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, CO2 inhalation.

Introduction

Migraine is a common, chronic, incapacitating neurovascular disorder characterized by attacks of severe headache, autonomic nervous system dysfunction, and in some patients, 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 monitoring 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 vaso-
motor reactivity of intracranial arteries in mi-
graine cases in headache-free periods, as well as during migraine attacks, the results are in-
conclusive [5,6,7]. Since some mutations in specific channel genes, neuronal voltage-gated
calcium channel and neuronal voltage-sensi-
tive sodium channel [8,9], have been demon-
strated 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 re-
activity 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, χ² test, respectively) ac-
cording to International Headache Society
(HIS) 2004, criteria for diagnosis and classifi-
cation of headaches [10] were included in the
study. Subjects with previous history of any
systemic diseases, cerebral vascular distur-
bances, coronary artery disease (CAD), ather-
sclerotic disorders and severe MCA stenosis
(over 30%) were excluded from the study. In-
ability to cooperate and having difficulty regis-
tering cerebral flow waves were two other crite-
ria for the exclusion of cases. No patient was us-
ing 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 dur-
ding an attack-free interval. Attack-free investi-
gations were made between 3 and 5 days after
an attack.

Data from the subjects were obtained in the
baseline condition and through CO₂ inhalation
period.

Trans-cranial Doppler measurements

Doppler measurements were performed by
TCD equipment (EME TC64B, EME Uberlin-
gen, Germany) with a 2 MHz probe in the pa-
ients at the resting supine position. The MCA
was insonated on the right side through the tem-
poral window and parameters of flow were
recorded at a depth of 50 mm. Cerebral vaso-
motor reactivity (VMR) was measured using
CO₂ inhalation test. After baseline blood flow
velocity recordings, the subjects were asked to
inhale a gas mixture containing 5% of CO₂ (O₂:
21%, N₂: 74%) using a face inhalation mask for
2 minutes. Flow velocity recording was contin-
ued during the CO₂ inhalation and systolic
blood flow velocity (Vsys), diastolic blood flow
velocity (Vdis) and mean flow velocity (Vmean)
values were recorded up to 5 minutes after ad-
ministration of CO₂. Cerebrovascular reactivity
(CR) was assessed at the point of maximal flow
velocity change according to the following for-
mula: CR= 100 (Vmax-V0)/V0, where V0 and
Vmax are the mean velocity values measured at
the depth of 50 mm in the MCA before CO₂ ad-
inistration (V0) and the maximum flow veloc-
ity after administration of CO₂ (Vmax) respec-
tively. Gosling’s pulsatility index (PI) was also
calculated automatically as: (Vsys-Vdis)/Vmean.

Statistical analysis

Data analysis was performed using SPSS
version 11.5. Matching of the two groups for
age and sex variables were evaluated using Fis-
cher’s exact test and χ² test, respectively. Fisch-
er’s exact test was used to compare baseline
flow velocity, systolic, diastolic and mean flow
velocities after CO₂ inhalation test and VMR
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 CO₂ 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 CO₂ 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 (Vmean) 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 CO₂ 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 (CO₂) in migraine cases. Decreased CO₂ 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
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 E2 (PGE2) generated by KATP and Calcium (Ca\textsuperscript{2+}) channel-dependent process [17]. NOS activity and NO production are greatly affected by intra- and extracellular sodium (Na\textsuperscript{+}) 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-
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.

References


