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ARTICLE

Patients with sickle cell disease are frequently excluded from the benefits of transcranial doppler screening for the risk of stroke despite extensive and compelling evidence

Pacientes com doença falciforme são frequentemente excluídos dos benefícios do screening com doppler transcraniano para avaliação do risco de acidente vascular cerebral, apesar de evidência extensa e convincente

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ABSTRACT

Transcranial doppler (TCD) is a strategic component of primary stroke prevention in children with sickle cell disease (SCD). This study was conducted to examine the TCD characteristics of children with SCD in nine different medical centers in Brazil. **Methods:** Transcranial doppler was performed in accordance with the Stroke Prevention Trial in Sickle Cell Anemia Protocol. **Results:** Of the 396 patients, 69.5% had homozygous SS hemoglobin. The TCD result was abnormal in 4.8%, conditional in 12.6%, inadequate in 4.3% and abnormally low in 1% of patients. The highest mean flow velocities were 121±23.83cm/s and 124±27.21cm/s in the left and right middle cerebral artery respectively. A total of 28.8% patients (mean age 9.19±5.92 years) were evaluated with TCD for the first time. **Conclusions:** The SCD patients were evaluated with TCD at an older age, representing an important missed opportunity for stroke prevention. Since TCD screening in patients with SCD is important to detect those at high risk for stroke, it is recommended that this screening should be made more readily available.

Keywords: sickle cell disease; ultrasonography, doppler, transcranial; stroke.

RESUMO

Doppler transcraniano (DTC) é um componente estratégico da prevenção primária do acidente vascular cerebral (AVC) em crianças com doença falciforme (DF). Este estudo foi realizado para examinar as características do DTC de crianças com DF em nove centros médicos diferentes no Brasil. **Métodos:** DTC foi realizado de acordo com o protocolo de Stroke Prevention Trial in Sickle Cell Anemia Protocol (STOP). **Resultados:** Dos 396 pacientes avaliados, 69,5% eram homozigotos para hemoglobina SS. DTC foi anormal em 4,8%, condicional em 12,6%, inadequado em 5,3% e anormalmente baixo em 1%. As máximas velocidades de fluxo médio foram 121 ± 23,83cm/s e 124 ± 27,21 cm/s nas artérias cerebrais media esquerda e direita, respectivamente. Um total de 28,8% dos pacientes (média de 9,19 ± 5,92 anos) foram avaliados com o DTC pela primeira vez. **Conclusões:** Pacientes com DF foram avaliados com DTC numa idade considerada avançada, o que representa uma importante oportunidade perdida para a prevenção de AVC nessa população. Uma vez que a triagem com DTC em pacientes com DF é essencial para detectar aqueles com alto risco de AVC, recomenda-se que essa triagem seja amplamente disponível no país.

Palavras-chave: anemia falciforme; ultrassonografia, doppler transcraniano; acidente vascular cerebral.

Transcranial doppler (TCD) is a non-invasive ultrasound first described by Aaslid et al.[1] in 1982 as a means of recording blood flow velocities in the basal cerebral arteries. It is relatively inexpensive, repeatable and portable, hence it is a more convenient means of monitoring cerebral blood flow velocities and vessel pulsatility than other neuroimaging techniques[2,3].

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For individuals with sickle cell disease (SCD), TCD is a recommended routine screening test for primary stroke prevention, serving as the key test in determining the need for chronic blood transfusion. In 2004, Fullerton et al.[4] reported a significant decline in the annual rates of admissions for a first stroke among Californian children with SCD following repeated TCD examinations and the implementation of a blood transfusion program. They found that the rate for a first stroke was 0.88/100 person-years in 1991 – 1998 compared to 0.50/100 person-years in 1999 and 0.17/100 person-years in 2000.

Despite its usefulness, TCD is highly operator-dependent, hence in many countries where TCD facilities are not widely available, the examination is unfortunately underutilized[2,3]. This descriptive cross-sectional study was conducted to examine the baseline characteristics and TCD results of children and adolescents with SCD who were screened in nine different medical centers in Brazil.

METHODS

This prospective cross-sectional study was carried out in nine medical centers from January 2013 to December 2013 (see acknowledgements). The patients were chosen by convenience method in which all consecutive patients with SCD evaluated with TCD during the study period were recruited. The study population consisted of children and adolescents with SCD who routinely attended the hematology clinic of their respective medical center. All the patients were in their steady state at the time of the study. Those with fever, acute illness, a painful crisis in the preceding four weeks or those who had a blood transfusion in the preceding month were not included. The study was approved by the Ethics Committee and all the participating centers gave their consent before starting the registry.

Demographics and clinical assessment of patients with sickle cell disease

Data on epidemiological characteristics (age and sex); hydroxyurea therapy, participation in a chronic blood transfusion program; SCD genotype; previous TCD ultrasonography data and past history of stroke were collected using a semi-structured questionnaire.

TCD ultrasonography

The mean maximum velocities in the right and left middle cerebral arteries (MCA) were recorded for each child, focussing attention on the highest mean flow velocities, *i.e.* time-averaged mean maximum velocity (TAMM) on either side of the MCA. Maximum flow velocity was recorded at an insonation depth of 40–60 mm. The findings were categorized as normal (70–169cm/s), conditional (170–199cm/s), abnormal (≥ 200cm/s) or abnormally low (< 70cm/s) velocities, according to the Stroke Prevention Trial in Sickle Cell Anemia Protocol. The frequency of flow velocity asymmetry defined as an interhemispheric flow velocity difference of at least 30 cm/s between segments in the MCAs, was also analysed. All TCDs were done by the same author (D.L.R.) who visited all the centres during the study period as part of a TCD itinerant program in SCD. A 2-MHz pulsed Doppler ultrasonograph (Model EME TC 2000, Nicolet, Madison, Wisc., USA) was used.

A total of 396 patients with SCD were evaluated in nine different medical centres. Two hundred and seven (52.3%) were males. The mean age of the patients was 9.97 ± 5.02 years with 99 (25.0%) patients in the age group 1-5 years. One hundred and twenty three (31.1%) patients were 6–10 years and the remaining 174 (43.9%) were older than 10 years. Most patients had hemoglobin SS disease (69.5%). The other genotypes were hemoglobin SC (11.0%); S-b-thalassemia (7.5%); and 12.1% with an unknown genotype. Thirteen (3.3%) of the 396 patients had a previous history of stroke. One hundred and four patients (26.3%) were using hydroxyurea and 20 patients (5.1%) were on periodic blood transfusion at the time of the screening.

Statistical analysis

Descriptive analyses, including means and standard deviations (SD), were used to describe the patients' characteristics. The independent samples t test was used to compare means between groups. Nonparametric data were compared using the Mann- Whitney test. Categorical variables were compared with the chi-square test. A two-tailed p-value of < 0.05 was considered statistically significant.

RESULTS

TCD profile of the 396 patients

The TAMM velocity was 121 ± 23.83 cm/s in the left MCA and 124 ± 27.21 cm/s in the right MCA. Three hundred and six (77.3%) patients had normal TCD velocities. A total of 69 patients (17.4%) had elevated TCD velocities ≥ 170cm/s; of whom 50 (12.6%) had conditional risk velocities of 170-199cm/s and 19 (4.8%) had abnormal risk velocities of ≥ 200cm/s. Four patients (1.0%) had abnormally low TCD velocities and 17 (4.3%) had inadequate temporal bone windows. Hence, a total of 73 patients had either a conditional, abnormally low or abnormal TCD. The frequency of flow velocity asymmetry was 7.6%.

Patients with a previous history of stroke had lower TAMM velocities in both the right and left MCA than those without a previous stroke (113.83 ± 0.8 cm/s versus 124.81 ± 27.4 cm/s, $p < 0.01$; and 116.67 ± 0.3 versus 129.31 ± 21.1 cm/s, $p < 0.01$, respectively). Similarly, those on chronic blood transfusion (CBT) had lower TAMM velocities in the right and left MCA (114.92 ± 2.09 cm/s versus 125.01 ± 27.6 cm/s, $p<0.01$; and

107.21 ± 1.22 versus 127.88 ± 4.1 cm/s, p < 0.01, respectively). However, there were no differences in blood flow velocities of those taking hydroxyurea and those not taking it.

One hundred and fourteen (28.8%) of the 396 patients were evaluated with TCD ultrasonography for the first time during the study period. Their mean age was 9.19 ± 5.92 years and 101 (88.6%) of them were older than two years, the recommended age for the first TCD evaluation. Five (4.4%) of the 114 patients who were evaluated for the first time had a history of stroke. Two (10.5%) of the 19 patients with abnormal risk velocities; 14 (28.0%) of the 50 with conditional risk velocities; two (50.0%) of the four with abnormally low velocities and nine (30.0%) of the 30 patients with blood flow asymmetry were evaluated for the first time with TCD during the study period.

Comparison of the 73 patients with abnormality in TCD velocity and the 306 patients with normal TCD velocities (excluding the 17 patients with inadequate temporal bone windows)

With respect to gender, previous stroke, the use of hydroxyurea and being the first TCD evaluation, the proportions of patients with normal TCD velocities and those with any abnormality in the TCD velocity (abnormal risk, conditional risk and abnormally low velocity) were similar (Table). However, patients with abnormality in TCD velocities were younger than those with normal TCD velocities (7.71 ± 4.13 versus 10.25 ± 4.94 years, p < 0.001), had more flow velocity asymmetry (p = 0.028) and were more frequently on chronic blood transfusion (p = 0.012).

DISCUSSION

The cost-effectiveness, portability and repeatability of TCD make it an ideal neuroimaging technique, especially for patients with SCD who need regular monitoring for primary stroke prevention[2,5,6]. Patients with SCD are at risk for a spectrum of brain injuries such as subclinical infarction, acute ischemic stroke and hemorrhage due to the high level of circulating irreversibly-sickled red blood cells and their adherence to the vascular endothelium. Hence, SCD patients with abnormal TCD velocities should be routinely treated with hypertransfusion therapy in order to lower sickle hemoglobin to less than 30% of total haemoglobin[7,8].

In this study, about five percent of the SCD patients from the nine medical centres had abnormal TCD velocities while 12.6% had conditional risk velocities. The frequency of asymmetry was 7.6%. Also, those with any form of TCD abnormality had more flow velocity asymmetry (p = 0.028) and were more frequently on chronic blood transfusion (p = 0.012) than those with normal TCD velocities. These findings are consistent with previous reports[8,9]. In a study evaluating Brazilian children with homozygous SS, 1.6% had abnormal TCD velocities and none of those with heterozygous SCD had any abnormality[10]. Another Brazilian series also demonstrated that TCD velocities of children with SCD from Sergipe, northeast Brazil, was similar to international standards[11].

A total of 13 patients (3.3%) had a previous history of stroke. The usefulness of TCD in patients with previous stroke is not well established. Patients with SCD and a history of stroke should be treated with periodic blood transfusion, another factor that could potentially alter TCD results[12,13]. Our study data was collected from practising TCD clinics in Brazil. Therefore, the indications for the examinations were at the discretion of the treating physicians. The ordering of TCD in patients with a previous stroke or on chronic blood transfusion reflects some lack of familiarity with the method and its indications.

Our study showed that 28.8% of the patients with SCD were evaluated with TCD ultrasonography for the first time during the study period and had the evaluation at an older

Table. Comparison of the 73 patients with abnormal, conditional or abnormally low TCD velocities and the 306 patients with normal TCD velocities.

Variables	Total (n = 379)*	Normal TCD velocities (n = 306)	Abnormal, conditional or abnormally low TCD (n = 73)	p-value
Age (mean ± SD) years	9.77 ± 4.90	10.25 ± 4.94	7.71 ± 4.13	< 0.001
Gender, n (%)				
Male	177	139 (45.4)	38 (52.1)	0.308
Female	202	167 (54.6)	35 (47.9)	
Previous stroke	6	5 (1.6)	1 (1.4)	0.125
No previous TCD examination	111	93 (30.4)	18 (24.7)	0.391
Hydroxyurea therapy	102	86 (28.1)	16 (21.9)	0.095
Chronic transfusion therapy	14	9 (2.9)	5 (6.8)	0.012
Flow velocity asymmetry	30	18 (5.9)	12 (16.4)	0.028

SD: Standard deviation; TCD: Transcranial doppler; Normal TCD velocities TAMM: 70–169 cm/s; Conditional TCD velocities TAMM: 170–199 cm/s, Abnormally low TCD velocities TAMM < 70 cm/s velocity, Abnormal TCD velcities TAMM ≥ 200 cm/s). TAMM: time-averaged mean maximum velocity - highest mean flow velocities on either side of the MCA; *The 17 patients with inadequate windows were not included.

age (mean age of 9.19 ± 5.92 years). It should be noted that 88.6% of patients who had TCD for the first time were older than two years. This represents a missed opportunity for stroke prevention, especially considering the fact that 4.4% of them had a past history of stroke and those with TCD abnormalities (i.e. those with abnormally low, conditional risk or abnormal risk velocities) were significantly younger than those with normal TCD velocities, (7.71 ± 4.13 versus 10.25 ± 4.94 years, $p < 0.001$). It is also a clear deviation from the guideline for TCD screening in SCD children, which recommends the first evaluation at the age of two years[12,13].

Although we did not examine factors responsible for late screening in the present study, several causes have been previously identified. Armstrong-Wells et al, in their report on utilization of TCD screening for primary stroke prevention in children with SCD, found that proximity to the screening center was the only independent predictor of TCD screening and that children living farther from a vascular laboratory were less likely to be screened[14]. Increased availability of TCD screening is therefore imperative to improve the utilization of this effective primary stroke prevention strategy.

Our study has some limitations. Firstly, 12.1% of the patients did not have a genotype determined in their medical records. This reflects the poor registration of medical information in some centers in the country, especially due to the lack of use of electronic medical records. Secondly, the clinical characterization of the patients with previous stroke and the reasons for chronic blood transfusion in our series were also not registered, for the same reason. Finally, the cross-sectional design of the present registry does not allow conclusions on the long-term stroke risk in our patients. However, the objective of our study was to describe the characteristics of TCD utilization in SCD patients in the country and to point out possible failures in the screening program in order to design improvement strategies. Public reporting has been associated with better outcomes and the basis for effective public reporting is the transparency of data[15]. Therefore, even with the above limitations, this study points out important gaps in the TCD screening process in patients with SCD in our country and can form the basis for redesigning the program in Brazil.

In conclusion, despite the extensive and compelling evidence that supports the use of TCD in patients with SCD, substantial numbers were excluded from the benefits of this intervention in early childhood in the nine centers evaluated. In developing countries, this exclusion commonly arises from limited access to healthcare facilities, dearth of TCD experts and facilities, and insufficient TCD standardization.

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