Short Communication

Migraine-linked characteristics of transcranial magnetic stimulation-induced phosphenes

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Transcranial magnetic stimulation is used to explore visual cortex hyperexcitability in migraine. We hypothesized that the phosphene threshold in subjects suffering from migraines with and without aura would be lower than in controls, and this phenomenon could be linked to higher pain and disability levels. We also implied that subjects with lower phosphene threshold could see more phosphenes of different colors and shapes. Our primary objective was to compare the phosphene threshold between migraine without aura, migraine with aura, and control groups and investigate which factors contribute to different phosphene parameters in migraineurs. Secondary objectives were to compare color, shape, and number of phosphenes between groups and assess pain and disability level correlation with the phosphene characteristics. Phosphene threshold in migraine without aura, migraine with aura, and control groups were $68 \pm 9.5\%$ vs. $75 \pm 12\%$, vs. $80 \pm 11\%$, respectively. Other phosphene parameters (number, color and shape) did not differ between groups. Average pain level during the attack did not correlate with phosphene threshold significantly, though the non-significant trend for negative correlation of migraine disability assessment scale score and a phosphene threshold has been found the higher was migraine disability assessment scale value, the lower was phosphene threshold ($\beta = -0.255$; $P = 0.139$). Other variables: gender, age, migraine subtype, migraine duration and use of hormone contraceptives – were not related to the phosphene threshold value. Our study provides additional data on visual cortex hyperexcitability in migraineurs, regarding transcranial magnetic stimulation with a figure-of-eight coil. Visual cortex excitability might be linked to higher disability.

Keywords

Migraine; phosphine; cortical excitability transcranial magnetic stimulation

1. Introduction

Migraine pathogenesis is an exemplar for cortical spreading depression (CSD) phenomenon caused by cortical hyperexcitability (Brigo et al., 2013; Lauritzen, 1994; Lauritzen et al., 2011). CSD can be described as a biphasic phenomenon, starting with depolarization involving neuronal and glial cells in the cerebral cortex, subcortical gray matter, or retina, followed by inhibition, leading to changes in ionic concentrations. Migraine auras are most often visual, apparently starting in Brodmann area 17 (Brigo et al., 2013; Lauritzen, 1994).

Transcranial magnetic stimulation (TMS) is one of the methods used to explore visual and motor cortex hyperexcitability in migraine. Visual cortex can be stimulated effectively with TMS, evoking a perception of the phenomena within the visual field, which are referred to as phosphenes. They are usually described as white or greyish luminous shapes. Although phosphenes are normally perceived as simple flashes of light, sometimes they can make more complex shapes and texture (Valiulis et al., 2010). In many studies, the perception of phosphenes elicited with TMS has been employed as a measure of visual cortex excitability in migraineurs. A reduced threshold for phosphene perception with TMS implies increased cortical excitability and *vice versa*.

Existing data on phosphene characteristics concerning migraine without aura (M0) and migraine with aura (MA) are controversial and methodologically heterogeneous. In patients suffering from both migraine types, some authors have found lower thresholds for phosphene (PT) induction than in normal volunteers (Aurora et al., 1998, 1999, 2003; Mulleners et al., 2001). In contrast, others (Afra et al., 1998) have found higher PT in migraineurs compared to healthy controls. According to a meta-analysis in 2012, type and size of electromagnetic coil, site of stimulation, and maximal delivered magnetic strength often differed in such studies, thus leading to the variability of results due to methodological differences (Brigo et al., 2012). In most of the studies, circular coils were used. Our study provides data on TMS with a figure-of-eight coil.

Our primary objective was to compare PT between M0, MA, and control groups. Secondary objectives were to compare color, shape, and number of phosphenes between groups. If such differences were found, we would plan to investigate if those factors correlate with pain and disability levels in migraineurs.

2. Methods

2.1 General study information

A cross-sectional study was conducted in November 2010 - March 2011 in Republican Vilnius Psychiatry Hospital. M0 and MA groups were elicited by using migraine and migraine with aura criteria proposed by the International Headache Society[1]. The research was approved by the Regional Bioethics Committee (2007-09-10, approval Number 37). Every participant read and signed the informed consent form before the study.

2.2 Study subjects

All subjects were naïve to TMS. Only those with active migraine (defined as at least one migraine attack during the previous year) were included in the study. Exclusion criteria were any other significant neurological pathology, history of seizures, age less than 18 years old, and pregnancy, use of any psychotropic drugs, or migraine prophylactic treatment. Headache intensity was assessed using the Visual Analogue Scale (VAS). Migraine severity was evaluated using the Migraine Disability Assessment Scale (MIDAS).

2.3 Transcranial magnetic stimulation

TMS was performed in the migraine interictal period, which was defined as a headache-free period with a minimum duration of 24 hours. Two investigators performed TMS. They both were unblinded to participants' diagnoses. TMS was performed using Medtronic Magpro X100 TMS stimulator with MagVenture Cool Coil B65 liquid-cooled figure-of-eight coil, which external diameter was 75 mm. Maximal magnetic field delivered by this device was 2.5 T. During the stimulation, 280 μs single impulses were used. The stimulation target area was 3 cm above the inion. Subjects were asked to wear a blindfold and to close their eyes to diminish any ambient light. Stimulator intensity was increased in 10% increments until subjects reported visual phenomena or 100% intensity was reached. Then the intensity was fine-tuned to determine the threshold at which phosphenes were just visualized. After that, ten different stimulus intensity levels were chosen from the phosphene threshold value in steps of 2% to cover subthreshold as well as suprathreshold values. Each intensity level was tested ten times in random order. A randomized list with the sequence of 100 stimuli was printed on a sheet, and the response (" + " symbol, if the subject perceived phosphene, and " − " if no phosphenes were seen) was fixed on it after each stimulus.

The investigators used sham stimulation in every subject: they turned over the coil, placed it to the head of the subject *vice versa,* and "stimulated" in this manner for 1 or 2 times. If the subject still claimed seeing phosphenes, while being stimulated with the coil turned over, those data were assumed irrelevant, and such subject's data were excluded from the study. Thresholds were calculated applying a sigmoidal fit to the data using the Boltzmann equation.

The half-maximal value, i.e., perception of phosphenes in five out of ten stimulations, was defined as PT (Fig. 1).

The primary objective was to compare PT, as well as phosphene number, color, and shape, between study groups. The subjects, who claimed to see the phosphenes during the sham stimulation, were excluded. In some subjects, the sigmoidal fit was not informative - those were excluded, too.

The correlation between PT and gender, age, migraine subtype, migraine duration in years, attack frequency, VAS and MIDAS values, and the use of hormone contraceptives were the secondary objectives of the analysis. Patients were classified into three groups according to attack frequency: 1 or more attacks per week; from one to several times per month and from one to several times a year.
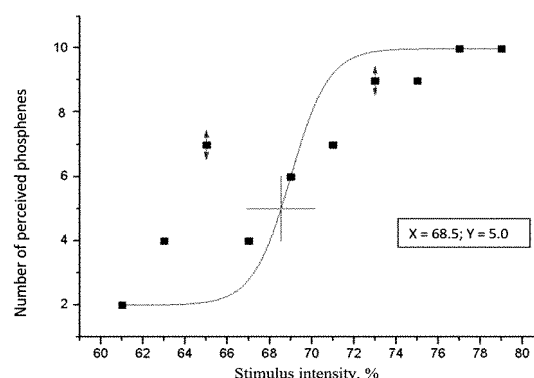

Figure 1. An example of the sigmoidal fit. This figure shows, how many times phosphenes were perceived while stimulating with different intensity (showed as black dots). The overall result of 100 stimuli in each subject was visualized as the sigmoidal fit. The intensity (X axis), which corresponded to 5 phosphenes perceived (Y axis) on the sigmoidal fit, was marked as the phosphene threshold.

2.4 Data analysis

Data analysis was performed using SPSS Version 17.0 for Windows. Parametrical data were analyzed for normality using the Shapiro-Wilk test. PT data were normally distributed, while age, MIDAS and VAS values were not. Normally distributed parametrical data were analyzed using a *t*-test to compare two groups and one-way ANOVA test with posthoc Bonferroni correction to compare three groups. Non-parametrical or not normally distributed data were analyzed using a Mann-Whitney test to compare two groups and the Kruskal-Wallis test to compare three groups. The correlation was assessed using the Pearson correlation coefficient for normally distributed parametrical data and Spearman correlation coefficient for other data. A *P*-value of less than 0.05 was considered statistically significant.

3. Results and discussion

3.1 Results

The subjects of our study were 53 subjects with no significant concomitant pathology, 12 of whom had migraine with aura (MA group), 17 − migraine without aura (M0 group), and 24 had no migraine (controls − C group). In the MA group, 9 subjects had visual aura and 1 had aura with speech disturbances (apha-

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[1] The international classification of headache disorders (2004) International Headache Society. *Cephalalgia* **24**, 9-160

sia). After performing the TMS, some participants dropped out of the study. The main reasons were not informative sigmoidal fits, inability to perceive phosphenes and failure to respond correctly to the sham stimulation. Detailed data on the study subjects are shown in Fig. 2.

Demographic and clinical data did not differ significantly between M0, MA, and control groups (Table 1).

PT was $68.1 \pm 9.5\%$ in the M0 group, $75.1 \pm 12.4\%$ in the MA group, and $79.7 \pm 11.0\%$ in the control group (Fig. 3). Phosphene shape, color, and a number did not differ between groups; the frequency of scotomas reported did not differ between groups either.
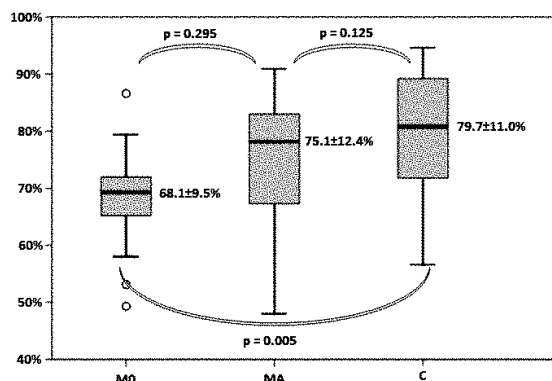

Figure 3. PT differences between M0, MA and control groups. Mean PT was $68.1 \pm 9.5\%$ in the M0 group, $75.1 \pm 12.4\%$ in the MA group, and $79.7 \pm 11.0\%$ in the control group. The difference was statistically significant only between M0 and control groups ($P = 0.005$). M0 — migraine without aura group, MA — migraine with aura group, C — control group, PT — phosphene threshold.

There was no significant correlation between PT and gender, age, migraine subtype, migraine duration in years, attack frequency, VAS values, and the use of hormone contraceptives. A non-significant trend for negative correlation of MIDAS score and a PT was discovered: the higher was MIDAS value, the lower was PT ($\beta = -0.255$; $P = 0.139$).

3.2 Discussion

We found that the phosphene perception threshold in migraineurs without aura is significantly lower than in healthy volunteers. Our findings are consistent with the hypothesis of visual cortex hyperexcitability in migraineurs without aura, providing additional data on visual cortex stimulation with the figure-of-eight coil. This is important because the figure-of-eight coils produce a focal stimulation under the center of the coil, and the circular coil causes diffuse stimulation of the underlying cortical area. It is also likely that a larger cortical area is stimulated with large circular coils.

A concept of cortical hyperexcitability in migraine is significant, since this is a promising aspect, considering the need for migraine diagnostics and more effective migraine therapies. It is well-known, that several effective drugs for migraine prophylaxis are antiepileptic medications (Evers et al., 2009; Loder et al., 2012), which act by reducing cortical excitability (Hoffmann et al., 2014).

Brigo et al. (2012) carried out a meta-analysis and found that patients suffering from M0 and MA have a lower PT compared to controls, when a circular coil single-pulse TMS is used; the difference using a figure-of-eight coil was not statistically significant. In another meta-analysis by Brigo et al. (2013) found that only the patients with MA have a lower PT compared with controls when a circular coil single-pulse TMS is used. As for M0 participants, only non-significant trends for lower PT values were found with circular coil TMS, and for higher PT values with figure-of-eight coil TMS. In contrast with these data, in our study PT in M0 patients was significantly lower than in control group. In MA mean phosphene threshold was higher than in M0 and lower than in control group, but this difference was not statistically significant. This can be explained by the fact that the number of participants in MA group was relatively small.

This result could also be hypothetically attributed to the fact that some subjects could be assessed in their postictal phase, since it has been reported, that the excitability of the cortex of the migraineurs can variate depending on the migraine attack phase:
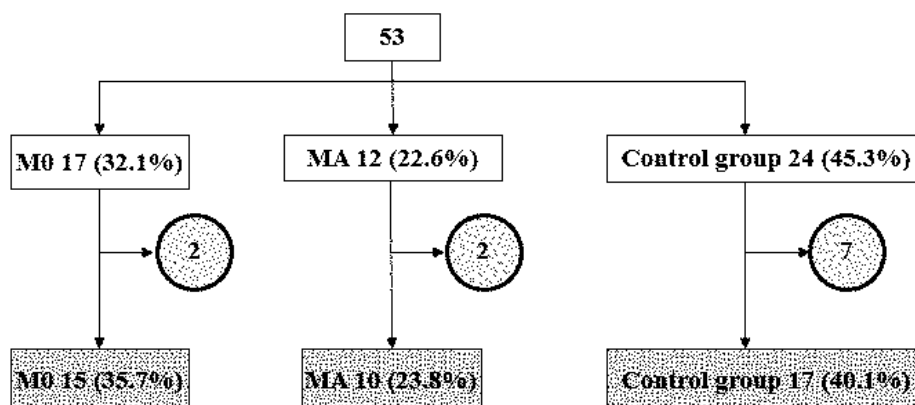

Figure 2. Study population. 53 subjects were investigated: 12 in MA group, 17 in M0 group and 24 controls. After performing the TMS, 2 subjects from both MA and M0 groups and 7 controls dropped out of the study. 42 participants were left: 10 in MA group, 15 in M0 group and 17 controls. M0 — migraine without aura group; MA — migraine with aura group.

Table 1. Demographic and clinical data. M0 — migraine without aura group, MA — migraine with aura group. MIDAS — Migraine Disability Assessment Scale. VAS — Visual Analogue Scale.

	M0, N = 15	MA, N = 10	Control, N = 17	P
Age, years	22.4 ± 1.8	22.7 ± 1.8	22.6 ± 1.4	0.898
Females, number (%)	11 (73)	10 (100)	14 (82)	0.214
MIDAS	18.8 ± 17.2	13.7 ± 13.4	-	0.846
VAS	6.7 ± 1.3	6.6 ± 0.9	-	0.993
Age of migraine onset, years	13.1 ± 4.8	14.0 ± 4.3	-	0.559
Migraine duration, years	9.1 ± 5.2	8.8 ± 4.8	-	0.631
Use of oral contraceptives, number (%) in females	2 (18)	1 (10)	1 (7)	0.969

while the preictal phase is characterized by the excitatory response, the postictal phase is inhibitory (Hoffmann et al., 2014). In our study, the subjects were assessed in the interictal period, even though, unfortunately, the data about the duration from the last attack were not collected.

TMS-induced phosphene threshold values tended to be inversely proportional to the level of migraine-caused disability assessed by MIDAS, while the duration of migraine in years and VAS score did not correlate with PT values in our study, in contrast with data, provided by Lo et al. (2008). They found that PT values correlate positively with higher pain level. However, in case of migraine, disability depends not only on pain, but also on a variety of other symptoms.

The results concerning TMS effect in cases of the acute and chronic migraine are still controversial. Single-pulse TMS over the occipital cortex occurred to be more effective than sham stimulation aborting acute migraine with aura attacks (Loder et al., 2012). On the contrary, the meta-analysis of 4 randomized controlled trials showed, that the effect of TMS on chronic migraine was not statistically significant (Sprenger and Goadsby, 2009). However, the site of stimulation in those trials was not occipital but left frontal cortex. More data is necessary to assess visual cortex excitability in chronic migraine and migraine without aura.

Acknowledgment

Conflict of interest

The authors declare no conflict of interest.

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