Evaluation of electrophysiological changes in migraine with visual aura

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Abstract:

PURPOSE: The purpose of this study was to evaluate the electrical responses in the retina and cortex of migraine patients with electrophysiological tests and compare with healthy controls.

MATERIALS AND METHODS: This prospective study included 18 migraine patients with visual aura and 28 healthy controls. Pattern-reversal visual evoked potentials (VEP) and flash electroretinography (fERG) of migraine patients during the headache-free period were compared with healthy controls.

RESULTS: There were statistically significant differences in VEP results: P100 and N75 amplitudes increased significantly (P = 0.025 and P = 0.007 respectively) and P100 latency decreased significantly in migraine patients (P = 0.022). Furthermore, fERG scotopic combined cone and rod amplitude increased significantly in migraine patients (P = 0.01).

CONCLUSION: Migraine brain displays abnormal visual evoked responses in between migraine attacks. In migraine eye, scotopic cone and rod response increased. The results of this study support the hyperexcitability of the retina and cortex in patients with migraine.

Keywords: Electretinography, migraine with aura, visual evoked potentials

Introduction

Photophobia, hypersensitivity to light, is a common symptom. It can occur due to ophthalmological disease affecting anterior and/or posterior segments such as dry eye, keratitis, uveitis, or a foreign body. Photophobia can also be a sign of neurological diseases such as migraine, meningitis, and intracranial tumors. Migraine is an episodic disabling headache disorder and affects up to 16% of the general population. The migraine headache is typically unilateral and throbbing. Particular nutrients, external stimuli, hunger, and insomnia can trigger migraine attacks. These attacks are divided into two main subtypes: migraine with aura (MA) and migraine without aura (MO). MA is defined as attacks of neurological symptoms that last not more than 60 min and may be followed or accompanied by headache. The most common aura symptoms are visual (e.g., scintillating scotoma), whereas sensory and aphasic auras are present in a smaller proportion of patients. Increased sensitivity to external stimuli such as light, sound, and smell is associated with headache attacks and is often reported in interictal period by migraine patients. Photophobia is an important diagnostic criterion of migraine and is observed in almost 90% of migraine patients. Photophobia in migraineurs can be also described as (i) increased sensitivity to light or glare, (ii) intensification of headache by light, and (iii) ocular pain or discomfort induced by light. It can be present during and in between attacks and also is seen in migraine with and without aura. Moreover, photophobia is increased sensory perception. Abnormal cortical processing in visual, trigeminal,
and autonomic areas plays a role in the development of photophobia. Nevertheless, the pathogenesis of photophobia is not very well understood yet.

Migraine brain is hyperresponsive; there exist abnormalities in cortical information processing. It is shown that migraineurs possess impaired thalamocortical drive and decreased cortical preactivation level in between attacks. Excitatory–inhibitory coupling is disrupted; meanwhile, decreased intracortical inhibition and increased excitation are responsible for migraine symptoms. MA patients have reduced gamma-aminobutyric acid levels in occipital cortex, indicating reduced local inhibition. Migraineurs have increased glutamate levels, which is one of the major excitatory neurotransmitters, in the primary visual cortex, occipital lobe, and right thalamus. It is suggested that increased glutamate levels induce a hyperexcitable cortex in migraine.

Similarly, a recent body of evidence suggests that migraine retina is hyperresponsive. Retinal photoreceptor (rod/con) and melanopsin-containing intrinsically photosensitive retinal ganglion cell (ipRGC) activation may contribute to migraine photophobia.

Migraine patients have vulnerable visual systems; photophobia is believed to be related to hypersensitivity of cortical neurons in primary visual cortex and extrastriate visual cortex. Further, in MA patients, cortical hypersensitivity to light is more pronounced and they are more prone to visual disturbance at least in certain visual regions. Interictal visual network connectivity is increased in patients with aura. Electrophysiological tests show present bioelectrical activity in the visual and nervous system, from the retinal pigment epithelium to the occipital cortex. These tests are noninvasive tests and provide accurate information. Since migraine is a functional brain disease, electrophysiological studies would assist in understanding migraine pathophysiology. Although there are many visual evoked potentials (VEP) studies in migraine patients, the results are controversial and there are few studies, in which VEP and ERG were evaluated together in MA. The aim of this study was to evaluate the visual system objectively from the retina to the visual cortex with electroretinography and VEP and contribute to the understanding of the pathophysiology of hyperexcitability in the visual pathway in migraine patients.

Materials and Methods

This prospective study was performed in Ankara Numune Training and Research Hospital between May 2018 and March 2019. The study was approved by the Local Ethical Committee of the Ankara Numune Training and Research Hospital (E-17-1388). The study protocol adhered to the Declaration of Helsinki. Informed consent was obtained from all participants.

Eighteen migraine patients who fulfilled the International Headache Society criteria for diagnosis of migraine with visual aura (Group 1) and 28 healthy volunteers (Group 2) were included in the study. All patients had detailed ophthalmological examinations (slit-lamp biomicroscopy, air-puff tonometry, and fundus imaging). Exclusion criteria for the migraine and control group were coexisting tension-type headache; neurological, connective tissue, and cerebrovascular disorder; smoking; alcohol abuse; antidepressive or antiepileptic drug usage; any systemic and ocular disorder including diabetes, glaucoma, age-related macular degeneration, and cataract; history of ocular surgery; and a refractive error of ≥±3 spherical equivalent. Subjects without recurrent migraine-like headaches were included in the control group.

All patients had attack-free period at least for a week before the measurement. All measurements were done at the attack-free period. Patients included in the study had corrected or uncorrected 1.0 visual acuity (evaluated with Snellen Chart) with normal biomicroscopic and fundus findings.

Visual evoked potential and electroretinography

In accordance with the International Society for Clinical Electrophysiology of Vision standards, the patients were tested by Metrovision brand, monpack model electrophysiology device for pattern-reversal VEP (pVEP) and flash electroretinography (fERG) tests at the same day. First pVEP was made using high-contrast (80%) checkerboard stimuli subtending the 120-min visual arc (min arc). The mean photic luminance was 50 cd/m². The standard flash stimulus was 3.0 photopic cd.s/m². After pupillary dilation, dark-adapted ERG, light-adapted ERG, and light-adapted flicker ERG were done. Hawlina–Konec loop electrodes were used. For dark adaptation, patients were kept in total darkness for 20 min. The standard flash stimulus was 1.0 photopic cd.s/m² for dark-adapted ERG. For light adaptation, patients were given 15 min to adapt to the light. The standard flash stimulus was 3.0 photopic cd.s/m² for light-adapted ERG. Rod response b-wave amplitude (µV) and cone response b-wave amplitude (µV) and flicker response (µV) were compared.

Statistical analysis

The statistical software package SPSS 18.0 (SPSS Inc., Chicago, Illinois, USA) for Windows was used for data analysis. Data distribution for normality was assessed.
using Kolmogorov–Smirnov test. Normally distributed data were analyzed with independent samples t-test, and nonnormally distributed data were analyzed with Mann–Whitney U-test. Independent samples t-test was used to compare the differences in the means of VEP P100 latency and N75 amplitude, rod scotopic and cone photopic amplitudes, and flicker amplitudes; Mann–Whitney U-test was used to compare the differences in the means of VEP P100 amplitude between the groups. Pearson’s correlation test was used to evaluate the correlation between variables and disease duration. The data were presented as mean ± standard deviations. P < 0.05 was considered statistically significant.

Results

Eighteen eyes of migraineurs with aura (16 women and 2 men; aged between 18 and 54) (Group 1) and 28 eyes of controls (22 women and 6 men; aged between 18 and 55) (Group 2) were included in the study. The right eyes of the patients were evaluated for the study. The migraine duration ranged from 0.5 to 25 years [Table 1]. In the analysis of VEP results, the mean P100 latency significantly decreased in migraine patients (P = 0.022). P100 amplitude and N75 amplitude significantly increased in migraine patients (P = 0.025 and P = 0.007, respectively) [Table 2 and Figure 1].

The analysis of scotopic responses on ERG showed an increase of scotopic combined cone and rod amplitudes in migraineurs (P = 0.01). There was no statistically significant difference in cone b-wave and flicker amplitudes in between the groups (P = 0.103 and P = 0.426, respectively) [Table 3 and Figure 2].

There was no significant correlation between electrophysiologic variables and migraine duration [Table 4].

Discussion

Using standard ERG and VEP stimulation parameters, this study showed that P100 and N75 amplitude is higher and P100 latency is lower in the MA group; also, scotopic combined cone and rod b-wave amplitude is different between controls and MA group. These findings suggest that both the retina and cortex are hyperexcitable in migraine patients with aura.

Table 1: Clinical and demographic details

| Variables               | Group 1 (n=18) | Group 2 (n=28) | P    |
|-------------------------|----------------|----------------|------|
| Age (years)*            | 40.28±9.30 (18-54) | 43.21±9.92 (20-59) | 0.319 |
| Sex (female/male)       | 17/1           | 22/6           | 0.220 |
| Duration of the disease (years)* | 9.47±7.57 (0.5-25) |                   |      |

*Mean±SD. SD=Standard deviation

Table 2: Pattern-reversal visual evoked potentials results in migraine patients versus healthy controls

| Variables               | Group 1 (n=18) | Group 2 (n=28) | P    |
|-------------------------|----------------|----------------|------|
| P100 latency (ms)       | 111.44±7.63 (101-127) | 117.39±9.23 (106-139) | 0.022 |
| P100 amplitude (µv)     | 12.97±5.76 (6.3-22.9) | 10.80±10.73 (2.5-57.80) | 0.025 |
| N75 amplitude (µv)      | 3.53±2.26 (0.8-8.40) | 1.86±0.91 (0.4-4.20) | 0.007 |

Figure 1: PVEP showing increased P100 and N75 amplitudes, decreased P100 latencies in a migraine patient (a) compared to a healthy person (b). PVEP = Pattern-reversal visual evoked potentials, VEP = Visual evoked potentials

Figure 2: Dark adapted ERG showing increased combined cone and rod amplitudes (b-wave) in a migraine patient (a) compared to healthy control (b). ERG = Electroretinography
This is consistent with recent transcranial functional magnetic resonance imaging (fMRI) studies. fMRI can detect and localize hypersensitive cortex. It is shown that fMRI activity fluctuation at resting state is higher in MA than MO, indicating cortical hyperexcitability in MA.[39] Similarly, in MA patients, fMRI showed that visual stimulation produced a greater response in primary visual cortex and lateral geniculate nuclei than MO and control group, indicating a direct relation between cortical hyperresponsiveness and migraine aura.[40,41] Hougaard et al. evaluated the blood oxygenation level-dependent (BOLD) responses of migraine patients using fMRI. They have recruited migraine patients suffering from visual aura occurring on the same side with headache. They found that after visual stimulation, fMRI-BOLD signals increase in several nonoccipital cortical areas of the symptomatic hemisphere when compared to contralateral hemisphere and healthy individuals. They concluded that hyperresponsiveness of the cortical visual areas found in their study causes visual dysfunction in migraine patients with aura.[42]

Table 3: Flash electroretinography results in migraine patients versus healthy controls

| Variables                              | Group 1 (n=18) | Group 2 (n=28) | P     |
|----------------------------------------|----------------|----------------|-------|
| ERG scotopic combined cone+rod response: b-wave amplitude (µv) | 224.83±42.45 (157-301) | 194.04±23.55 (151-241) | 0.01  |
| ERG cone response: b-wave amplitude (µv) | 87.55±19.78 (56.9-141) | 78.78±11.90 (65.60-101) | 0.103 |
| ERG flicker: Response (µv) | 67.84±17.36 (38.40-100) | 64.20±9.81 (49-103) | 0.426 |

ERG=Electroretinography

Table 4: Correlations between variables and migraine duration

| Variables                              | r    | P     |
|----------------------------------------|------|-------|
| P100 latency (ms)                      | 0.09 | 0.71  |
| P100 amplitude (µv)                    | 0.07 | 0.75  |
| N75 amplitude                          | 0.19 | 0.44  |
| ERG scotopic combined cone+rod response: b-wave amplitude (µv) | 0.13 | 0.58  |
| ERG cone response: b-wave amplitude (µv) | -0.10 | 0.68  |
| ERG flicker response (µv)              | 0.20 | 0.40  |

ERG=Electroretinography

PVEP measures the cortical cell response against pattern stimuli. The source of N75 (N1), early component of VEP, is the visual cortex. P100 (P1) peak is recorded at a mean latency of 100 ms. P100 is generated in dorsal extrastriate cortex of the middle occipital gyrus. Habituation of VEP, a normal response of brain, indicates decrementation of VEP amplitudes as a response to repeated stimuli. Habituation is deficient in MA and MO patients in interictal period and the habituation is normal in ictal period. Although changes in VEP amplitude and latencies have been reported in migraine patients, the results are different. Coppola et al. exhibited greater VEP amplitudes in migraine patients with complex neurological aura than healthy controls. While a study reported an increase in P100 latency and a decrease in P100 amplitude, another study also demonstrated an increase in P100 amplitude in patients with short duration of disease and a decrease in amplitude in MA patients with longer than 30 years of duration. Sand et al. reported higher N1P1 and P1N2 amplitudes in MA patients compared to MO and controls. The differences in the study results may be due to the genetic discrepancies in patients or due to the variations such as cycles of migraine, migraine phenotypes (whole migraine group, migraine type with or without aura, and different aura types: visual aura and complex aura), duration of migraine, and differences of electrophysiological protocols used in the studies.

Migraine cortex is currently regarded as hyperexcitable. In migraine patients, hyperexcitability to the stimulus may be visual, auditory, or olfactory. The results of this study support hyperexcitability in migraine cortex. This is consistent with recent transcranial functional magnetic resonance imaging (fMRI) studies. fMRI can detect and localize hypersensitive cortex.
nerve disease or enucleated for any reason, photophobia is not seen. The authors concluded that for exacerbation of headache by light, photic signals produced in the retina are needed to be transmitted by the optic nerve to central neurons that process nociceptive signals from the meninges.\(^{[9]}\)

Bernstein et al. compared the fERG and pVEP results between migraineurs and controls in interictal phase. They found that the rod-driven b-wave was larger in the migraineurs than controls in dark and light adapted eyes; neither retinal cone driven a wave nor flash VEP (fVEP) potentials differed between the groups. They concluded that retinal rods may be responsible for the light sensitivity in migraineurs.\(^{[27]}\) The result of ERG is parallel with our findings. We have found scotopic amplitudes are significantly higher in migraineurs than controls and there were not significant differences between cone b-wave amplitudes. The results of VEP are inconsistent with our study. This difference in results may have been observed as a result of the following. Our study group only consists of MA patients to which pVEP was done. Meanwhile, in the other study, MA and MO patients were evaluated in the same group and fVEP was used.

A migraine patient may feel a room that is dark for others as too bright. The dimmest light conditions that can stimulate the rods may be perceived as disturbing by migraineurs. When we interpret this information with the results of this study, we can speculate that rods may contribute formation of migraine photophobia.

A limitation of our study is its small sample size. Second, although all patients suffer from MA, headache characteristics of the study participants are absent.

### Conclusion

This study demonstrates that migraine brain exhibits different visual evoked responses in between attacks than nonmigraineurs. Furthermore, in the migraine eye, scotopic cone and rod response increased. ERG abnormalities seen in migraineurs suggest that retinal dysfunction can contribute to the abnormal cortical response.

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### Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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