Aurasız Migren Hastalarının Farklı Frekanslardaki Görsel Uyarılmış Potansiyeller ile Değerlendirilmesi

Evaluation of Migraine Without Aura Patients by Visual Evoked Potentials with Different Spatial Frequencies

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Abstract

Objective: The objective of our study was to investigate changes in pattern reversal visual evoked potentials (PVEPs) of migraine without aura patients recorded with two different check sizes (15’ and 62’) in accordance with International Society for Clinical Electrophysiology of Vision (ISCEV) standards during the interictal period.

Materials and Methods: Patients' demographic data were documented from headache diaries of patients, such as duration of disease, headache characteristics, the number of attacks in a month, the average duration of attacks, complaints accompanying headache, mean severity of headache according to visual analog scale. Twenty migraine patients without aura and 14 healthy volunteers were examined with PVEPs recorded with two different check-sizes (15’ and 62’). The stimulation sequences were randomized both for the check-size of checkerboard and the side of stimulation (right-15’, right-62’, left-15’, left-62’). The latency of N75, P100 and peak-to-peak amplitude of N75-P100 were analyzed.

Results: There were no statistical difference between healthy subjects and migraine without aura patients in the means of latency and amplitude of PVEPs results for both check-sizes (p>0,05).

Conclusion: In migraine patients without aura, we did not detect magnocellular pathway dysfunction by PVEPs with different spatial frequencies. Studies on larger patient groups and combining PVEPs with psychophysical tests are needed.
Keywords: Migraine without aura, pattern reversal-VEP, spatial frequency

1. Introduction

Pattern visual evoked potentials (PVEPs) are electrical potentials that are generated by the occipital cortex as a response to a sensory stimulus. The responses obtained allow assessment of integrity and function of pathways from the eye photoreceptors to the visual cortex [1]. PVEPs records are used both for diagnosis and follow-up of many neurological diseases such as demyelinating diseases, ischemic optic neuritis, nutritional and toxic amblyopia, Leber’s hereditary optic atrophy, and adrenoleukodystrophy [2] and for assessment of functions of visual cortex in migraine [3].

From the early 1980s, many studies have been performed where patients with migraine were evaluated with PVEPs, but conflicting results were obtained between the patients and the control groups in terms of P 100 latency and N75-P100 amplitudes. Brinciotti et al [4] Mariani [5] et al, Lai [6] et al, Drake [7] et al, Schoenen [8] et al, Rossi [9] et al and Sener 10 et al performed studies on migraine patients with and/or without aura and reported N75-P100, N75 and/or N145 amplitude and/or latency within normal limits, but Polisch [11] et al and Tagliati [12] et al reported reduced N75-P100 and/or N70 amplitude in migraine patients with aura (MA), and Kenard [13] et al, Raudina [14] et al, reported an increase in PN75-100 amplitude and/or latency in migraine patients with and without aura.

In addition to those standard studies on PVEPs, there are studies where parameters used for stimulating visual cortex - such as size, contrast and application frequency of squares - were changed. Stimulation with squares of different sizes allows to individually examine functions of parvocellular (P) and magnocellular (M) visual pathways and to investigate their role in the pathophysiology of migraine [15]. By using different check sizes, one study indicated magnocellular pathway dysfunction in MA patients [16]. Another study identified a higher P100-N145 amplitude stimulated with square sizes of 3′ and 62′ in MA patients, and higher N70-P100 amplitude stimulated with square size of 62′ [15]. There are limited number of studies regarding migraine without aura (MWO) patients and the results are conflicting.

In the review of all those studies, it is presented in studies performed before diagnosis criteria of International Headache Society-I (IHS-I) were published that patient groups were less homogeneous; although PVEPs substantially varied in peri-ictal, ictal and postictal periods, they were not adequately controlled in patient groups; and PVEP methodologies were different from each other. It is said that such methodologic and technique differences might have affected the study results [16,17,18 19]. International Society for Clinical Electrophysiology for Vision (ISCEV) standards were published for visual evoked potentials in 2009 and recommended using for clinical studies [20].

The objective of our study is to investigate PVEPs characteristics of MWO patients interictally and record with pattern – VEP method using two different sizes of check (15′ and 62′) in accordance with ISCEV standards and show if magnocellular and parvocellular pathways are affected differently from each other.

2. Materials and methods:

Patients:

This study was performed at Neurology Clinic of Adana Numune Training and Research Hospital retrospectively. This study included 20 patients who were diagnosed with MWO according to international classification of headache disorders diagnostic criteria III - beta (ICHD III β) [21]. Patients who had any systemic disease [e.g. diabetes Mellitus (DM), hypertension (HT)], neurological disease other than migraine and ophthalmologic disease, were on medication other than treatment for migraine attacks, who smoked cigarette and consumed alcohol, had a family history of epilepsy, and had pathology in hemogram and biochemical tests [vitaminB12, folic acid, free-t3, free-t4, thyroid-stimulating hormone (TSH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), urea, creatinine, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride (TG)] and cerebral imaging were excluded from the study.

Patients’ demographic data were documented such as the duration of disease, headache characteristics, the number of attacks a month, average duration of attacks, complaints accompanying headache, mean severity of headache according to visual analog scale (VAS) [22], the medication used for attacks from headache diary of patients. Patients who used migraine prophylaxis minimum 3 months before examination were excluded from the study. Neurological examination was performed, including patients’ fundus oculi, visual acuity, visual field examinations. The patients and healthy subjects were examined by an ophthalmologist and their examinations were normal. Hemogram and biochemical tests (vitaminB12, folic acid, free-t3, free-t4, TSH, AST, ALT, GGT, urea, creatinine, total cholesterol, HDL, LDL, TG ) were performed and all of the patients were assessed with cerebral magnetic resonance imaging (MRI). PVEPs were recorded minimum of 48 hours after patient had headache and minimum of 24 and maximum of 72 hours before the following headache (in the interictal period).

Fourteen healthy volunteers were included in the study as control group. Patients who had any neurologic disease, history of meningitis or encephalitis, congestive heart failure, hypertension, diabetes mellitus, autoimmune diseases, psychiatric diseases, substance abuse (smoking), mental retardation, history of malignancy, long-term steroid use, history of trauma, and patients who had ophthalmologic disease (glaucoma and anterior or posterior segment disorders ext.) and had pathology in routine blood tests and cerebral imaging were excluded from the study.
All participants were explained the study, and informed consent was obtained from all individual participants included in the study. The study is approved by the ethics committee of the hospital.

**PVEP Method**

Patients were seated on a comfortable chair in front of the monitor. Patients were asked to calmly look at a red fixation point in the center of monitor. The other eye of patients was covered with a plaster. Patients with refractive error wore their glasses during examination.

All records and analyses were performed using Neuro MEP Micro EMG/EP system (Neurosoft, Inova, Russia). Ag/Ag Cl electrodes were used for all records. According to international 10/20 system, active electrode was placed on Oz, reference electrode was placed on Fz, and ground electrode was placed on the right earlobe. All impedances were usually kept below 5 kOhm and always below 10 kOhm. The black & white checkerboard pattern with two different sizes of check (15’ and 62’) was used for stimulation of VEP. This pattern varied in frequency of 3 Hz. The stimulant was delivered from an LCD monitor in 17° diameter (contrast 95%, average brightness) that was placed 120 cm away from participants. The band-pass filter of signal was 0.3-1000 and artifacts above 100 µV were automatically rejected. 100 waves without artifact were averaged, and the time for analysis was 300 msec. This averaging was repeated two times and superimposed to evaluate reproducibility of responses. VEP was taken in accordance with ISCEV standards [20]. The stimulation sequence was randomized both for the check- size of checkerboard and the side to be stimulated (right-15’, right-62’, left-15’, left-62’). Random allocation software 1.0 was used for randomizing.

**Statistical Analysis**

The study data was uploaded on the computer via “SPSS (Statistical Package for Social Sciences) for Windows 23.0 SPSS Inc, Chicago, IL)” and evaluated. Descriptive statistics were presented in mean±standard deviation, median (minimum-maximum), frequency distribution and percentage. Pearson’s Chi-Square Test and Fisher’s Exact Test were used for evaluation of categorical variables. Compliance of variables with normal distribution was assessed using visual (histogram and probability graphics) and analytic methods (Shapiro-Wilk Test). For normally distributed variables, Student’s T test was used for statistical significance between two independent groups, and Paired Sample T Test was used between two dependent groups; for not normally distributed variables, Mann-Whitney U Test was used for statistical significance between two independent groups, and Wilcoxon Signed Ranks Test was used between two dependent groups as statistical method. Statistical significance level is considered p<0.05.

3. Results:

In this study, a total of 34 women were examined of whom 20 were MWO patients and 14 were completely healthy individuals of control group. The mean age of those who were examined was 31.15±8.89 (19-50) years; mean age of patient group was 29.11±9.47 (19-48) years, and mean age of control group was 33.93±7.47 (23-50) years, and age of study groups was similar (p=0.071). Table 1 provides some clinical characteristics of migraine patients.

<table>
<thead>
<tr>
<th>Table 1. Clinical characteristics of migraine patients (n=20)</th>
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<tbody>
<tr>
<td><strong>Duration of disease</strong></td>
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<tr>
<td><strong>Number of attacks per month</strong></td>
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<tr>
<td><strong>Pain Side</strong></td>
</tr>
<tr>
<td>Bilateral [Number (%)]</td>
</tr>
<tr>
<td>Right or left [Number (%)]</td>
</tr>
<tr>
<td>Left [Number (%)]</td>
</tr>
<tr>
<td>Right [Number (%)]</td>
</tr>
<tr>
<td><strong>Duration of pain attack</strong></td>
</tr>
<tr>
<td><strong>Pain Score (average vas/month)</strong></td>
</tr>
</tbody>
</table>

| **Pain Characteristics** | |
| Throbbing [Number (%)] | 15 (75.0) |
| Nausea + Vomiting [Number (%)] | 8 (32.0) |
| Photophobia [Number (%)] | 12 (60) |
| Phonophobia [Number (%)] | 12 (60) |

X: Mean; S: Standard deviation

*A patient had a pain of multiple characteristics; percentage was calculated over number of patients.

The pattern VEP was individually applied on the right and left eye of 20 patients and 14 health individuals included in the study, and total of 3 measurements were performed for each eye: N75-P100 amplitude, N75.
latency, and P100 latency. When right and left eyes of the migraine group and healthy control group was compared, there was not a statistically significant difference between migraine patients’ right and left eye regarding N75-P100 amplitude, N75 latency, and P100 latency (p>0,05). At the same time when right and left eyes of the migraine group and healthy control group was compared, there was not a statistically significant value between healthy controls’ right and left eye regarding N75-P100 amplitude, N75 latency, and P100 latency. (p>0,05). For that reason, we designed the patient group as consisting of 40 eyes and control group consisting of 28 eyes. N75-P100 amplitude, and N75 and P100 latency were similar (p>0,05) that were obtained pattern-VEP and performed with 15’ and 62’ check-size of eyes within patient and control groups. No statistically significant differences were found in N75-P100 amplitude and N75 and P100 latency obtained with 15’ and 62’ check-size between patient and control groups (p>0,05) (Table 2).

Table 2. The patients’ group and the controls group of N75 and P100 latency and N75-P100 amplitude values at 62 and 15 check sizes.

<table>
<thead>
<tr>
<th></th>
<th>Patient group (n=40)</th>
<th>Control group (n=28)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N75-P100 amplitude</td>
<td>62</td>
<td>16,67±5,70</td>
<td>15,95±4,99</td>
</tr>
<tr>
<td>N75-P100 amplitude</td>
<td>15</td>
<td>17,76±9,92</td>
<td>16,11±4,34</td>
</tr>
<tr>
<td>N75 Latency</td>
<td>62</td>
<td>78,85±3,98</td>
<td>79,48±3,75</td>
</tr>
<tr>
<td>N75 Latency</td>
<td>15</td>
<td>85,65±3,67</td>
<td>86,46±2,89</td>
</tr>
<tr>
<td>P100 Latency</td>
<td>62</td>
<td>107,14±5,87</td>
<td>108,51±4,84</td>
</tr>
<tr>
<td>P100 Latency</td>
<td>15</td>
<td>108,85±4,68</td>
<td>108,68±3,38</td>
</tr>
</tbody>
</table>

X: Mean, S: Standart deviation

4. Discussion:
The objective of our study was to show whether magnocellular and parvocellular pathways were affected to a different extent by reviewing pattern-VEPs records of MWO patients in the interictal period obtained with 62’ and 15’check-sizes. Records were kept in accordance with ISCEV standards.

In the present study, we did not find statistically significant difference between N75-P100 amplitude and N75 and P100 latency obtained with 15’ and 62’ check-sizes between patient and control groups.

We interpreted from our study that examining patients with different check-sizes of pattern-VEP may not be sensitive enough to prove magnocellular pathway dysfunction. Combining psycho-physical tests that assess pre cortical dysfunction of spatial and temporal processing of visual stimulants and PVEPs should be considered.

Studies using magnetoencephalography (MEG) and functional magnetic resonance imaging (fMRI) showed that C1 and N75 (N1) are originated from V1 [23,24] and generators of later components P100 and N145 (N2) had been localized to the extrastriate visual cortex [23, 25]. The N75 wave reflects the activity of the fovea and primary visual cortex whereas the N145 wave reflects the activity of the visual association area. N2 component is suggested to consist of a parvocellular (contour processing) and magnocellular (luminance processing) component [16]. When the literature is reviewed there are studies supporting magnocellular pathway dysfunction predominance. It has been hypothesized that latencies of all VEP components increase with increasing spatial frequency [16]. In migraineurs, N2 latency may delay due to an attenuated or absent N130 and/or a relatively predominant N180. This might reflect an imbalance of the two visual pathways with relative predominance of magnocellular pathway [26]. Supporting this idea, in a study, when small checks were presented to a group of migraine patients, N2 latency was prolonged at high spatial frequencies (2,0 cpd and 4,0 cpd). The latencies were normal at low spatial frequencies (0,5 cpd and 1,0 cpd). The authors thought that this might reflect an imbalance between two pathways [16]. Benedeck et al. had found that contrast sensitivity reduction of to low spatial frequency stimuli which magnocellular pathway neurons are involved in processing and proposed a greater impairment of magnocellular pathway than parvocellular pathway involvement [27]. In another study, the authors put forward that intracortical inhibition is decreased or excitation is increased within magnocellular extrastriate pathways in the days preceding a migraine attack [28]. A recent study used gratings instead of checkerboard pattern and found that migraine patients had increased N2 amplitude in high frequency gratings compared to controls and suggested these data are in line with cortical hyperexcitability. They also showed higher amplitude in MWO patients than MA patients [31, 29].
Conversely there are studies arguing against magnocellular pathway involvement dominance. A study by Coleston et al evaluated migraine patients using psychophysical tests, and a pre cortical dysfunction was detected in spatial and temporal processing of visual stimulants. This dysfunction involved both magnocellular and parvocellular pathways. The authors suggested that this dysfunction might be due to ischemia developed by recurrent migraine attacks, or persistent interictal cerebral blood flow anomalies in the occipital lobe. Another explanation was that recurrent dysfunction at cortical level might lead to retrograde geniculate disorder, thus the pre cortical visual response might be affected [30]. Another finding in the literature that primary visual cortex’s contrast sensitivity function may be impaired in migraine patients. Retina, lateral geniculate nucleus or lesions of V1 area in human and primates cause severe impairment in contrast sensitivity. A study by McKendrick et al evaluated migraine patients and a loss in low spatial frequency contrast sensitivity was detected due to reduced functions of both M and P pathways [31]. A psychophysical assessment of migraineurs revealed S-cone deficits with a greater area of the retina showing integrative network compensations need to be factored [32]. A study by Yenice et al detected reduced contrast sensitivity in low and high spatial frequencies in patients with migraine [33]. Our study does not support the magnocellular pathway involvement either. Migraine pathophysiology has not been fully elucidated. Studies using PVEPs like our study helps to understand the pathophysiology of migraine. Our study has a number of limitations. There were limited number of patients, 20 in the patient groups and 14 in the control group. Data such as attack frequency a month and mean duration of headache of patients were obtained from headache diaries, but dose of ergotamine and/or triptans used for treatment of attacks was not exactly known, therefore it was not evaluated. Future studies can be planned with more patient groups, including medication used for treatment of attacks.

5. Conclusions:
In migraine patients without aura, we did not detect magnocellular pathway dysfunction by PVEP with different spatial frequencies. Studies on larger patient groups and combining PVEP with psychophysical tests are needed.

References