RESEARCH ARTICLE

Transcranial Doppler in hemoglobin SC disease

Camilo Vieira^{1,2} | Carolina Nogueira Costa de Oliveira³ | Ludmila Araújo Borges de Figueiredo³ | Rayra Pereira Santiago^{2,4} | Corynne Stephanie Ahouefa Adanho^{2,4} | Sanzio Silva Santana^{2,4} | Caroline Lang Burak⁵ | Isa Menezes Lyra⁵ | Marilda Souza Goncalves^{2,4}

¹Ambulatório Pediátrico de Doença Cerebrovascular, Hospital Universitário Professor Edgard Santos, Universidade Federal da Bahia, Bahia, Brazil

²Centro de Pesquisas Gonçalo Moniz, Fundação Oswaldo Cruz, Bahia, Brazil

³Universidade Salvador, Bahia, Brazil

⁴Departamento de Análises Clínicas e Toxicológicas, Faculdade de Farmácia, Universidade Federal da Bahia, Bahia, Brazil

⁵Departamento de Hematologia, Hospital Universitário Professor Edgard Santos, Universidade Federal da Bahia, Bahia, Brazil

Correspondence

Camilo Vieira, Pediatric Cerebrovascular Disease Outpatient Center, Hospital Universitario Professor Edgard Santos, Universidade Federal da Bahia, Rua Augusto Viana. s/n, Canela, Salvador, Bahia 40110-060, Brasil.
Email: dr.camilovieira@gmail.com

Abstract

Background: Stroke is a severe clinical disorder in sickle cell disease (SCD), and few studies have evaluated transcranial Doppler (TCD) flow velocities in hemoglobin SC disease (HbSC). The guidelines for stroke risk are based on evaluations in sickle cell anemia (SCA) or HbS/ β thalassemia.

Procedure: In this study, we compare cerebral blood flow in patients with SCD stratified by genotypes. A total of 1,664 pediatric patients with SCD underwent TCD velocity screening, and the time-averaged maximum mean velocity (TAMM) was determined in the middle cerebral artery (MCA), anterior cerebral artery (ACA), and distal intracranial internal carotid artery (ICA).

Results: Abnormal velocities were not identified in the ACA; therefore, we only use ICA and MCA velocities. TAMM from the left and right in the ICA and MCA was 134.3 ± 32.0 and 134.4 ± 32.6 cm/s in patients with SCA, and 105.2 ± 20.6 and 104.7 ± 20.0 cm/s in the patients with HbSC, respectively. Mean TAMM between right and left ICA/MCA was 134.5 ± 30.5 cm/s in the SCA group, and 104.9 ± 19.3 cm/s in the HbSC group. Notably, our data show that TCD velocities were significantly lower among the patients with HbSC compared to SCA. TAMM was negatively correlated with hemoglobin and hematocrit in both genotypes.

Conclusion: These results suggest that a different cut-off value for abnormal TCD velocities could be considered for patients with HbSC. Additional studies are warranted to determine the actual risk of stroke in HbSC genotype associated with this possible TCD risk value.

KEYWORDS

hemoglobinopathies, neurology and sickle cell, sickle cell disease, transcranial Doppler ultrasound

1 | INTRODUCTION

Stroke is a common clinical manifestation in sickle cell disease (SCD) in children of 1 year or older.^{1–5} However, there are differences in stroke incidence among the SCD genotypes, with a rate of 0.61/100 patients/year for sickle cell anemia (SCA) patients, 0.17/100 patients/year for hemoglobin SC disease (HbSC), 0.11/100 patients/year for HbS/ β^+ thalassemia, and 0.11/100 patients/year for HbS/ β^0 thalassemia.³

The transcranial Doppler (TCD) monitors the cerebral mean blood flow velocities of patients with SCD allowing the identification of

those with an increased risk to developing stroke.^{6–10} The stratification of stroke risk can be determined by measuring the average maximum velocity or the time-averaged maximum mean velocity (TAMM) in the distal intracranial internal carotid artery (ICA), anterior cerebral artery (ACA), and middle cerebral artery (MCA). Values ≥ 200 cm/s are considered of high risk, whereas values < 170 cm/s are considered of low risk; speeds ≥ 170 cm/s and < 200 cm/s are considered conditional.⁶ After the first episode of stroke in SCA patients, there is a 46–90% risk of stroke recurrence without prophylactic red cell transfusion therapy.^{11,12} Despite the high incidence of stroke in patients with HbSC compared with the pediatric population without SCD,^{3,4} few studies have evaluated flow velocities by TCD in this patient subset, using TCD values for measuring risk stratification that are obtained from SCA or HbS/ β thalassemia patients.^{3,6,11} Therefore, theoretically, these values may not extrapolate well to patients with HbSC. The aim

Abbreviations: ACA, anterior cerebral artery; HbSC, hemoglobin SC disease; ICA, Intracranial internal carotid artery; MCA, Middle cerebral artery; SCA, sickle cell anemia; SCD, sickle cell disease; SD, standard deviation; STOP, Stroke Prevention in Sickle Cell Anemia; TAMM, time-averaged maximum mean velocity; TCD, transcranial Doppler

of this study is to compare the characteristics of cerebral blood flow among patients with SCA and HbSC using TCD.

2 | METHODS

Patients with SCD evaluated from August 2011 to May 2015 in the Pediatric Cerebrovascular Disease Outpatient Center at the Hospital Universitario Professor Edgard Santos of the Universidade Federal da Bahia were included in the study. Only genotype HbSS and HbSC between 2 and 16 years old were included. Patients with a prior overt stroke event, on hydroxyurea therapy, with a simple transfusion in the last 3 months or on chronic blood therapy regimens were not included in the study. One examiner performed the TCD in all patients using the same device (Doppler; probe 2 Mhz model, Ezdop, Germany). The TAMM was determined in the ICA, ACA, and MCA. Since we did not identify abnormal values in the ACA, we only consider the highest velocity obtained of ICA and MCA. If TAMM in all arteries was between 70 and 170 cm/s, the examination was considered normal; the TAMM ≥ 170 cm/s, but less than 200 cm/s, in any one artery was considered conditional; the TAMM ≥ 200 cm/s in an artery was considered abnormal, and the TAMM < 70 cm/s was considered low. The failure to detect the flux wave during the examination was characterized as inadequate. Patients were analyzed and stratified according to SCD genotypes (SCA and HbSC). Venous blood was collected from patients for hematological analysis using electronic cell counter Ruby Cell Dyn (Abbott Diagnostics, Lake Forest, IL).

The Shapiro–Wilk test was used to determine the quantitative variables distribution and the independent Student's *t*-test was used to compare the means among the groups of quantitative variables with normal distribution. The Spearman's rank correlation coefficient was used to measures the linear relation between quantitative data. The results were considered significant if the *P* value was less than 0.05. The data analysis was performed using SPSS version 21 (SPSS Inc., Chicago, IL).

This study was approved by the Research Board of the Secretary of Health of the state of Bahia (SESAB) 054/2011, and all parents or guardians provided written informed consent in accordance with the Helsinki Declaration of 1975 and its revision.

3 | RESULTS

A total of 2,774 patients with SCD were evaluated with TCD examination from August 2011 to April 2015 in the Pediatric Cerebrovascular Disease Center at the Hospital Universitario Professor Edgard Santos of the Universidade Federal da Bahia. A total of 1,110 patients were excluded (some had more than one exclusion criteria): standard deviation (SD) genotype: 10; sickle cell beta thalassemia: 70; age less than 2 years old or more than 16 years old: 75; prior overt stroke: 116, blood transfusion therapy: 183; hydroxyurea use: 656. A total of 1,664 SCD were investigated, with a mean $\pm$ SD age of 6.5 ± 3.8 years, and 48.6% were females; 1106 (66.5 %) patients with SCA were investigated, with

FIGURE 1 Time-averaged maximum mean velocity in the internal carotid artery and middle cerebral artery (ICA/MCA) in children and adolescents with sickle cell disease (HbSS and HbSC) ($P < 0.0001$; independent Student's *t*-test)

a mean age of 6.8 ± 3.9 , and 47% were females. In addition, 558 (33.5 %) patients with HbSC were investigated, with a mean age of 6.0 ± 3.5 years, and 51.6% were females.

The mean TAMM was 124.5 ± 31.8 and 124.4 ± 32.2 cm/s in the right and left ICA/MCA, respectively. The mean TAMM in the left and right ICA/MCA was 134.3 ± 32.0 and 134.4 ± 32.6 cm/s in the patients with SCA, and 105.2 ± 20.6 and 104.7 ± 20.0 cm/s in the patients with HbSC, respectively. A mean TAMM between right and left ICA/MCA was 134.5 ± 30.5 cm/s in the SCA group, and 104.9 ± 19.3 cm/s in the HbSC group (Fig. 1). These differences were statistically significant ($P < 0.001$).

Hemoglobin and hematocrit were assessed in a smaller number of these patients. We evaluated 68 patients with HbSC and 79 patients with HbSS. The TAMM was correlated with hemoglobin and hematocrit in both genotypes. In the HbSC genotype, a negative correlation was found between TAMM and hemoglobin ($R = -0.3390$, $P = 0.007$), and between TAMM and hematocrit ($R = -0.3470$, $P = 0.0057$) (Figs. 2A and 2B). In the HbSS genotype, a negative correlation was also found between TAMM and hemoglobin ($R = -0.2310$, $P = 0.0447$) and between TAMM and hematocrit ($R = -0.2649$, $P = 0.0208$) (Figs. 2C and 2D).

4 | DISCUSSION

A few studies have evaluated TCD examination of a large number of patients with SCD.^{13,14} Adams et al.¹³ published the TCD results from the Stroke Prevention in Sickle Cell Anemia (STOP) study, which was a clinical trial that included 5613 SCD children; they found that 67% of patients with SCD exhibited normal TCD results, 17.6% exhibited conditional TCD results, 9.3% exhibited abnormal results, and 6.1% exhibited inadequate TCD evaluation. Another important study was performed by Enninfu-Eghan et al.,¹⁴ which evaluated the occurrence of stroke and the response to transfusion therapy in 475 patients with SCD over 8 years of follow-up prior to TCD examination, and in 530 patients with SCD over 8 years of follow-up with TCD. However, after some loss, the analysis of 404 patients with SCD revealed 14.4% with conditional TCD, 12.5% with abnormal, and 0.7% with an inconclusive

FIGURE 2 Correlations of maximum TMMV with markers of severity in patients with HbSS and HbSC. (A) Correlation between hemoglobin and TMMV in HbSC patients; (B) correlation between hematocrit and TMMV in HbSC patients; (C) correlation between hemoglobin and TMMV in HbSS patients; (D) correlation between hematocrit and TMMV in HbSS patients

TABLE 1 Differences in transcranial Doppler (TCD) ultrasound screening among sickle cell anemia (HbSS) and sickle cell SC disease (HbSC)

Transcranial Doppler result, N (%)						
Genotype	Normal, N (%)	Conditional, N (%)	Abnormal, N (%)	Inconclusive, N (%)	Low, N (%)	Total
HbSS	832 (75.2)	158 (14.3)	80 (7.2)	19 (1.7)	17 (1.5)	1,106
HbSC	536 (96.1)	5 (0.9)	4 (0.7)	6 (1.1)	7 (1.3)	558
Total	1,368 (82.2)	163 (9.8)	84 (5.0)	25 (1.5)	24 (1.4)	1,664 (100)

TCD evaluation. Additionally, the use of blood transfusion was successful in lowering TCD velocity among the patients with SCD, which was also demonstrated by Kwiatkowski et al.¹⁵

Our results differed from a previous report with 85 Brazilian children and teenagers with SCD, which found lower numbers of abnormal TCD.¹⁶ However, the difference between these two studies may be explained by the sample size, once our study evaluated a larger number of patients with SCD.

Deane et al.¹⁷ evaluated 47 TCD tests from patients with HbSC and showed a TMMV velocity in the MCA of 94 cm/s. In our study, patients with HbSC had an average TMMV velocity of 104.9 ± 19.3 cm/s in the MCA/ICA. Rees's study did not identify individuals with high speeds according to the STOP protocol.⁶ This study analyzed a greater number of children and teenagers with HbSC, and the comparison of patients with SCA showed that the TMMV velocities in patients with HbSC were significantly lower, in accord to previous report from our group.¹⁸ Using the current TCD velocity definitions of stroke risk for SCA, only 0.7% of patients with HbSC presented a high risk of stroke (Table 1). However, the differences in the mean TMMV velocities in the both MCA/ICA of SCA (134.5 ± 30.5 cm/s) and patients with HbSC (104.9 ± 19.3 cm/s) may suggest that different cut-off values should be

used to define abnormal cerebral artery blood flow velocity and stroke risk for this genotype.

The average TMMV velocity in the MCA/ICA in patients with HbSC was 104.9 cm/s, with a SD of 19.3 cm/s, which allows us to consider a normal rate (two standard deviations) in patients with HbSC values above 143.5 cm/s. In this case, velocities >143.5 cm/s could be considered as a cut-off point for patients with HbSC. According to this parameter, 39 (7.0%) individuals in our study would have high values. In the study conducted by Deane et al.,¹⁷ the TMMV velocity in the 98th percentile was 128 cm/s and the authors could not assign stroke risk to this population.

We found that TMMV was negatively correlated with hemoglobin and hematocrit in both genotypes. In a previous report, the increase in cerebral blood flow and flow velocity are associated with chronic anemia.⁶ These disorders can lead to cerebrovascular damage and stroke.⁶

In the present study, less than 1.6% of patients with HbSC presented TMMV higher than 170 cm/s. However, the mean MCA/ICA velocities were different between SCA and HbSC. A TMMV higher than 143.5 cm/s can be considered as abnormal, but whether or not it means an increase in stroke risk is unknown. Follow-up brain

MRI/MRA imaging, serial TCD exams, and close clinical monitoring would be needed to determine the actual risk of stroke for patients with HbSC with TAMM in this range.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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