Abnormal transcranial Döppler ultrasonography in children with sickle cell disease

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Background: *Stroke is a potentially fatal complication of sickle cell disease in children between 2-16 years and transcranial Döppler has been recommended as a screening method in these cases.*

Objective: *The main goal of this study was to correlate transcranial Döppler results to complications related to stroke in sickle cell disease and baseline characteristics of the population.*

Methods: *This was an observational study of children and adolescents with ages between 2-16 years with sickle cell disease who were followed in three centers.*

Results: *From January 2008 to July 2009, 902 patients were enrolled in this study. The median age was 6.5 years (range: 1.8-15.8), 52.3% were male, 74.4% had hemoglobin SS; 221 (28.6%) had at least one complication associated with sickle cell disease. A total of 773 patients performed transcranial Döppler; in 91.2% this was a method of screening. Conditional or abnormal transcranial Döppler results were more common in patients with sickle cell disease complications versus those without complications (ODDS ratio = 3.18; 95% Confidence interval = 1.92-5.27). There was a significant difference in the frequency of conditional or abnormal transcranial Döppler results in patients with abnormal laboratory results compared to those without abnormalities (OR=4.03); 95% confidence interval = 2.30-7.06.*

Conclusions: *Conditional or abnormal transcranial Döppler results were significantly more frequent in patients with complications of sickle cell disease confirming the increased risk of stroke in this subgroup of patients. This observation reinforces the recommendation of transcranial Döppler as a screening test for all patients with sickle cell disease with ages between 2 and 16 years.*

Keywords: *Ultrasonography, Döppler, transcranial; Anemia, sickle cell; Stroke; Cerebrovascular circulation, Child*

Introduction

Strokes are a well known and potentially fatal complication of sickle cell disease (SCD). Based on currently available data, transcranial Döppler ultrasonography (TCD) is recommended as a screening method for all children between 2 and 16 years of age with SCD, allowing the identification of patients at high risk of strokes, such as those with blood flow velocities in the internal carotid artery (ICA) and middle cerebral artery (MCA) above 200 cm/s. This strategy offers the opportunity for appropriate decisions about primary prevention of cerebrovascular disease in this population[1-4].

Prospective randomized trials demonstrated that regular blood transfusions substantially decrease the probability of a first stroke in children with SCD and abnormal TCD, and that discontinuation of transfusion therapy results in an inadmissible increase in blood flow velocities, consequently restoring the risk of stroke[5,6]. Although long-term adverse events associated with regular transfusions include iron overload, oral chelation therapy has proved to be a convenient and efficient method of reducing iron burden with acceptable tolerability[7]. In spite of the extensive and compelling body of evidence supporting the use of TCD in children with SCD, an unreasonable number of patients is probably still excluded from the benefits of this intervention due to limited access to adequately equipped healthcare facilities and because of insufficient TCD standardization, especially in developing and underdeveloped countries.

Therefore, we conducted an observational, cross-sectional study involving children and adolescents with SCD, including an estimate of cerebrovascular abnormalities in Brazilian children and adolescents with SCD and the correlation between these abnormalities and baseline characteristics of the study population

Methods

Study design

This was an observational, cross-sectional study of TCD in a cohort of 902 two- to 16-year-old patients with clinical diagnosis of SCD consecutively seen at three Brazilian hematology centers. As the goal of this study was to show complications associated with stroke related to SCD, 129 patients with previous imaging of hemorrhagic stroke or any other

recommendation for chronic transfusions were excluded. Thus, a population of 773 patients was analyzed. This study protocol was approved by independent Ethics Committees at each participating center. Written informed consent was obtained for each patient prior to admission to the study.

Study assessments

Identical equipment and software were used (2-MHz pulsed Döppler Nicolet EME) in the three units.

Transtemporal and transforaminal windows were meticulously studied and the highest time-averaged maximum mean velocity (TAMMV) of the MCA, distal internal carotid artery (dICA), anterior cerebral artery (ACA), bifurcation (BIF), posterior cerebral artery (PCA), vertebral artery and basilar artery were recorded. TCD was performed when patients were in their baseline conditions, without any complications. The criteria for classification was based on a TAMMV flow in the dICA and proximal MCA, and was considered 1) normal when TAMMV < 170 cm/sec; 2) conditional when TAMMV >170 and ≤ 200 cm/sec, and 3) abnormal when TAMMV > 200 cm/sec. A 2nd confirmatory exam was required for abnormal cases as previously described by Adams et al. [5]. As this was an observational study, all other procedures were left to the physician's discretion. The following data were obtained from the clinical records of the patients: adenotonsillar hypertrophy, obstructive sleep apnea, acute chest syndrome, systolic hypertension, history of dactylitis before the age of 2 years, family history of strokes and history of meningoencephalitis.

For this study we considered laboratory predictors of silent infarction at the time of the first TCD: 1) genotype; 2) presence or absence of alpha thalassemia; 3) total hemoglobin below 7.0 g/dL; 4) total leukocyte count above 15 x 10^9/L in the absence of any infection and 5) platelet count above 500 x 10^9/L.

Statistical analysis

Demographic and baseline characteristics, and laboratory data were analyzed using frequencies for qualitative variables and median and range for the variable age. Correlations between abnormal TCD results and baseline characteristics were assessed using the Pearson Chi-Square test or Fisher's exact test. A probability value < 0.05 was considered significant. Odds Ratio (OR) with 95% confidence interval (95%CI) was used to measure the comparison between normal or abnormal TCD. All analyses were performed with the Statistical Package for Social Sciences (SPSS®) version 16.

Results

Patient population and clinical characteristics

Of the 773 patients who performed TCD, 53.8% were male and the median age was 6.5 years (range: 1.8 to 15.8). The most prevalent genotype was Hb SS (74.4%). Coexistence of SCD and thalassemia was observed in 6.5% of the study population. Laboratory abnormalities, consisting of total hemoglobin level below 7.0 g/dL, leukocyte count above 15 x 10^9/L in the absence of infection, and/or platelet count above 500 x 10^9/L were observed in 11.6% of the patients. A total of 221 (28.6%) patients had at least one complication associated with SCD, including adenotonsillar hypertrophy, sleep apnea, acute chest syndrome, systolic hypertension, history of dactylitis before the age of 2 years, and history of meningoencephalitis. Family history of strokes, obtained from 219 of the study sample, was present in 8 (1.0%) cases. Baseline and demographic characteristics are fully depicted in Table 1.

Table 1 - Baseline and demographic characteristics of 773 patients

Variable		Value
Median age, years (range)		6.5 (range 1.8 to 15.8)
Gender, n (%)	Male	416 (53.8)
	Female	357 (46.2)
Genotype, n (%)	Hb SS	575 (74.4)
	Hb S Beta^0	10 (1.3)
	Hb SC	188 (24.3)
Coexisting thalassemia, n (%)	Yes	47 (6.1)
	No	671 (86.8)
	Unknown	55 (7.1)
Complications of SCD*, n (%)	Yes	221 (28.6)
	No	419 (54.2)
	Unknown	133 (17.2)
Laboratory abnormalities**, n (%)	Yes	90 (11.6)
	No	528 (68.3)
	Unknown	155 (20.1)

*Complications of sickle cell disease comprised adenotonsillar hypertrophy, sleep apnea, acute chest syndrome, systolic hypertension, history of dactylitis before the age of 2 years and history of meningoencephalitis: ** Laboratory abnormalities consisted of total hemoglobin below 7.0 g/dL, total leukocyte count above 15 x 109/L in the absence of infection and platelet count above 500 x 109/L

Transcranial Döppler ultrasonography

TCD was used as a screening method in 91.2% of cases (705 patients). The reasons for performing TCD in the remaining 68 patients included headache (35%), first episode of stroke or transient ischemic attack (31%), cognitive deficiency (16%), seizures (9%), dizziness (3%), sleep disturbances (3%) and recurrent episode of strokes (3%). TCD was normal in 681 (88.1%) of the subjects, conditional in 54 (7.0%) and abnormal in 31 (4.0%). The TCD was inadequate in 7 (0.9%).

Conditional or abnormal TCD results were significantly more frequent among patients with complications of SCD than among those without complications of SCD (OR = 3.18; 95%CI = 1.92-5.27) (Table 2). There was a significant difference in the frequency of conditional or abnormal TCD results in patients with laboratory abnormalities compared to those without (OR= 4.03; 95%CI = 2.30-7.06) (Table 2). Conditional or abnormal TCD results were significantly more frequent in patients submitted to TCD as screening than diagnosis by physicians.

Table 2 - Distribution of clinical and laboratory characteristics of 773 patients with sickle cell disease according to transcranial Döppler ultrasonography

Variables	Categories	TCD abnormal	TCD normal	OR (95%CI)	p-value
		n(%)	n(%)		
Gender	Male	46 (54.1)	366 (53.7)	1.02	1.000
	Female	39 (45.9)	315 (46.3)	(0.65-1.60)	
Genotype	SS	82 (96.5)	487 (71.5)	10.88	< 0.001*
	Others	3 (3.5)	194 (28.5)	(3.40-34.87)	
Complications of SCD	Yes	42 (59.2)	176 (31.3)	3.18	< 0.001*
	No	29 (40.8)	386 (68.7)	(1.92-5.27)	
Laboratory abnormalities	Yes	24 (35.3)	64 (11.8)	4.09	< 0.001*
	No	44 (64.7)	480 (88.2)	(2.33-7.17)	
Coexisting thalassemia	No	82 (98.8)	583 (92.7)	6.45	0.032*
	Yes	1 (1.2)	46 (7.3)	(0.88-4.76)	
TCD method	Screening	16 (18.8)	47 (6.9)	3.13	0.001*
	Routine	69 (81.2)	634 (93.1)	(1.68-5.81)	

SCD: Sickle cell disease: TCD: Transcranial Döppler ultrasonography: OR: Odds ratio; 95%CI: 95% confidence interval

*p-value < 0.05: Fisher Exact Test

Discussion

Several complications of SCD were proved to be significantly correlated with adverse outcomes among children and adolescents[8]. Chronic anemia has previously been shown to correlate with an increased risk of stroke and death in childhood, potentially as a consequence of flow disorders that may result in cerebrovascular injury[8-10]. Likewise, an elevated leukocyte count was demonstrated to be an independent predictor of the severity of SCD and was associated with an increased risk of stroke, possibly due to the adverse effect of neutrophils on the vascular endothelium[11-13].

In children with SCD and nocturnal hypoxemia caused by obstructive apnea, vascular narrowing and increased cerebral blood flow were observed in TCD; this leads to a greater likelihood of strokes[14]. In addition, recurrent tonsillitis and adenotonsillar hypertrophy is often present in children with SCD and sleep apnea, probably as a result of chronic infection associated with iron-deficient erythropoiesis; adenotonsillectomy has been shown to diminish the chance of strokes in this setting[15,16].

Acute chest syndrome was found to be significantly associated to stroke in patients with SCD suggesting that in the presence of damaged cerebral vessels, cerebral infarction may be triggered by hypoxia related to pulmonary disease[9]. Furthermore, a possible infectious etiology for stroke has been hypothesized; *Chlamydia pneumoniae*, the main cause of acute chest syndrome, has been linked to the development of strokes in the general population[17]. Purulent meningitis was also significantly more frequent in patients with SCD and strokes than in those without strokes[18].

Irrespective of the risk factors, the current SCD guidelines recommend the use of TCD as a screening for risk of stroke in all 2- to 16-year-old children with SCD at least once per year[1-4]. This study allowed us to standardize the TCD exam in two Brazilian hematology centers and to implement the test in a third one. Examination of an artery by TCD is called insonation. The TCD probe is placed on areas of the skull where the cranial bone is thin and it emits an ultrasonic beam directed to the studied artery (MCA or ICA). The reflected signal is processed by a transducer to obtain a wave-form (conventional or non-imaging TCD) used to determine the blood flow velocity, the direction of blood flow, and to calculate other useful parameters (such as the pulsatility index). It is important to remember that the blood flow velocity varies naturally with age. Blood flow is low after birth in the MCA, but increases rapidly during the first days of life. Velocities of 100 cm/s are reached between the ages of 4 and 6 years, and after this age, the blood flow velocity gradually decreases throughout the rest of life[19,20].

The Brazilian Guideline for TCD in children and adolescents between 2-16 years with SCD[2] recommends a frequency of TCD depending on the result of the blood flow velocity. In this study the prevalence of abnormal TCD was 1.2% (8 patients) and of conditional TCD it was 6.5% (45 patients). These prevalences are very different to those observed in the literature. The Stroke Prevention Trial in Sickle Cell Anemia (STOP) reported a prevalence of abnormal TCD in 6.72% of the studied patients (130/1934)[5].

Conclusion

Our study demonstrated that conditional or abnormal TCD results were significantly more frequent among patients with complications of SCD compared to those without complications of SCD, confirming the increased risk of stroke in the former subgroup of patients. However, it is worthy to note that this finding should not be used as a tool for the selection of patients for TCD examinations, since the proportion of conditional or abnormal results did not differ when the method was used for screening or for the evaluation of physician suspicions. This observation reinforces the recommendation of TCD as a screening test for all patients between 2 and 16 years of age with SCD.

References

1. Goldstein LB, Adams R, Alberts MJ, Appel LJ, Brass LM, Bushnell CD, Culebras A, Degraba TJ, Gorelick PB, Guyton JR, Hart RG, Howard G, Kelly-Hayes M, Nixon JV, Sacco RL; American Heart Association/American Stroke Association Stroke Council; Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; Quality of Care and Outcomes Research Interdisciplinary Working Group; American Academy of Neurology. Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: the American Academy of Neurology affirms the value of this guideline. Stroke. 2006;37(6):1583-633. Erratum in: Stroke. 2007;38(1):207.

2. Lobo CL, Cançado RD, Leite AC, Anjos AC, Pinto AC, Matta AP, et al. Brazilian Guidelines for transcranial döppler in children and adolescents with sickle cell disease. Rev Bras Hematol Hemoter. 2011;33(1):43-8.

3. Adams R, McKie V, Nichols F, Carl E, Zhang DL, McKie K, et al. The use of transcranial ultrasonography to predict stroke in sickle cell disease. N Engl J Med. 1992;326(9):605-10.Comment in: N Engl J Med. 1992;326(9):637-9.
4. Adams RJ. TCD in sickle cell disease: an important and useful test. Pediatr Radiol. 2005;35(3):229-34.
5. Adams RJ, McKie VC, Hsu L, Files B, Vichinsky E, Pegelow C, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Döppler ultrasonography. N Engl J Med. 1998;339(1):5-11. Comment in: N Engl J Med. 1998;339(20):1477-8.
6. Adams RJ. Big strokes in small persons. Arch Neurol. 2007;64(11):1567-74.
7. Vichinsky E, Onyekwere O, Porter J, Swerdlow P, Eckman J, Lane P, Files B, Hassell K, Kelly P, Wilson F, Bernaudin F, Forni GL, Okpala I, Ressayre-Djaffer C, Alberti D, Holland J, Marks P, Fung E, Fischer R, Mueller BU, Coates T; Deferasirox in Sickle Cell Investigators. A randomised comparison of deferasirox versus deferoxamine for the treatment of transfusional iron overload in sickle cell disease. Br J Haematol. 2007;136(3):501-8.
8. Miller ST, Sleeper LA, Pegelow CH, Enos LE, Wang WC, Weiner SJ, et al. Prediction of adverse outcomes in children with sickle cell disease. N Engl J Med. 2000;342(2):83-9. Comment in: N Engl J Med. 2000;342(21):1612-3.
9. Ohene-Frempong K, Weiner SJ, Sleeper LA, Miller ST, Embury S, Moohr JW, et al. Cerebrovascular accidents in sickle cell disease: rates and risk factors. Blood. 1998;91(1):288-94.
10. Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med. 1994;330(23):1639-44. Comment in: N Engl J Med. 1994;331(15):1022-3.
11. Balkaran B, Char G, Morris JS, Thomas PW, Serjeant BE, Serjeant GR. Stroke in a cohort of patients with homozygous sickle cell disease. J Pediatr. 1992;120(3):360-6.
12. Bratt J, Palmblad J. Cytokine-induced neutrophil-mediated injury of human endothelial cells. J Immunol. 1997;159(2):912-8.
13. Fadlon E, Vordermeier S, Pearson TC, Mire-Sluis AR, Dumonde DC, Phillips J, et al. Blood polymorphonuclear leukocytes from the majority of sickle cell patients in the crisis phase of the disease show enhanced adhesion to vascular endothelium and increased expression of CD64. Blood. 1998;91(1):266-74.
14. Kirkham FJ, Hewes DK, Prengler M, Wade A, Lane R, Evans JP. Nocturnal hypoxaemia and central-nervous-system events in sickle-cell disease. Lancet. 2001;357(9269):1656-9.
15. Wali YA, al-Lamki Z, Soliman H, al-Okbi H. Adenotonsillar hypertrophy: a precipitating factor of cerebrovascular accident in a child with sickle cell anemia. J Trop Pediatr. 2000;46(4):246-8.
16. Hill CM, Hogan AM, Onugha N, Harrison D, Cooper S, McGrigor VJ, et al. Increased cerebral blood flow velocity in children with mild sleep-disordered breathing: a possible association with abnormal neuropsychological function. Pediatrics. 2006;118(4):e1100-8. Comment in: Pediatrics. 2007;120(1):235-6; author reply 236-7.
17. Hoppe C. Defining stroke risk in children with sickle cell anaemia. Br J Haematol. 2005;128(6):751-66. Comment in: Br J Haematol. 2006;133(2):210; author reply 211.
18. de Montalembert M, Beauvais P, Bachir D, Galacteros F, Girot R. Cerebrovascular accidents in sickle cell disease. Risk factors and blood transfusion influence. French Study Group on Sickle Cell Disease. Eur J Pediatr. 1993;152(3):201-4.
19. Kassab MY, Majid A, Farooq MU, Azhary H, Hershey LA, Bednarczyk EM, et al. Transcranial Döppler: an introduction for primary care physicians. J Am Board Fam Med. 2007;20(1):65-71.
20. Adams RJ, Nichols FT, Hess DC. Normal values and physiological variables. In: Newell D, Aaslid R, editors. Transcranial Döppler. New York: Raven Press; 1992. p.41-8.

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