HYPEREXCITABILITY OF OCCIPITAL CORTEX IN MIGRAINE

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ABSTRAC

Purpose: *The hypothesis that generalized hyperexcitability of the cerebral cortex, more pronounced in the visual area, is a cornerstone in migraine pathophysiology remains unclear.* ***Methods:*** *We stimulated visual cortex using a 90-mm circular coil placed over the occipital scalp in healthy controls and patients with migraine with aura (MA) and without aura (MO) during the interictal period. Twenty-four MA patients, 14 MO patients and 21 healthy controls were studied. Threshold level and prevalence of stimulation-induced phosphene production were compared among MA, MO and HC groups.* ***Results:*** *The difference in proportion of subjects with phosphene generation in MA and control groups (MA 100% versus control 52.4%, p=0.000) and in MO and control (MO 92.8% versus 52.4%, p=0.000) were significant, but there was no significant difference between MA and MO (p=0.056). The difference in threshold levels in MA (MA 48.6%) and controls (98.2%) and in MO (MO 68%) and controls were significant (p=0.001 and p=0.001 respectively). There was also a significant difference between MA and MO (p=0.01).* ***Conclusion:*** *Our data strongly suggest that the occipital cortical neurons may be hyperexcitable in migraineurs, at least during the interictal period.*

Key Words: *Migraine, Cortical Excitability, TMS.*

INTRODUCTION

The cause and mechanisms of migraine remain uncertain. The occipital cortex has an important role in the elaboration of a migraine attack. Ninety percent of migraine patients with aura have visual disturbances such as blind spots or scotoma, fortification spectra and photopsias (1). That migraine patients may have an interictal cortical hyperexcitability was suggested by several studies (2, 3, 4). Furthermore enhanced excitability of occipital cortex neurons has been proposed as the basis for spontaneous or triggered onset of the migraine aura (5). However neurophysiological evidence for hyperexcitability of occipital cortex between attacks is controversial. For instance, some studies have demonstrated differences in the amplitude of the visual evoked responses in migraineus compared with controls (6, 7), whereas others have shown no abnormalities (8-11). Aurora et al (4) confirmed hyperexcitabilty of the occipital cortex in MA patients using transcranial magnetic stimulation (TMS). However, Afra et al claimed that cortical

hyperexcitability is not a hallmark of migraine pathogenesis and that, on the contrary, elevation of activation threshold and intact intracortical inhibitory mechanisms support a reduction of cortical excitability between attacks, at least in migraine with aura (12).

TMS has provided a noninvasive and most direct method for investigating the physiology and excitability of occipital cortex. Excitability of the visual cortex can be estimated in individual subjects by determining the TMS threshold for phosphene induction, and group differences can be sought by assessing the prevalence of phosphenes at maximal stimulator output. There are only two small studies in which the excitability of occipital cortex using TMS in migraineurs have been investigated (4,12).

In this study, we have measured the TMS threshold for phosphene induction and prevalence of phosphene produced by occipital magnetic stimulation in migraineurs and healthy controls.

METHODS

Subjects

Fifty-nine subjects were examined, including 24 patients with migraine with aura (MA): mean age 37±7 years (21 women, 3 men), 14 patients with migraine without aura (MO): mean age 36±8 years (21 women, 3 men) and 21 healthy controls: mean age 37±2 years (21 women, 3 men). The diagnoses were established according to the International Headache Society criteria. None of the subjects had headache, received analgesic drugs for a week, or received any drug capable of modifying cortical excitability such as psychotropic agents, anticonvulsants, beta-blockers and other prophylactic antimigraine therapies for four weeks. All subjects gave their informed consent.

Stimulation and Recordings

The subjects were comfortably seated in a quiet, dark room and their eyes were covered with a black band. Then, occipital cortex stimulation was performed with a Magstim 200 stimulator connected to a 90-mm-diameter circular coil centered in a vertical position on the inion-nasion line, 7 cm rostral to the inion. Subjects were not informed what to expect, but were asked to report all sensory experiences during stimulation. Subsequently, stimulator intensity was increased in steps of 10% until subjects either reported seeing phosphene (bright scintillations) or until the maximum (100%) intensity of stimulation was reached. Stimulation intensity lower than 100% was then fine-tuned to determine the threshold at which phosphenes could just be visualised in those subjects reporting this experience. In those subjects who did not report seeing phosphene until 100% stimulation intensity was achieved, the stimulator was then moved 1 cm in upward and downward directions to define an optimum point for stimulation and the procedure was repeated. Clockwise coil current was used for excitation of the left visual cortex and counterclockwise for the right. The threshold at which phosphenes were generated was recorded in each subject of the three groups.

Statistical analyses

Fisher's exact test (two tailed) was used to analyse the differences in phosphene production and log rank test was done to compare the threshold levels for phosphene generation between the three groups.

RESULTS

All the 24 migraine patients with aura, 13 of the 14 migraine patients without aura and 11 of the 21 healthy control reported phosphene on occipital cortex stimulation (Table 1, Fig 1). These were reported as short-lasting white flashes or spots. The difference in the proportion of subjects with phosphene generation in MA and control groups (MA 100% versus control 52.4%,

Table - 1: Mean threshold level and prevalence values of phosphene generation in migraine and control groups*.

	Migraineurs	MA	M O	HC
Prevalence of phosphene (%)	97.9	100	92.8	52.4
Threshold for phosphene (%)	57.3	48.6	68.0	89.2

* MA=migraine with aura, MO=migraine without aura, HC=healthy control

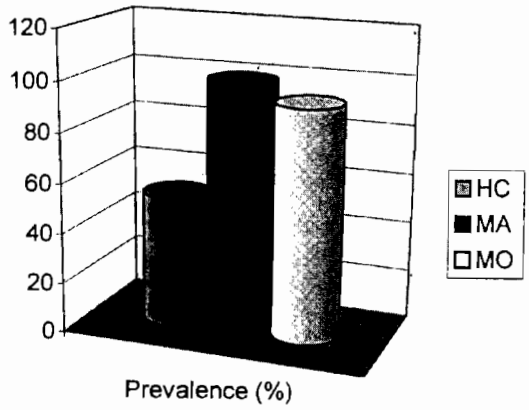

Fig. 1: Prevalence of observing phosphene in healthy controls (HC), patients with migraine with aura (MA) and patients with migraine without aura (MO).

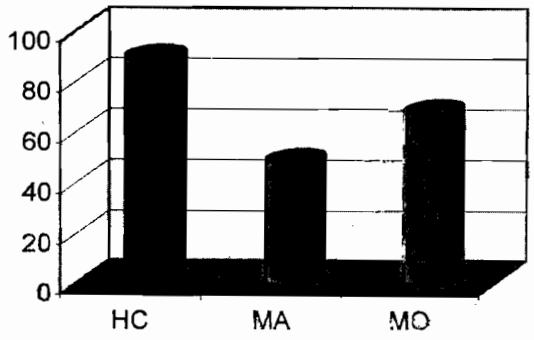

Fig. 2: Threshold for phosphene generation in healthy controls (HC), patients with migraine with aura (MA) and patients with migraine without aura (MO).

p=0.000) and in MO and control (MO 92.8% versus control 52.4%. p=0.000) were significant. There was no significant difference of phosphene generation between MA and MO patients (p=0.056).

The difference in the threshold levels in MA (48.6%) and control (98.2%) and in MO (68%) and control were significant (p=0.000 and p=0.001, respectively) (Table 1, Fig 2). There was also significant difference between MA and MO (p=0.01). All threshold levels for MA and MO patients were lower than the lowest level in the control group.

DISCUSSION

We assessed the excitability of visual cortices of migraineurs compared with healthy controls by using TMS. TMS is the most direct neurophysiological tool confirming the excitability threshold of the occipital cortex. Our results confirm that the threshold for observing phosphene is lower in MA patients than it is in MO patients and in healthy controls. On the contrary, Afra et al determined that MA patients had thresholds for phosphene generation similar to those in MO and healthy volunteer groups (12). However, Aurora et al propose that there may be a spectrum for TMS phosphene generation with MA patients having the lowest threshold and normal subjects with the highest threshold (4). They suggest that subjects with migraine without aura may have a threshold between that of MA patients and normal subjects. Our data prove this hypothesis.

The prevalence of phosphene during TMS was similar in MA patients and MO patients. It was significantly different between each migraine group and controls. Aurora et al had also found that the difference in the proportion of subjects with phosphene generation in MA and control groups was significant (MA100% versus control 27.3%, p=0.001) (4). On the contrary, Afra et al unexpectedly found that the prevalence of phosphene in MA patients was lower than healthy controls (MA 56% versus healthy controls 89%) and the prevalence of phosphene in MO (82%) was similar to healthy controls (12). This difference between our findings and those of Afra et al. may be due to differences of age, sex, race, genetic factors or methodological factors.

Our data strongly indicate that the occipital cortex neurons could be hyperexcitable in migraineurs, at least during the interictal period, particularly in MA. Although these findings are consistent with the findings of Aurora et al (4), they do not correlate well with Afra et al (12). Some studies have also demonstrated a larger amplitude of visual evoked responses in

migraineurs compared with controls, indicating cortical hyperexcitability (13), whereas others found no abnormalities (14). Magnetoencephalographic and phosphorus magnetic resonance spectroscopic evidence also exists supporting the presence of interictal central neuronal hyperexcitability in migraineurs (15).

Enhanced excitability of occipital cortex neurons has been proposed as the basis for spontaneous or triggered onset of the migraine aura (16). Cortical hyperexcitability as a genetic predisposition (16) or as an acquired abnormality (17), is a hallmark of migraine pathogenesis. That migraine patients may have an interictal hyperexcitability was suggested by various studies of the visual system showing increased amplitudes of VEP (2, 3), more intense illusions to grating patterns (18) as well as faster low-level performance (19) on psychophysical visual tests and hypersensitivity to environmental light stimuli (20). It was postulated that a generalized hyperexcitability of the cerebral cortex, more pronounced in visual areas because of a greater neuron /glia ratio, might be a cornerstone in migraine pathophysiology (16). Various electrophysiologic studies demonstrated generalized hyperexcitability (21, 22). Low brain magnesium (23, 24), especially selective occipital cortex magnesium deficiency at least in familial hemiplegic migraine (FHM) (23), would promote such a dysfunction. FHM may be due to a channelopathy. Presynaptic voltage-gated P/Q type neuronal calcium channel abnormality would influence presynaptic neurotransmitter release, possibly of excitatory amino-acid systems or inhibitory serotonergic systems, leading to postsynaptic neuronal excitability (25). It was postulated that visual dysfunction in migraine with aura might be secondary to loss of inhibitory GABAergic interneurons in the striate cortex due to repeated parenchymal insults during auras (17). Disorder of mitochondrial energy metabolism (16,26) and abnormality of glutamate metabolism (27) have also been identified.

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