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Cerebral hypercapnia-induced vasomotor reactivity in migraine with and without aura: a case-control study

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Abstract

Background: Dysfunction of the autonomic nervous system has long been a subject of considerable debate and a large number of studies have disclosed contradictory results.

The aim of this study was to compare cerebral vasomotor reactivity in migraine with aura (MWA) patients with migraine without aura (MWO) ones.

Methods: Ten MWA patients (7 females and 3 males; mean age: 39.70 years, SD: 12.03 years) and 10 age and sex-matched cases with MWO (P=0.303, P=1.000, respectively) underwent cerebral vasomotor reactivity (VMR) measurement using trans-cranial Doppler imaging of the middle cerebral artery (MCA). All patients were examined during an attack-free interval.

Results: A statistically significant decrease in VMR value was seen in the migraine with aura group (2.8%, P=0.048); also systolic, diastolic and mean flow velocities were significantly greater in these patients (113.31, 59.13, 73.88, P=0.021, P=0.017 and P=0.049, respectively).

Conclusion: Age-independent decrease in cerebral vasomotor reactivity in MWA as compared to MWO could support genetic involvement of brain autonomic control pathways in MWA rather than MWO. Nitric oxide (NO) plays a major role, as a second messenger, in cerebral autonomic activity. Genetic involvement of its metabolic pathways may be a good explanation for observed dysfunction in MWA. Further molecular investigations could clarify this question.

Keywords: migraine with aura, migraine without aura, vasomotor reactivity, CO_2 inhalation.

Introduction

Migraine is a common, chronic, incapacitating neurovascular disorder characterized by attacks of severe headache, autonomic nervous system dysfunction, and in some patients, an aura involving neurologic symptoms [1]. Changes in the diameter of intracranial arteries might have a major role in the pathophysiology of migraine [2]. Trans-cranial Doppler Ultrasound (TCD) is currently used as a sensitive, real time tool for monitorization of cerebral blood flow velocity (CBFV). From the first clinical application by Aaslid in 1982 [3], TCD has

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been extensively used in clinical routine [4]. Though several studies have found alterations in velocity of blood flow and in cerebral vasomotor reactivity of intracranial arteries in migraine cases in headache-free periods, as well as during migraine attacks, the results are inconclusive [5,6,7]. Since some mutations in specific channel genes, neuronal voltage-gated calcium channel and neuronal voltage-sensitive sodium channel [8,9], have been demonstrated in migraine with aura (MWA) but not in migraine without aura (MWO), it seems that the basic pathophysiology follows different rules in the two subtypes of migraine. Therefore, the differences in hypercapnia-induced cerebral vasoactive response could further establish the basic differences in the pathophysiology of MWA and MWO and that these two conditions could be speculated as two different entities. We could not find any previous study concerning the differences between cerebral vasomotor reactivity in migraine with aura and migraine without aura.

Methods

Subjects

Ten patients with migraine with aura (MWA) (7 females and 3 males; mean age: 39.70 years, SD: 12.03 years) and 10 age and sex matched migraine without aura ones (P=0.303, Fischer's exact test; P=1.000, χ^2 test, respectively) according to International Headache Society (HIS) 2004, criteria for diagnosis and classification of headaches [10] were included in the study. Subjects with previous history of any systemic diseases, cerebral vascular disturbances, coronary artery disease (CAD), atherosclerotic disorders and severe MCA stenosis (over 30%) were excluded from the study. Inability to cooperate and having difficulty registering cerebral flow waves were two other criteria for the exclusion of cases. No patient was using prophylactic antimigraine medications or had used analgesic drugs for 48 hours before examination. Attack frequency ranged from 1 to 4 per month. All patients were examined during an attack-free interval. Attack-free investigations were made between 3 and 5 days after an attack.

Data from the subjects were obtained in the baseline condition and through CO_2 inhalation period.

Trans-cranial Doppler measurements

Doppler measurements were performed by TCD equipment (EME TC64B, EME Uberlingen, Germany) with a 2 MHz probe in the patients at the resting supine position. The MCA was insonated on the right side through the temporal window and parameters of flow were recorded at a depth of 50 mm. Cerebral vasomotor reactivity (VMR) was measured using CO_2 inhalation test. After baseline blood flow velocity recordings, the subjects were asked to inhale a gas mixture containing 5% of CO_2 (O_2: 21%, N_2: 74%) using a face inhalation mask for 2 minutes. Flow velocity recording was continued during the CO_2 inhalation and systolic blood flow velocity (V_{sys}), diastolic blood flow velocity (V_{dia}) and mean flow velocity (V_{mean}) values were recorded up to 5 minutes after administration of CO_2. Cerebrovascular reactivity (CR) was assessed at the point of maximal flow velocity change according to the following formula: $CR= 100\ (V_{max}-V_0)/V_0$, where V_0 and V_{max} are the mean velocity values measured at the depth of 50 mm in the MCA before CO_2 administration (V_0) and the maximum flow velocity after administration of CO_2 (V_{max}) respectively. Gosling's pulsatility index (PI) was also calculated automatically as: $(V_{sys} - V_{dia})/V_{mean}$.

Statistical analysis

Data analysis was performed using SPSS version 11.5. Matching of the two groups for age and sex variables were evaluated using Fischer's exact test and χ^2 test, respectively. Fischer's exact test was used to compare baseline flow velocity, systolic, diastolic and mean flow velocities after CO_2 inhalation test and VMR

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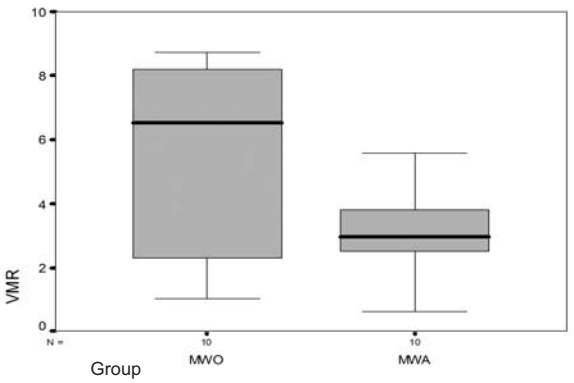

Fig. 1. VMR values were significantly smaller in the MWA group (VMR: vasomotor reactivity, MWA: migraine with aura, MWO: migraine without aura)

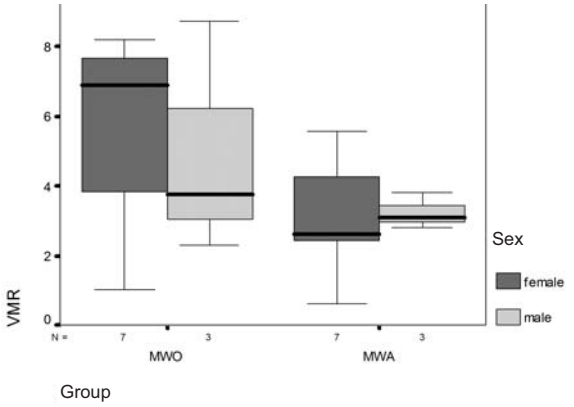

Fig. 2. Differences in VMR values were not significant between males and females in the two migraine subtype groups.

between the two groups. Univariate repeated measures analysis of variance with Greenhouse-Geisser and Huynh-Feldt adjustments for the degrees of freedom were applied to compare mean flow velocity and CR during the CO_2 inhalation test. Bonferroni's corrections were applied for multiple comparisons.

Results

A statistically significant difference was seen between baseline velocity values of the two groups (113.31 vs. 76.13 P=0.044) as a greater value in the migraine with aura group. Vasomotor reactivity was significantly lower in the migraine with aura group in comparison to the migraine without aura group (2.8% vs. 6.7% P= 0.048) (Fig. 1) ; that lacked its statistical significance after corrections for multiple comparisons analysis (P=0.105, 95% Confidence Interval = -4.575 - 0.476) with an estimated power of 0.366. Systolic, diastolic and mean flow velocities were significantly greater in the MWA group subjects (113.31, 59.13, 73.88, P= 0.021, P=0.017 and P=0.049, respectively). Mean flow velocity after CO_2 inhalation test conserved its significance after applying the corrections for multiple comparisons analysis in a univariate general linear model (P=0.017, 95% confidence interval = 4.517 – 39.435) with an estimated power of 0.707. There was a significant difference between Gosling's pulsatility index (PI) in the two groups (0.73,0.34 P=0.047, Fischer's exact test). On the other hand, no correlation was found between age and VMR and mean arterial flow velocity (V_{mean}) values (Pearson correlation=0.076, P=0.749 and Pearson correlation=-0.223, P= 0.345; respectively) and also gender had no effect on the differences seen in the two groups (Fig. 2).

Discussion

In our study, the baseline blood flow velocity in MCA in the MWA group was greater than the MWO group. On the other hand, MWA subjects showed weaker vasomotor response to blood CO_2 level increase.

Several studies have already been accomplished regarding cerebrovascular responsiveness to induced hypercapnia state in migraine patients. However, different results have been achieved through multiple studies. Zwetsloot et al [7] found normal vasomotor reactivity to carbon dioxide (CO_2) in migraine cases. Decreased CO_2 reactivity during the migraine attack was reported by Harer and Von Kummer [11] while Sakai and Meyer [12], Thomas et al [13], Harer and Von Kummer [11] and Thomsen et al [14] found increased vasomotor reactivity in the headache-free period. These differences in the

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obtained results could result from different study methodologies and different sampling and matching methods as well.

The above-mentioned discussion suggests that gender may play an important role in cerebral blood flow regulation and the basic mechanism of migraine. Whereas, none of the previous studies concerning the effects of hypercapnia on cerebral blood flow and comparison of cerebrovascular reactivity to hypercapnia in migraine and non-migraine patients have matched their study groups regarding the subjects' gender. Therefore, observed differences among results of cerebral blood flow velocity and vasomotor reactivity in previous experimental and clinical studies have shown that mechanisms underlying short-term hypoxia or hypercapnia-induced increase in cerebral blood flow involve, to a great extent, nitric oxide (NO) metabolism and regulation pathways; nitric oxide synthase (NOS) activation plays the most important role in this pathway [15,16, 17,18]. In prolonged hypercapnia, an induction in endothelial NOS (eNOS), and not neuronal NOS (nNOS), mRNA expression plays the most contributory role, as well. This seems to be mediated by prostaglandin E_2 (PGE_2) generated by KATP and Calcium (Ca^{2+}) channel-dependent process [17]. NOS activity and NO production are greatly affected by intra- and extra-cellular sodium (Na^+) content, and it has been showed that salt loading attenuates the conversion of L-arginine to NO in the endothelium of the renal vasculature in salt-sensitive patients with essential hypertension [19]. The suppression effect of salt administration on plasma NO concentration could occur by several mechanisms, including altered transport of L-arginine through the endothelial membrane, decreased activity of enzyme nitric oxide synthase , and an increased breakdown or excretion of NO [20].

Several studies have demonstrated the differences in sodium metabolism between males and females [21-26] and suggested that these differences result from regulatory effects of sex hormones on the activity of Na+/H+ exchanger [27], $Na^+/K^+/2Cl^-$ co-transporter [28,29] and Na^+/K^+ ATPase [30,31,32] channels. So that female sex hormones suppression could primarily be attributed to the different male-to-female ratios in case and control groups shown in various studies.

All the above-mentioned statistics were age-independent, and there was no correlation between age and VMR and Vmean values. These observations together could suggest the involvement of cerebral vascular regulatory mechanisms in migraine with aura rather than migraine without aura. In a subtype of migraine with aura (familial hemiplegic migraine; FHM) detection of various genetic mutations in ion channels, neuronal voltage-gated calcium channel [33] and neuronal voltage-sensitive sodium channel [34], emphasizes this hypothesis. Application of corrections and repeated measurement analysis faded the statistical significance of difference between VMR values in the two groups of migraine with and without aura. However, because of the small sample size, the estimated power for the analysis was very low (power= 36.6%). Therefore, larger studies with greater sample sizes will clarify more the state of observed difference.

Cerebral vascular regulatory mechanism consists of two pathways including neuronal and vascular regulations. Autonomic dysfunction has been reported previously in migraine patients [35-39]. On the other hand, it has been shown that NO is the strongest regulatory agent in the cerebrovascular response to hypercapnia [15-18], and also plays an important role in central and peripheral autonomic pathways [40-42]. Hence, each of the factors that affect NO metabolism and activity pathways in cerebral vasculature could be involved in the basic pathophysiology of migraine with aura. This finding brings about two suggestions. First, migraine with aura and migraine without aura are two different entities regarding the basic patho-

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physiological mechanisms, and it may be necessary to revise the place of the two headaches in the headache classification system and similar therapeutic protocols, despite the clinical similarities between them. Second, NO metabolism and regulation pathways may be considered as important therapeutic targets for treatment of migraine, especially migraines with aura.

Finally, we suggest that matching for subjects' gender in study groups may be necessary to obtain more distinct and actual results in migraine studies. Also, a larger study with greater sample size and clear-cut limitations is necessary to clarify more our study results.

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