neurological events resulting from cerebral

microinfarcts[8, 9]. The presence of significant deficits in the neurocognitive functioning of children with SCD has been reported in several case-control studies, and are present even in patients who had not experienced a stroke[11].

Our data also exhibited a trend towards a correlation between TDU with PSI and total IQ, suggesting that an individual with normal TDU tends to have worse PSI, as well as lower total IQ. In a meta-analysis study evaluating cognitive functions in children with SCD, significant differences in statistical tests were found[2]. We hypothesize that a more significant correlation may be found if these tests were applied to a larger sample.

Nonetheless, another factor should be considered as a potential confounder, influencing the statistical results: patients who had small brain infarcts that could not be identified by TDU examinations. Although the stroke detection protocol used in this study has shown to be effective according to the literature, there are more advanced techniques, such as computed tomography angiography, that are highly sensitive for identifying small brain infarcts[10]. Therefore, cognitive impairments may be associated with silent infarcts, as they cause brain micro-injuries[12]. Periodic neuropsychological assessment, in line with standard imaging exams, can be a great ally in identifying and monitoring neurological damages resulting from the disease.

Abbreviations

IQ	Total Intelligence Quotient
PRI	Perceptual Reasoning Index
PSI	Processing Speed Index
SCD	Sickle cell disease
STOP	Stroke Prevention Trial in Sickle Cell Anemia
TDU	Transcranial Doppler Ultrasound
VCI	Verbal Comprehension Index
WISC-IV	Wechsler Intelligence Scale for Children – 4 th Edition
WMI	Working Memory Index

Declarations

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Conflicts of interest/Competing interests: The authors have no competing interests to declare that are relevant to the content of this article.

Availability of data and material: The data that support the findings of this study are available from the corresponding author upon request.

Code availability: Not applicable.

Authors' contributions: All authors contributed to the study conception and design. Material preparation and data collection were performed by Bruno Silva, Tamara Tavares da Cruz, Fernando Mendes Paschoal-Junior, Ana Emília Vita Carvalho, Alessandro Cardoso Rodrigues and Larissa Nobre Lopes. The analysis and the first draft of the manuscript were written by Diana Oliveira Ribeiro, Bruno Silva and Ândrea Ribeiro-dos-Santos. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval: All procedures performed in this study involving human participants were conducted in accordance with the ethical standards of the institutional and research committees and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards, and was previously approved by the Research Ethics Committee of Pará State University Center (approval number 1.941.530/2017).

Consent to participate: The patients took part in this study on a voluntary basis, received no remuneration, and had previous approval from their parents or legal guardians.

Consent for publication: Not applicable.

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Figures

Figure 1