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# Asymmetric distribution of visual evoked potentials in patients with migraine with aura during the interictal phase

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PURPOSE. *One of the most commonly described electrocortical phenomena in patients with migraine is an increased interhemispheric asymmetry, in response to different sensory stimuli. This study aims to evaluate the bioelectrical activity of both occipital cortices in patients with migraine with visual aura (MA) during the interictal period, and its possible relationship with visual symptoms.*
METHODS. *The authors recorded visual evoked potentials (VEPs) simultaneously from the left (O1) and right (O2) occipital cortices (80% contrast 60', 30', 15', and 7.5' checkerboard stimuli reversed at 2 Hz) in 22 patients with MA and 20 control subjects. The main outcome measure was interhemispheric asymmetry (IA) for both implicit time and amplitude, defined as the difference between the left and right scalp derivation (in absolute values).*
RESULTS. *IA was significantly different in patients with MA with respect to controls when employing 60' ($p<0.001$) and 15' ($p<0.05$) checkerboard stimuli for implicit times, and 60' ($p<0.05$) checkerboard stimuli for amplitudes. On the other hand, IA was not statistically different ($p>0.05$) in patients with MA with respect to controls when employing 30' and 7.5' checkerboards for both implicit times and amplitudes, and 15' checkerboards for amplitudes. No correlations were found between IA and age, onset of disease, attack frequency, or side of headache/aura.*
CONCLUSIONS. *Patients with MA presented asymmetries in VEP responses not related to visual aura or to headache side during the pain-free phase. These abnormalities may be ascribed to abnormal visual information processing, resulting in a different cortical activation when both foveal and parafoveal stimuli are used. (Eur J Ophthalmol 2007; 17: 828-35)*

KEY WORDS. *Migraine, Visual evoked potentials, Interhemispheric asymmetry*

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## INTRODUCTION

Many patients with migraine experience different visual symptoms and photophobia, and in a subgroup of patients focal neural disturbance (aura), more frequently of visual nature, precedes the headache phase. The typical migraine aura appears as scintillation-scotoma that begins at the center of the visual field and moves peripherally within 10 to 15 min and afterwards is usually followed by headache.
Both fMRI (1) and electrophysiologic (2) studies seem to confirm that migraine aura (MA) is the clinical correlate of a neural event named cortical spreading depression (CSD), which consists of a neuronal depolarization activi-

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ty, followed by a wave of depression spreading from the occipital cortex to the parietal and temporal lobe (3). However, the CSD phenomenon does not explain the permanent perpetuation of the migraine attacks, e.g., the subtle factors that cause the migraine disease, which, if present, should also be detectable in the pain-free period, representing underlying dysfunctions.

Several studies have searched for interictal neural alterations that may predispose to migraine attacks. In particular, using electrophysiologic techniques (which allow the in vivo analysis of the migraineur's electrocortical phenomena in response to different types of sensory stimuli), it was observed that patients with MA may show an increase of asymmetry in interhemispheric bioelectrical activity with respect to normal subjects (4-11). Since the most frequent aura symptoms are visual disturbances, several studies evaluated the possible differences in interhemispheric bioelectrical activity of the visual cortices by visual evoked potential (VEP) recordings. Nevertheless, these studies present nonhomogeneous visual stimulation techniques and different patient selection criteria (6-11).

Therefore, our study aims to assess, in a selected group of patients with MA, the likely presence of an asymmetric occipital evoked activity during the pain-free phase and its possible relationship with visual aura.

## MATERIALS AND METHODS

### *Patients*

Twenty-two patients, 10 male and 12 female (age range 14–55 years, mean age 33.6±11.4 years) with migraine with visual aura (MA subjects), fulfilling the diagnostic criteria defined by the International Classification of Headache Disorders (II edition, 2004), were enrolled in this study. Patients with other types of focal neurologic auras (for example, sensory or dysphasic speech alterations) were excluded.

For patients with MA, inclusion criteria were as follows:

- No previous history of other neurologic diseases, systemic hypertension, diabetes or other metabolic disorders, connective or autoimmune diseases
- Best-corrected Snellen visual acuity of 10/10
- Intraocular pressure less then 18 mm Hg
- Refractive errors, when present, within ±1 spherical diopter
- No other ocular or retinal pathology
- Headache-free for the duration of the examination

Further exclusion criteria for patients with MA were as follows:

- Evidence of brain lesions on magnetic resonance imaging, only performed in this group of subjects
- Migraine attacks in the 3 days preceding and following the recording session
- Use of prophylactic antimigraine therapy

None of the patients with MA reported a prevalent side for the development of aura symptoms.

The clinical characteristics and relative visual symptoms of patients with MA enrolled are reported in Table I.

Patients with MA were compared to 20 age-matched control subjects (8 male and 12 female, mean age 33.4±10.6 years) enrolled following the same inclusion criteria used for MA patient enrollment, and without personal or familial history of migraine.

The research followed the tenets of the Declaration of Helsinki. The protocol was approved by the local IRB. Upon recruitment, each patient gave informed consent.

### *VEP recordings*

On the basis of previously published studies (12, 13) the following electrophysiologic evaluations were performed.

Subjects under examination were seated in a semi-dark,

**TABLE I -** CLINICAL CHARACTERISTICS AND SYMPTOMS OBSERVED IN PATIENTS WITH MIGRAINE AURA

| Clinical characteristics | Mean ± SD or n |
|---|---|
| Migraine onset, yr | 13.9±6.0 |
| Attack frequency/mo | 3.4±1.2 |
| Headache symptoms | |
| Headache side | |
| > On right side | 10 |
| Alternating | 4 |
| Bilateral | 2 |
| Unilateral/bilateral | 6 |
| Visual complaints | |
| Phosphenes | 4 |
| Phosphenes and visual field deficits | 4 |
| Scintillation scotoma and visual fogging | 4 |
| Fortification spectra | 2 |
| Scintillation scotoma | 6 |
| Visual fogging and photophobia | 2 |

acoustically isolated room in front of the display surrounded by a uniform field of luminance of 5 cd/m$^2$. Prior to the experiment, each subject was adapted to the ambient room light for 10 minutes to obtain a constant pupil diameter. Mydriatic or miotic drugs were never used. Stimulation was monocular (in the randomly selected right or left eye) after occlusion of the other eye. Visual stimuli consisted of full-field checkerboard patterns (contrast 80%, mean luminance 110 cd/m$^2$) generated on a TV monitor (70 Hz refresh rate) and reversed in contrast at a rate of 2 reversals/s. At the viewing distance of 114 cm, the single check edges subtended 60', 30', 15', and 7.5' of visual angle (14). The monitor subtended 18°, and a small red target (0.5°) was placed in the center of the stimulus field to maintain stable fixation. The refraction of all subjects was corrected according to the viewing distance. The bioelectric signal was recorded using Ag/AgCl cup-shaped electrodes fixed with collodion in the following positions: active electrode at O1 (left occipital cortex), O2 (right occipital cortex), and Oz (middle occipital cortex) following the International System 10-20 (15); common reference electrode at Fpz; and common ground on the left arm. The interelectrode resistance was kept below 3 KOhms. The bioelectric signal was amplified (gain 20,000), filtered (bandpass 1–100 Hz) and averaged (200 artefact-free events were averaged for every trial) by BM 6000 (Biomedica Mangoni, Pisa, Italy). The analysis time was 250 ms. The transient VEP response is characterized by a number of waves with three successive peaks of negative, positive, and negative polarity. In normal subjects, these peaks were identified according to their respective latencies: N75 as the most negative peak between 60 and 90 ms after the stimulus, P100 as the most positive peak following N75 at a latency of 80 to 125 ms, and the N135 as the most negative peak following P100 at a latency of 125 to 150. For both P100 implicit time and N75-P100 amplitude, we considered interhemispheric asymmetry (IA) as the difference between the left (O1) and right (O2) electrode derivations, always expressed in absolute values (i.e., without algebraic sign): P100 O1 implicit time = X ms, P100 O2 implicit time = Y ms, absolute IA = X–Y; N75-P100 O1 amplitude = X microvolts, P100 O2 amplitude = Y microvolts, absolute IA = X–Y.

During the recording session, VEPs were recorded at least twice, and the resulting waveforms were superimposed to check the repeatability of the results. We randomized the order of check size presentation to avoid the order effect. The noise peak-to-peak amplitudes were measured in a temporal window corresponding to that at which the response component of interest (i.e., N75-P100) was expected to peak. Signal-to-noise ratios (SNRs) for this component were determined, either in the short or long averaging record, by dividing the peak amplitude of the component by the noise in the corresponding temporal window. In all subjects and patients, VEP SNRs, determined with both recording times, were $^3$2.8 in all the steps of the experimental procedure.

For all VEP recordings, implicit times (P100) and peak-to peak amplitudes (N75-P100) of each of the averaged waves were directly measured on the displayed records by means of a pair of cursors.

### *Statistics*

Normal limits were obtained from control subjects by calculating mean values plus 2.5 standard deviations for VEP P100 implicit times and mean values plus or minus 2.5 standard deviations for VEP N75-P100 amplitudes.

The difference between MA patients and control subjects was evaluated by 1-way analysis of variance separately for implicit time and amplitude, considering the different checks sizes as dependent variables. Moreover, multivariate analysis of variance was performed to obtain a Wilks-lambda value as strength of the correlation between migraine (considered as a predictor) and percentage of asymmetry (considered as a dependent variable). The correlation between interhemispheric asymmetry (in positive values) and the side of headache/aura was evaluated, when possible, with $\chi$-square test. Pearson correlation test was adopted to evaluate the correlation between all electrophysiologic parameters and age, onset of disease, and attack frequency. A $p<0.05$ was considered significant for all statistical evaluations.

## RESULTS

Examples of VEP recordings simultaneously obtained in Oz, O1, and O2 from a normal subject and from an MA patient are shown in Figure 1.

Mean data and relative statistical analysis of electrophysiologic parameters observed in control subjects and MA patients are presented in Tables II and III.

Grouped bar charts of mean IA values for each group are presented in Figure 2.

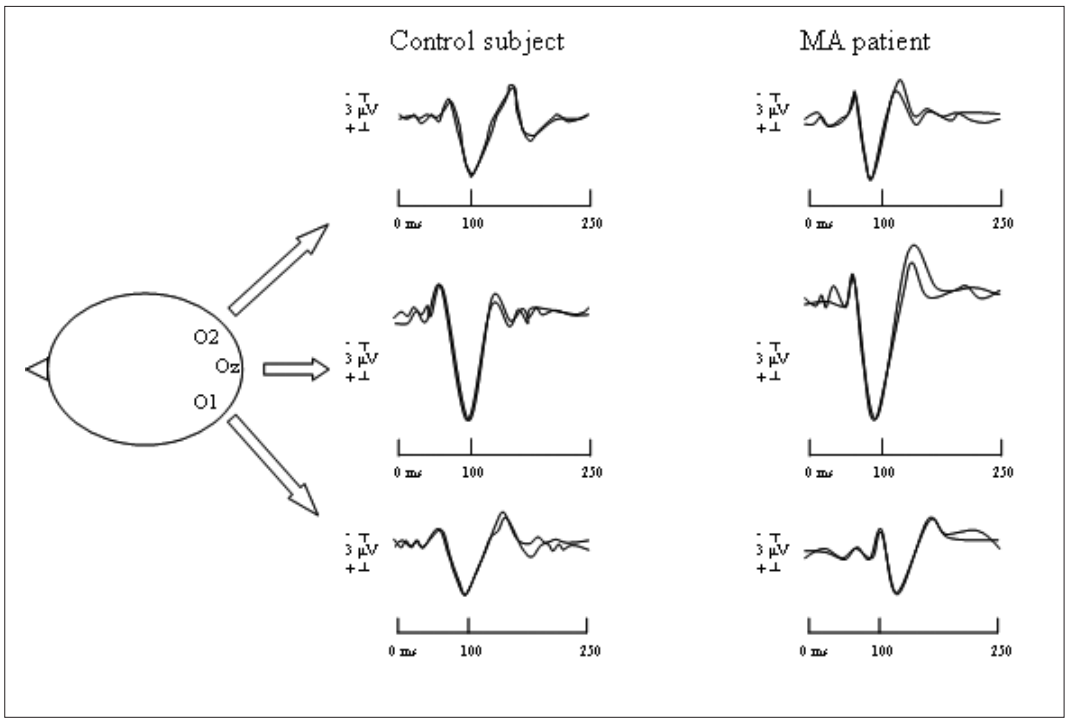


**Fig. 1 -** *Layout of visual evoked potentials (in response to 60' check) simultaneously recorded in the left (O1), middle (Oz), and right (O2) occipital sites in one control subject and one patient with migraine with visual aura (MA). The stimulation was monocular in right eye. With respect to the control subject, the patient with MA shows an increased interhemispheric asymmetry of P100 implicit time and of N75-P100 amplitude.*

**TABLE II -** MEAN VALUES ± 1 STANDARD DEVIATION OF VISUAL EVOKED POTENTIAL (VEP) PARAMETERS OBSERVED IN CONTROLS AND IN PATIENTS WITH MIGRAINE WITH AURA (MA)

| **Electrophysiologic parameters** | | **60'** | **30'** | **15'** | **7.5'** |
|---|---|---|---|---|---|
| VEP | Controls | 102.6±2.8 | 102.1±4.2 | 106.9±3.7 | 114.7±7.9 |
| P100 implicit time | MA | 101.9±4.2 | 101.5±2.3 | 106.6±5.1 | 113.1±8.7 |
| Oz (ms) | A vs C (F1,40) | 0.442, p=0.510 | 0.342, p=0.562 | 0.067, p=0.797 | 0.387, p=0.537 |
| VEP | Controls | 11.3±3.2 | 8.6±3.0 | 9.9±3.7 | 5.5±2.7 |
| N75-P100 amplitude | MA | 9.3±4.8 | 8.5±4.9 | 7.8±5.5 | 4.7±5.7 |
| Oz (µV) | A vs C (F1,40) | 2.274, p=0.139 | 0.004, p=0.947 | 1.931, p=0.172 | 0.335, p=0.566 |
| VEP | Controls | 103.6±2.8 | 102.3±4.4 | 106.6±4.4 | 114.7±8.4 |
| P100 implicit time | MA | 103.0±5.6 | 102.1±4.9 | 107.5±6.8 | 113.2±7.9 |
| O1 (ms) | A vs C (F1,40) | 0.190, p=0.668 | 0.030, p=0.859 | 0.253, p=0.618 | 0.343, p=0.561 |
| VEP | Controls | 5.8±2.1 | 4.9±2.0 | 4.9±1.7 | 2.9±1.3 |
| N75-P100 amplitude | MA | 4.9±1.9 | 4.3±1.6 | 4.4±2.4 | 2.8±2.0 |
| O1 (µV) | A vs C (F1,40) | 1.755, p=0.193 | 1.179, p=0.284 | 0.497, p=0.484 | 0.034, p=0.854 |
| VEP | Controls | 103.6±3.4 | 102.2±4.7 | 107.1±4.9 | 114.3±8.6 |
| P100 implicit time | MA | 105.4±4.3 | 102.6±3.4 | 108.9±6.1 | 113.8±8.5 |
| O2 (ms) | A vs. C (F1,40) | 1.992, p=1.166 | 0.095, p=0.760 | 1.040, p=0.314 | 0.040, p=0.842 |
| VEP | Controls | 5.8±2.1 | 4.2±1.6 | 4.6±1.8 | 3.0±1.4 |
| N75-P100 amplitude | MA | 4.7±1.9 | 4.4±2.0 | 3.9±2.2 | 2.3±1.1 |
| O2 (µV) | A vs. C (F1,40) | 3.611, p=0.064 | 0.076, p=0.784 | 1.040, p=0.314 | 3.860, p=0.056 |

60', 30', 15', and 7.5' are referred to the minutes of visual arc subtended by the single check during the visual stimulation.
O1 = Left derivation; O2 = Right derivation; A = One-way analysis of variance

**TABLE III -** MEAN VALUES ± STANDARD DEVIATION OF INTERHEMISPHERIC ASYMMETRY (IA) OBSERVED IN CONTROLS AND IN PATIENTS WITH MIGRAINE WITH AURA (MA)

| IA | | 60' | 30' | 15' | 7.5' | Wilks lambda |
|---|---|---|---|---|---|---|
| Implicit time | Controls | 1.2±0.9 | 2.0±1.5 | 1.9±1.8 | 1.8±1.5 | |
| (ms) | MA | 3.6±2.9 | 3.5±3.8 | 4.6±4.6 | 3.9±5.3 | 0.657 |
| | A vs C (F1,40) | 12.248, p=0.001 | 2.558, p=0.118 | 5.842, p=0.020 | 2.667, p=0.110 | p=0.003 |
| | Controls | 0.9±0.6 | 1.3±1.6 | 1.1±0.8 | 0.9±0.8 | |
| Amplitude | MA | 1.6±1.0 | 1.5±1.2 | 1.9±1.8 | 1.0±1.6 | 2.047 |
| (μV) Controls | A vs C (F1,40) | 5.763, p=0.021 | 0.306, p=0.583 | 3.044, p=0.089 | 0.050, p=0.824 | p=0.108 |

60', 30', 15', and 7.5' are referred to the minutes of visual arc subtended by the single check during the visual stimulation.
A = One-way analysis of variance

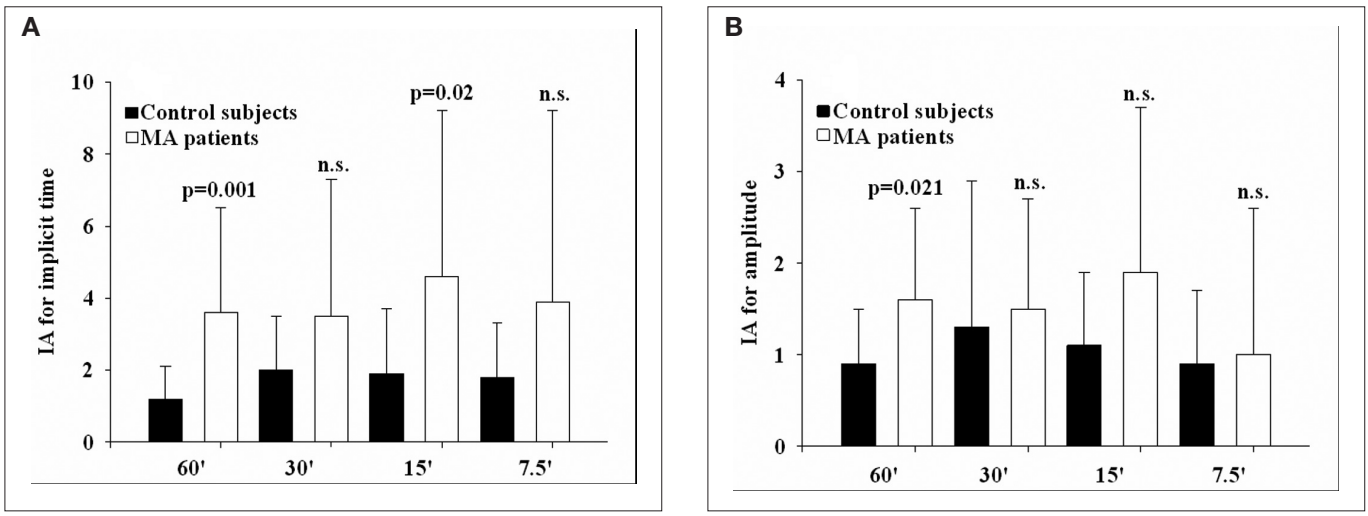


**Fig. 2 -** *Grouped bar charts of interhemispheric asymmetry (IA) values in response to 60, 30, 15, and 7.5 min arc checks observed in control subjects and in patients with migraine with visual aura (MA).* **(A)** *IA for P100 implicit times;* **(B)** *IA for N75-P100 peak-to-peak amplitudes. ns = nonsignificant group differences.*

### *VEP P100 implicit times and N75-P100 amplitudes*

By considering individual MA patients, we observed the following abnormal VEP responses.

- On Oz derivation: delayed VEP P100 implicit times in 2 (9.1%) out of 22 MA patients when 60' checks were used and in 1 (4.5%) out of 22 MA patients using 15' checks
- On O1 derivation: delayed VEP P100 implicit times in 3 (13.6%) out of 22 MA patients when 60' checks were used, in 1 (4.5%) out of 22 MA patients using 30' checks, and in 3 (13.6%) out of 22 MA patients using 15' checks
- On O2 derivation: delayed VEP P100 implicit times in 2 (9.1%) out of 22 MA patients when 15' checks were used

No further VEP abnormalities were detected in MA patients and in particular, all MA patients showed VEP N75-P100 amplitudes (recorded in Oz, O1, and O2 in response to 60', 30', 15', and 7.5' checks) within normal limits.
On average, VEP P100 implicit time and VEP N75-P100 amplitude observed in MA patients were similar ($p<0.05$) to those found in the control group.

### *Interhemispheric asymmetry*

By considering individual patients with MA, we observed the following abnormal IA responses: 1) increased IA im-

plicit times in 10 (45.4%) out of 22 patients with MA when 60' checks were used, in 5 (22.7%) out of 22 patients with MA using 30' checks, in 5 (22.7%) out of 22 patients with MA using 15' checks, and in 6 (27.3%) out of 22 patients with MA using 7.5' checks; and 2) increased IA amplitudes in 4 (18.2%) out of 22 patients with MA when 60' checks were used, none using 30' checks, in 5 (22.7%) out of 22 patients with MA using 15' checks, and in 2 (9.1%) out of 22 patients with MA using 7.5' checks.

On average, IA implicit time values observed in patients with MA were significantly ($p<0.05$) increased with respect to controls when 60' and 15' of visual stimulation were used. When 30' and 7.5' of visual stimulation were employed, patients with MA showed higher IA implicit times than controls, but they did not reach statistical significance ($p>0.05$). Therefore, IA amplitude values were significantly ($p<0.05$) increased with respect to controls when 60' of visual stimulation were used, but not using the other three visual stimulations.

Multivariate analysis of variance showed that IA of implicit times (as dependent variable) was significantly related to the diagnosis of migraine with aura (as predictor), and this correlation was only evident for two spatial frequencies, 60' and 15' of visual angle (see Tab. III). This was not the case when we considered IA of amplitudes as dependent variable.

No significant correlations ($p>0.05$) were found between interhemispheric asymmetry and side of visual aura or headache, age, onset of disease, and attack frequency.

## DISCUSSION

Our study aimed to assess, in a group of patients with MA experiencing not strictly lateral headache/aura, the presence of an asymmetric occipital evoked activity during the interictal period, with full-field pattern reversal visual stimulus.

Patients with MA showed no differences in VEP P100 implicit times and VEP N75-P100 peak-to-peak amplitudes when compared to controls independently from the spatial frequencies used and occipital derivation (e.g., Oz, O1, and O2). Nevertheless, when analyzing individual VEP responses, some patients with MA showed delayed implicit times (recorded in the left or right occipital derivation) not correlated with the side of aura or headache.

Considering VEP responses obtained in the middle occipital derivation (Oz), our results in patients with MA are in contrast with other studies showing a delay in VEP P100 implicit time (16-19) or an increase in VEP N75-P100 amplitude (9, 10, 16, 17, 19-23) with respect to normal subjects. On the other hand, our results are in agreement with other studies reporting no significant differences between patients with MA and normal subjects (11, 24-26).

Considering VEP implicit time and amplitude obtained in the lateral occipital derivation (O1 and O2), our results are in agreement with the major findings in the literature reporting no significant differences between patients with MA and normal subjects (8-11). On the contrary, few studies report differences between patients with MA and normal subjects and, in particular, reduced VEP amplitudes recorded in the occipital derivation ipsilateral to the aura side (8) or increased VEP amplitudes recorded contralaterally to the aura side (9, 10). This is also in contrast with our results reporting an absence of correlation between changes in VEP implicit time or amplitude and the side of visual aura/headache. Instead, our lack of correlation is in agreement with the results reported by Nyrke et al (6) and Logi et al (11).

Taking into account that full-field pattern reversal stimuli normally elicit symmetric lateral responses (9), and that we chose to not utilize a hemifield stimulus since the patients enrolled had not experienced a strictly lateral headache/aura, the main finding of our work is represented by the observed higher interhemispheric asymmetry in patients with MA when compared to control subjects. In particular, we reached statistical significance with P100 implicit times and using checks subtending 60 and 15 min of visual arc. The interhemispheric asymmetry of the implicit times derived using the other two spatial frequencies (30 and 7.5 min of arc checks) did not reach statistical significance, probably due to the high degree of variability of responses. The multivariate analysis of variance reveals that this electrophysiologic pattern is specific to patients with MA, only for implicit times.

To our knowledge, this is the first experimental work in patients with MA that analyzes interhemispheric asymmetry between the bioelectrical responses of the left and right occipital derivations, by using different spatial frequencies.

It is difficult to compare our results with those already published in the literature, since previous studies employed different techniques and parameters of visual stimulation, and several studies enrolled a non-homogeneous group of patients with migraine.

Nyrke et al, (6) using steady-state VEPs in patients with

MA during attack-free intervals, observed transient interhemispheric asymmetries and amplitude fluctuations not correlated with side of aura/headache. The authors discuss that their results probably suggest a neural disorder or a defective interaction between neural and vascular function in patients with MA. Tagliati et al (8) and Shibata et al (9, 10) using multichannel recordings of transient VEPs showed an asymmetry of VEP topographic amplitude distribution in patients with MA. They were able to correlate these asymmetries with side of visual aura, because they enrolled only patients with MA with exactly lateralized visual disturbances, and only employed one spatial frequency (e.g., 7.5' checks [8], and 30' checks [9, 10]). These authors suggest the existence of an asymmetric neural activity in the posterior hemispheric regions (8) or the existence of a defective interhemispheric inhibition probably as a result of the long history of disease, or GABAergic neurotransmitter dysfunctions (9, 10). Logi et al (11) found an asymmetry in VEP P100 amplitude distribution and in N70 components with low check size (14.3 min of arc), not related to side of aura/headache, but they did not distinguish between patients with and without aura and their results were ascribed to hypothesized cortical or thalamic-hypothalamic abnormalities.

In agreement with Nyrke et al (6) and Logi et al (11), we did not find any correlation between the side of visual aura or headache and lateralized VEP abnormalities, probably because our patients with MA showed mono/bilateral symptoms not always localized on one specific side. An alternative possible explanation for this lack of correlation involves the phenomenon of paradoxical lateralization of the visual evoked response. Using a 16° hemifield pattern reversal stimulus, it was demonstrated that the response to a hemifield stimulus was recorded not over the hemisphere in which the response was generated, but from the scalp over the contralateral hemisphere (27). It was hypothesized that the generator neurons with such a field size are on the medial and posteromedial surface of the visual cortex, and the VEPs are therefore best recorded from electrodes on the opposite side of the head. However, when stimulation is confined to the macular area itself, the generator neurons are more orientated in an anterior-posterior direction in the occipital pole, and the VEPs are best recorded by electrodes on the same side of the head (27). Therefore, considering our stimulus parameters, it cannot be excluded that in some patients with MA the signals recorded over the left scalp originated in the right hemisphere of the brain, whereas in others the signals originated in the left hemisphere of the brain, and that could be a reason for the lack of correlation between the side of headache/aura and the VEP abnormalities.

Our finding of asymmetric VEP distribution during the interictal phase in patients with MA can be interpreted in light of the available knowledge on migraine pathophysiology. At present, the only pathogenetic event that seems to explain the migraine aura is the CSD phenomena. Many authors have investigated the possible existence of inherited factors that should be better detectable in the interictal migraine phase, and are capable of determining inherent thresholds for this electrophysiologic phenomenon. There are studies favoring the existence of neurotransmitter abnormalities in migraine patients during the interictal period. In particular, there is neurophysiologic evidence for low central serotonergic (28, 29) as well as cholinergic disposition (30).

Therefore, it is possible to hypothesize that our electrophysiologic responses may be the result of dysfunctions in subcortical aminergic neurotransmitter release: these dysfunctions may alter visual information processing via the thalamo-cortical pathway in patients with MA, determining different occipital hemispheric activation in response to visual stimuli. Whether such anomalous information processing could predispose towards the development of CSD, and thus migraine aura, via abnormal thalamo-cortical stimulation, remains to be determined.

In conclusion, our patients with MA may present asymmetries in VEP responses which seem not related to visual aura or to headache side, during the pain-free phase. These abnormalities can be attributed to abnormal visual information processing, resulting in a different cortical activation.

*Proprietary interest: None.*

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