ORIGINAL ARTICLE

Cerebrovascular reactivity in migraineurs

Vasorreatividade cerebral em migranosos

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ABSTRACT

Cerebrovascular reactivity (CR) assessed by transcranial Doppler (TCD) has been evaluated among migraineurs with conflicting results. We assessed the CR using the breath holding index (BHI) among 228 migraineurs during ictal or interictal phase and 56 controls. Migraineurs exhibited increased BHI values in the interictal phase and reduced BHI in the ictal phase when compared to controls.

Keywords: Transcranial Doppler Ultrasonography; Migraine disorders; Headache; Cerebrovascular circulation.

RESUMO

A vasorreatividade cerebral medida pelo Doppler transcraniano tem sido avaliada em pacientes com migrânea com resultados conflitantes. Nós avaliamos a vasorreatividade cerebral utilizando o índice de apnéia (IA) em 228 pacientes com o diagnóstico de migrânea nas fases ictal e interictal e 56 controles. Os pacientes apresentaram valores do IA aumentados durante a fase interrictal e reduzidos durante a fase ictal quando comparados aos controles.

Descritores: Ultrassonografia Doppler transcraniana; Migrânea; Cefaleia; Circulação cerebrovascular

INTRODUCTION

Migraine is one of the most common types of primary headaches in clinical practice, but its pathophysiology is not completely elucidated. The mechanism of migraine headaches appears to involve the activation of the trigeminocervical pain system by stimuli elicited by neuronal and/or vascular dysfunction,[1] which may be due to genetic mutations associated to ion-transporting mechanisms.[2]

Conflicting results about cerebrovascular reactivity and cerebral blood flow velocities have been described among migraineurs. A few studies have reported an increased cerebrovascular reactivity (CR),[3,4] while others a normal and even a reduced CR.[5-8]

The diagnosis of migraine headaches can be usually made on clinical grounds alone in most patients. However, it would be interesting to find a complementary assessment tool to support its diagnosis. Cerebrovascular reactivity assessed by transcranial Doppler could be a noninvasive and cost effective tool that could possibly help in the differential diagnosis of primary headaches.

The aim of this study is to compare the CR among patients with migraine and controls. Our hypothesis is that migraineurs show different CR status when compared to controls.

METHODS

Two hundred and twenty eight consecutive migraineurs were included in the study under informed consent conditions (mean age = 33.82 years; range = 13 - 67; women= 189). One hundred and fifty nine patients were evaluated in the interictal period: 71 suffering from migraine with aura (MA) and 88 from migraine without aura (MWA). In addition, we evaluated 69 patients during headache attacks: 36 with MA, 33 with MWA. We compared the results to a control group of 56 individuals

with no personal history of headache (mean age = 42.41 years; range = 15-75; 31 women). All patients were recruited from the neurology clinic of Santa Luzia Hospital in the city of Brasília - Brazil, from February 2003 to June 2005. None of the patients was using prophylactic antimigraine medication. Neither patients nor controls had any antecedent of major disease and no vascular risk factors such as hypertension, diabetes, dyslipidemia, smoking. Diagnosis of migraine was made according to the 1988 international classification of headache disorders - 1 (ICHD-I).[9] In 2004 a revised international classification of headache disorders (ICHD-II) was published.[10] Since we had already started recruiting patients using the ICHD-1, we carried on our study using this previous classification. The study was conducted with full approval by the institutional review boards.

The transcranial Doppler (TCD) study was carried out in a quiet room with the individuals in supine position, always during the afternoon. The reactivity to hypercapnia was measured by the breath holding index (BHI). The index was obtained by dividing the percentage increase in mean flow velocity occurring during breath-holding by the time (30 seconds) subjects held their breath after a period of three minutes of normal breathing. We considered the peak maximum value of the velocity curve, which usually occurs a few seconds after the release. This method has been validated as effective as methods requiring carbon dioxide inhalation or acetazolamide administration. We used an EZ-Dop transcranial Doppler instrument (DWL Elektronische Systeme GmbH), with a 2-MHZ transducer fitted on a headband. The mean of right and left BHI values were calculated.

ANOVA test and Tukey post hoc pairwise comparisons were applied for comparisons on continuous variables among the groups. The level of significance was set at 0.05.

RESULTS

All patients were able to hold their breath during 30 seconds when submitted to the test. Mean values of BHI for migraineurs and controls are given in Table 1.

Table 1 - BHI mean values and P values between groups

	Interictal (Inc)	Ictal (Ic)	Controls (C)	P-Value Inc vs. Ic	P-value Inc vs. Ic	P-value Inc vs. Ic
BHI values	1.35	0.82	1.04	<0.001	<0.001	<0.001

* BHI - Breath Holding Index

We found an increased BHI among migraineurs in the interictal phase when compared to the control group (migraine-interictal = 1.35; range = 0.37-2.87; controls = 1.04; range = 0.535-1.177; p-value<0.001). During migraine attacks, a significant decrease in BHI was observed when compared to controls (migraineurs-ictal = 0.82; range = 0.18-1.505; controls = 1.04; range = 0.535-1.177; p-value < 0.001).

The BHI mean values were similar when comparing migraineurs with aura and without aura in the ictal phase (MA-ictal = 0.87; range = 0.18-1.41; MWA-ictal = 0.78; range = 0.305-1.505; p = 0.214) and interictal phase (MA-interictal = 1.35; range = 0.37-2.87; MWA-interictal = 1.36; range = 0.465-2.305; p-value = 0.778).

DISCUSSION

Headache is a usual patient complaint in almost every medical specialty. The very common occurrence of this symptom in our population can lead to an expressive economic loss and can also limit patients in ordinary life activities. In the United States migraine affects about 12% of the population, being three times more prevalent in women than men, negatively affecting daily functioning of most patients.[11] In Brazil, the prevalence of migraine is estimated to be about 15%, being 2.2 times more prevalent in women.[12]

The use of the ICHD criteria for migraine headaches can be considered a reliable tool to its diagnosis in most patients. A large population-based study showed that self-reported migraine among women was confirmed in 87% when applying the ICHD-II criteria for migraine or probable migraine without aura.[13] Although most patients can be diagnosed on clinical grounds using the ICHD-II criteria, sometimes the correct diagnosis of migraine represents a challenge for both clinical practice and clinical research.

The transcranial Doppler has been evaluated by some studies as a potential tool for this purpose. Studies that measured CR in the interictal phase have yielded conflicting results, which may be due to different study methodologies. Silvestrini et al. reported similar BHI in controls and in patients during headache free periods. In this study the BHI was calculated using the mean cerebral blood flow (CBF) 4 seconds after the release.[14] Another study found an exaggerated interictal BHI in migraineurs without aura compared with the control group.[4] This study considered the maximum point of CBF to calculate CR, which was the methodology used in our study.

Studies that used different stimuli (e.g.; CO2 inhalation, hyperventilation) reported normal[5,6] or reduced[7,8] CR in the interictal period. Other studies using methods such as Xenon blood flow studies, SPECT, PET, and functional magnetic resonance also reported discordant results. The different methods of CR measurement is a major factor that limits comparison between studies.

Migraineurs might have an increased CR during the headache-free period due to alterations in their autonomic tonus. These patients might have a state of vagal hyperactivity during headache free periods leading to an enhanced vasodilatatory response. Furthermore, it has been reported that migraineurs present an enhanced secretion and response to nitric oxid.[15]

A previous comparison between tension-type headache (TTH) and migraine using the transcranial Doppler was performed by Rosengarten et al., measuring the evoked flow velocity in the posterior cerebral artery utilizing a visual stimulation paradigm.[16] This study showed that TTH patients had similar flow velocity response during the ictal and interictal periods, which was also comparable to controls. The same evaluation in migraineurs demonstrated that CR was reduced during the ictal phase when compared to the interictal phase, suggesting an impaired vasodilatation reserve during the ictal phase.

Our study has several limitations. Individuals evaluated in the ictal phase were not the same ones tested in the interictal phase. We did not control for the presence of carotid stenosis, which can influence the breath holding index. However, the mean age of the migraineurs and the control group was relatively low to be influenced by this variable.

In addition, due to the wide BHI variability found among migraineurs, it does not seem possible to set a BHI cutoff value to define migraine using the transcranial-Doppler. However, it is tempting to consider that a significant CR variation between ictal and interictal phase in a single patient could be an additional information to the diagnosis of migraine. Further research evaluating CR of the same patient during ictal and interictal phases of migraine would be of great value.

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