Arq Neuropsiquiatr 2008;66(2-B):360-364

TRANSCRANIAL DOPPLER IN SICKLE CELL ANAEMIA

Evaluation of brain blood flow parameters in children of Aracaju, Northeast - Brazil

Hyder Aragão de Melo[1], José Augusto S. Barreto-Filho[2], Roberto César P. do Prado[2], Rosana Cipolotti[2]

Abstract – Background: Environmental factors interfere on sickle cell anaemia (SCA). Transcanial Doppler (TCD) is important to evaluate cerebrovascular disease. **Objective:** To evaluate brain haemodynamic profile of children with SCA in Sergipe. **Methods:** Cross sectional study (group1: SCA patients aged 3-18; group2: age and sex matched healthy individuals). Baseline brain flow was evaluated. **Results:** Group1=34 patients; group 2=81 controls. SCA patients had mean velocity (MV)=125.69 cm/s±23.40; pulsatility index (PI)=0.66±0.10; middle cerebral artery ratio (MCAr)=14.53±15.23; right anterior cerebral artery/right middle cerebral artery=0.77±0.20; left anterior cerebral artery/left middle cerebral artery=0.78±0.20. Controls had MV=79.44±15.54; PI=0.82±0.11; MCAr=13.19±13.77; right anterior cerebral artery/right middle cerebral artery=0.80±0.16; left anterior cerebral artery/left middle cerebral artery=0.84±0.18. MV and PI differences were statistically significant between groups. MV was related to age but not to gender. **Conclusion:** MV evaluation using TCD was similar to international standards and possible to be used in our setting.

KEY WORDS: transcranial Doppler, sickle cell anaemia, cerebral blood flow, pulsatility, children.

Doppler transcraniano em portadores de anemia falciforme: estudo dos parâmetros de fluxo sangüíneo cerebral em crianças de Aracaju, Sergipe.

Resumo – Introdução: Aspectos ambientais interferem na apresentação da anemia falciforme (AF). Doppler transcraniano (DTC) é útil na avaliação do risco para doença cerebrovascular em pacientes com AF. **Objetivo:** Avaliar o perfil hemodinâmico cerebral de crianças com AF em Sergipe. **Método:** Estudo transversal (grupo1: portadores de AF 3-18 anos; grupo2: indivíduos saudáveis, pareados por idade e gênero). Foram avaliadas medidas de fluxo sangüíneo cerebral basal. **Resultados:** Grupo1 (n=34): velocidade média (Vm)=125,69 cm/s ±23,40; índice de pulsatilidade (Ip)=0,66±0,10; relação entre artéria cerebral média (ACMs)=14,53±15,23; artéria cerebral anterior (ACA)/ACM direita=0,77±0,20; ACA/ACM esquerda=0,78±0,20. Grupo 2 (n=81): Vm=79,44 cm/s ±15,54; Ip=0,82±0,11, relação entre ACMs=13,19±13,77, ACA/ACM direita=0,80±0,16; ACA/ACM esquerda=0,84± 0,18. Vm foi maior e Ip menor no grupo1. Vm se correlacionou com idade mas não com gênero. **Conclusão:** O perfil hemodinâmico cerebral de crianças com AF em Sergipe assemelha-se às referências internacionais. Não se observou interferência de fatores ambientais sobre os resultados.

PALAVRAS-CHAVE: Doppler transcraniano, anemia falciforme, fluxo sanguíneo cerebral, pulsatilidade, crianças.

It is well established that environmental conditions may interfere on the presentation and severity of sickle cell disease (SCD). The levels of fetal haemoglobin, concomitant occurrence with alfa-thalassemia and the different haplotypes related to hemoglobin S (HbS) may act as genetic modulators and be influenced by the environment, socioeconomic status (SES), nutrition, preventive measures and access to health services[1-3]. Previous studies with SCD children in Aracaju (Northeast, Brazil) showed impaired growth, similarly as it had been observed in Jamaica and different of the observed in industrialized countries[4]. In a study using information of autopsies from SCD patients the main causes of death were infection (48%), cerebrovascular disease (10.2%) and treatment complications (7%)[5]. The incidence of stroke is estimated as 0.61 per 100 patients/year and that there is a

Department of Medicine and University Hospital, Federal University of Sergipe, Aracaju SE, Brazil: [1]MD, MSc; [2]MD, MSc, PhD.

Received 18 July 2007, received in final form 27 February 2008. Accepted 20 March 2008.

Dr. Hyder Aragão de Melo – Rua Dom José Thomaz 473 - 49015-090 Aracaju SE - Brasil. E-mail: hyder@infonet.com.br

chance of occurrence of such event was of 11% up to the second decade of life, but increasing to 40% in the next 3 years for a second *ictus*[6,7]. Transcranial Doppler (TCD) is an ultrasonographic method that uses 1 to 2 MHz pulses which can penetrate skull. It was first used clinically by Aaslid in 1982[8]. It is considered of low cost and free of side effects. Its use in clinical research for SCD is justified by the disease's physiopathology, which involves great cerebral vessels, the same very well accessed by TCD[6]. The hemodynamic parameters of blood flow in children with SCD without antecedent of stroke can be seen on Chart.

Aracaju is the capital and largest city in Sergipe state. Located in the North-eastern costal area of Brazil, it has a tropical climate and rain fall index of 1000 mm to 2000 mm. The municipality population is 520,207[9] reaching 900,000 population in its metropolitan area. The Paediatric Haematology clinic at University Hospital - Federal University of Sergipe is the reference service for the entire state and neighbour locations (Bahia and Alagoas). Three hundred SCD patients from 0 to 26 years of age are followed free of charge in this clinic. In general, patients are of low socioeconomic status and literacy, but they get partial support from 2 NGOs which provide assistance during their stay in Aracaju and to get medicines.

We report, using TCD, the blood flow profile of great cerebral vessels of SCD patients free of cerobrovascular disease in Sergipe.

METHOD

This was a controlled cross sectional study. The sample evaluated constitutes 10% of the entire population and was enrolled sequentially during their routine appointments. We selected homozygous HbS patients after 3 years of age (as it is necessary the patient collaboration). Patients with antecedent of cerebrovascular disease, using hydroxiurea, who had been submitted to blood transfusion or had any clinical event in the 30 previous days, were excluded. Controls (2 per case) were school children without any chronic disease, paired by age and gender. Anemic children (Hb<11g/dL) were excluded.

TCD evaluations were performed using the same device (WAKI-I, Átis Medical®, monochannel, probe of 2 MHz), by the same examiner and technique: patients were positioned dorsally and oriented about the procedures; they were asked to not laugh, speak, hold breath or sleep. The middle cerebral artery (MCA), anterior cerebral artery (ACA), posterior cerebral artery (PCA), vertebral (AV) and basilar were evaluated. Each vessel was examined through its proper bone window (MCA, ACA, PCA via temporal window e VA e basilar via occipital windows) according to Aaslid technique[10]. Ultrasound signal was deepened by 2 millimetres each time and the highest speed was chosen, in accordance with STOP study[6,11]. After TCD a blood sample was collected.

Results were analysed using SPSS-15.0 software. For each patient it was considered one record of medium velocity (mV) and of pulsatility index (Pi), which corresponds to the arithmetic average of mV of the MCA and respective Pi of both sides. Normality of data was evaluated using Shapiro-Wilk test. Continuous variables were compared using t test for independent samples, and other continuous variables using Mann-Whitney test. Categorical variables were compared using the Chi Square test for the 2 groups. Significance level was established as 5% ($p<0.05$).

The project was approved by the Federal University of Sergipe Ethics Committee.

RESULTS

Thirty four SCD patients (Group 1) and 80 controls (Group 2) were studied. Age varied from 3 to 18 years and gender had similar distribution. Hemoglobin and hematocrit values were significantly lower in SCD group (Table 1). This group presented higher mV and lower Pi than group 2. Relation between CMAs, and ACA/MCA were not significant in both sides (Table 1).

Medium velocity was similar for paired vessels when considered each group. Speed values for each vessel were statistically higher in group 1, when compared to the correspondent in group 2 (Table 2). There were not VM differences between genders except for PCA in group 2. In this group women had higher mV.

Group 1 had significantly lower Pi than control group in all vessels. Otherwise, there was similarity between paired vessels for each group (Table 3). Correlation coefficient was significant for age in both groups (group1: r=0.495; *p*=0.03 and group 2: r=0.430; *p*=0.000). Hematocrit levels were related to mV in group 2 (r=0.229; *p*=0.04) but not in SCD group (r=0.158; *p*=0.37).

DISCUSSION

This study shows that there are differences in cerebral blood flow between SCD patients and children without hematological disease, even without any antecedent of previous cerebrovascular disease. Medium velocity analysis shows speed increase in group1 when compared to group 2 in all studied vessels, which is in accordance with Newell data[10]. This finding must be evaluated together with ACMs and ACA/ACM relations. If we can see differences when only speed is considered, this is not maintained when vascular relations are considered. This happens because high speed is typical of hiperdynamic status like anemia. When one calculates relations among vessels, individual values disappear but can be found when the relation is evaluated among groups. Previous studies indicate higher stroke risk when relation between ACMs is higher than 50% (normal relation 20%) and ACA/MCA is lower than 1.2 (Chart). Both groups showed values within these limits.

Table 1. Characteristics studies between groups

Feature	Group 1 (N=34)	Group 2 (N=80)	Referencial values**	p#
Gender masc – total pac (%)	18 (52%)	43 (53.1%)		0.989[A]
Age – years (interval min-max)	9.55±4.67 (3–18)	9.82±4.51 (3–18)		0.779[B]
Ht (%)*	24.74±5.77 (17.90–39.50)	36.99±3.30 (30.50–44.80)	21.1±2.3[2]	0.000[B]
Hg (g/dL)*	8.19±1.87 (6–13)	12.1±1.10 (9.90–14.70)	7.4±0.8[2]	0.000[B]
mV (cm/s)*•	125.69±23.40 (75.5–177)	79.44±15.54 (43.50–118)	100–130[1]	0.000[C]
Pi*•	0.66±0.1 (0.46–0.88)	0.82±0.11 (0.56–1.04)	Minor than childrens without Hematologic disease[1]	0.000[C]
Relation between MCA◆	14.53±15.23 (0–82.72)	13.19±13.77 (0–66.10)	50% (mean<20%)[1]	0.534[B]
Relation between ACA/MCA right◆	0.77±0.22 (0.35–1.32)	0.8±0.16 (0.43–1.18)	<1.22	0.623[C]
Relation between ACA/MCA left◆	0.78±0.20 (0.31–1.10)	0.84±0.18 (0.45–1.50)	<1.22	0.341[B]

*Presentation mean±standard deviation; •Average velocitys at middle cerebral artery (average between MCA right and left); **Data are of the sickel cell anemia childrens; #Difference between Group 1 and Group 2; [1]Babikian, 1999[8]; [2]Adams, 1998[6]; [A]Chi-square; [B]Mann-Whitney; Ht, hematocrit; Hg, hemoglobin; mV, mean velocity of middle cerebelar arteries; Pi, pulsatility index; MCA, middle cerebral artery; ACA, anterior cerebral artery.

Table 2. Mean velocity in vases.

Average speed (L=left; R right)	Group 1 (N=34)	Group 2 (N= 80)	Referencial values*	p**
MCA L (cm/s)	126.24±27.33 (78–180)	78.16±18.48 (40–124)	110–130	0.000[A]
MCA R (cm/s)	125.15±24.78 (73–178)	80.72±16.55 (44–124)	110–130	0.000[A]
ACA L (cm/s)	97.12±27.81 (40–150)	64.35±14.00 (35–109)	85–110[1]	0.000[A]
ACA R (cm/s)	94.44±23.85 (51–133)	63.54±15.52 (34–118)	85–110[1]	0.000[B]
PCA L (cm/s)	65±21.43 (33–118)	46.62±10.19 (26–67)	65–85[1]	0.000[A]
PCA R (cm/s)	73.53±20.62 (30–110)	49.43±9.94 (32–84)	65–85[1]	0.000[B]
AV L (cm/s)	82.76±19.96 (36–120)	52.52±14.09 (21–110)	–	0.000[B]
AV R (cm/s)	84.91±20.11 (39–122)	54.33±13.01 (26–103)	–	0.000[B]
Basilar (cm/s)	93.79±21.10 (39–137)	59.67±13.97 (16–95)	–	0.000[A]

*Presentation mean±standard deviation (min-max); *This dados are of the sickel cell anemia children; **Difference between Group 1 and Group 2[1] (Adams, 1998[6]); [A]t student test; [B]Mann-Whitney; MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; AV, vertebral artery L, left; R, right.

Table 3. Pulsatitlity index in vases.

Pulsatility index (L=left, R=right)	Group 1 (N=34)	Group 2 (N=80)	p**
MCA L	0.66±0.12 (0.41–0.97)	0.83±0.15 (0.37–1.15)	0.000[A]
MCA R	0.66±0.12 (0.45–0.94)	0.80±0.12 (0.54–1.06)	0.000[A]
ACA L	0.68±0.16 (0.34–1.06)	0.81±0.15 (0.42–1.14)	0.000[A]
ACA R	0.63±0.12 (0.37–0.85)	0.80±0.17 (0.42–1.34)	0.000[A]
PCA L	0.68±0.12 (0.42–1)	0.84±0.16 (0.46–1.29)	0.000[A]
PCA R	0.65±0.1 (0.49–0.90)	0.80±0.17 (0.43–1.25)	0.000[B]
VA L	0.62±0.10 (0.41–0.90)	0.76±0.16 (0.45–1.34)	0.000[B]
VA R	0.62±0.09 (0.49–0.85)	0.78±0.16 (0.53–1.28)	0.000[B]
Basilar	0.56±0.11 (0.26–0.82)	0.86±0.36 (0.54–3.22)	0.000[B]

*Presentation mean±standard deviation (min-max); these data are of the sickle cell anemia children; referencial values: minor than childrens without hematologic disease[1]; **Difference between Group 1 and Group 2; [1]Babikian, 1999[8]; [A]t student test; [B]Mann-Whitney; MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; AV, vertebral artery L, left; R, right .

Chart. Reference values for sickle cell disease patients.

Feature	Referencial values
MCA	100–130 cm/s
ACA	85–110 cm/s
PCA	65–85 cm/s
Pulsatility index	Minum than normal childrens
Relation between MCAs	<50%
Relation ACA/MCA	<1.2
Relation velocity/age	Not relation
Relation velocity/hematocrit	Negative

MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery. Babikian, 1999.

As high MV indicates high blood flow, in this case caused by chronic anaemia, low Pis were expected because a lower resistance is required for the arteries to receive increased flow. Otherwise for both groups relations between mV and age and mV and hematocrit are inversely proportional. Both findings are in agreement with Babikian's[8] in a study with similar group of patients and controls.

In our study there was no gender difference in flow MV, except for PCA in control group. This finding differs from a previous study[12], but in that study participants were adults (predominantly women) without chronic disease. In our data there is not difference in cerebral arteries mV between genders in SCD patients, similarly to previous study in children[8].

Clinical presentations of SCD may be altered by genetic and environmental factors[2,13,14]. Genetic factors include proportion of fetal hemoglobin, association with alfa thalassemia and with G6PD deficiency, esferocitosis and anti-oxidants enzymes, as well as with the haplotypes[15]. Environmental factors include physical environment, nutrition, and access to medical, social and psychological support[2]. The hot weather in Brazilian Northeast and low SES and schooling level are factors that may worsen our parameters. These particularities have been shown in previous studies for both weight and height impairment[4] and for insidious cerebrovascular disease. But when cerebral blood flow in children with SCD is considered, our findings are similar to the ones in different places, which makes DTC a good tool to routinely follow SCD patients, using the references from international studies.

In conclusion, cerebral blood flow profile in children with SCD showed higher cerebral speed flow and lower pulsatility index than in health children. Relation between MCAs and ACAs/MCAs were not different when both groups were compared showing that the hiperdynamic effect of chronic anaemia is homogenous for these arteries. Cerebral blood flow previously described is adequate

for our population. There were not any environmental findings that suggest interference on hemodynamic parameters obtained with TCD.

REFERENCES

1. ANVISA, Manual de diagnóstico e tratamento de doenças falciformes, Brasil. Brasília 2002. Disponível em http://www.anvisa.gov.br/divulga/public/sangue/hemoglobinopatia/diagnostico.pdf Acess 15 November 2005.
2. Naoum PC. Interferentes eritrocitários e ambientais na anemia falciforme. Rev Bras Hematol Hemoter 2000;22:5-22.
3. Romero WER, Renauld GFS. Haplótipos de la hemoglobina S: importancia epidemiológica, antropológica y clínica, Rev Panam Salud Publica 1998;3:1-8.
4. Cipolotti R, Caskey MFB, Franco RP, et al. Childhood and adolescent growth of patientes with sickle cell disease in Aracaju, Sergipe, northeast Brazil. Ann Trop Paediatr 2000;20:109-113.
5. Manci EA ,Culberson DE,Yang YM, et al. Causes of death in sickle cell disease: an autopsy study. Br J Haematol 2003;123:359-365.
6. Adams RJ, McKie VC, Hsu L, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial doppler ultrasonogrphy, N Engl J Med 1998;339:5-11.
7. Ohene-Frempong K, Weiner SJ, Sleeper LA, et al. Cerebrovascular accidents in sickle cell disease: rates and risk factors. Blood 1998;91:288-294.
8. Babikian VL, Wechsler LR, Toole JF. Transcranial doppler ultrasonography, 2nd ed. USA: Butterworth-Heinemann, 1999.
9. IBGE. Censo demográfico, http://www.ibge.gov.br/home/estatistica/populacao/contagem2007/popmunic2007layoutTCU14112007.pdf. Acess 04 December 2007.
10. Newell DW, Aaslid R. Transcranial Doppler. New York: Raven Press, 1992.
11. Nicchols FT, Jones AM, Adams RJ. Stroke prevention in sickle cell disease (STOP) study guidelines for transcranial Doppler testing. J Neuroimaging 2001;11:354-362.
12. Barbosa MF, Nitamar Abdala N, Carrete H Jr. Doppler transcraniano convencional em voluntários assintomáticos variabilidade e valores de referência para parâmetros de fluxo sanguíneo. Arq Neuropsiquiatr 2006;64:829-838
13. Marouf R, Grupta R, Haider MZ, Adekile AD. Silent brain infarcts in adult Kuwaiti sickle cell disease patients, Am J Hematol 2003;73:240-243.
14. Pegelow CH, Wang W, Granger S, et al. Silent infarcts in children with sickle cell anemia and abnormal cerebral artery velocity. Arch Neurol 2001;58:2017-2021.
15. Pante-de-Sousa G, Mousinho-Ribeiro RC, Santos EJM, et al. Origin of the hemoglobin S in a Northern Brazilian population: the combined effects of slave trade and internal migrations. Genet Mol Biol 1998;21.