Araştırma Makalesi (Research Article)

Migren ve Gerilim Tipi Baş Ağrısı Hastalarında Pattern Reversal ve Flaş Görsel Uyarılmış Potansiyeller

Pattern Reversal and Flash Visual Evoked Potentials in Patients with Migraine and Tension-Type Headache

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Özet

Amaç: Migren ve gerilim tipi baş ağrısı (GTBA) en sık izlenen primer baş ağrılarıdır. Migren ve GTBA hastalarına görsel uyarılmış potansiyelleri (GUPlar) uygulayarak, bu primer baş ağrılarının patofizyolojisi ile ilgili bilgilerin elde edilmesi amaçlandı.

Gereç ve Yöntemler: Sağlıklı bireyler, epizodik migren ve epizodik GTBA hastaları bu prospektif çalışmaya dahil edildi. Tüm katılımcılara pattern reversal ve flaş GUPlar uygulandı. Hastalar interiktal dönemde iken GUP uygulandı. Ayrıca migren ve GTBA hastalarının baş ağrı şiddetleri Vizüel Analog Skala (VAS) ile analiz edildi.

Bulgular: Otuz bir sağlıklı birey, 27 GTBA hastası ve 31 migren hastası bu prospektif çalışmaya dahil edildi. Gruplar arasında yaş ve cinsiyet farklı değildi ($p>0,05$). Migren hastalarının VAS skorları (8,0±1,2), GTBA hastalarının VAS skorlarına (6,5±1,1) göre daha yüksekti ($p<0.001$). Kontrol, GTBA ve migren hastalarının sağ/sol P100 dalga latanslarının ortalaması sırasıyla 89,8±7,5/91,0±6,2, 91,0±4,9/91,3±5,2, 97,6±8,1/97,1±7,5 ms idi. Kontrol, GTBA ve migren hastalarının sağ/sol P2 dalga latanslarının ortalaması sırasıyla 104,7±15,9/104,8±14,5, 98,6±11,5/98,7±10,8, 115,5±16,3/118,3±6,2 ms idi. Migren grubunun P100, P2, N3, P3 dalgalarının latansları gerilim tipi baş ağrısı ve kontrol grubuna göre daha yüksekti ($p<0.05$).

Sonuç: Bu çalışma migren hastalarının GUP latanslarının kontrol ve epizodik GTBA hastalarına göre daha yüksek olduğunu göstermiştir. Bu bulgular migrenin patofizyolojisinde periferik mekanizmaların yanı sıra santral mekanizmaların rol oynadığına ve epizodik GTBA'nın periferik dokulardan kaynaklandığına işaret edebilir.

Anahtar kelimeler: Migren, Gerilim tipi baş ağrısı, Görsel uyarılmış potansiyeller

Abstract

Objective: Migraine and tension-type headache (TTH) are the most common primary headaches. It was aimed to obtain information about the pathophysiology of these primary headaches by performing visual evoked potentials (VEPs) to patients with migraine and TTH.

Material and Methods: Healthy individuals, episodic migraine, and episodic TTH patients were included in this prospective study. Pattern reversal and flash VEPs were performed to all participants. VEP was applied while the patients were in the interictal period. In addition, headache severity of migraine and TTH patients were analyzed with Visual Analogue Scale (VAS).

Results: Thirty-one healthy individuals, 27 TTH patients, and 31 migraine patients were included in the study. Age and gender were not different between the groups ($p>0.05$). VAS scores of migraine patients (8.0±1.2) were higher than those of TTH patients (6.5±1.1) ($p <0.001$). The mean right/left P100 wave latencies of control, TTH, and migraine patients were 89.8±7.5/91.0 ± 6.2, 91.0±4.9/91.3±5.2, 97.6±8.1/97.1±7.5 ms, respectively. The mean right/left P2 wave latencies of control, TTH, and migraine patients were 104.7±15.9/104.8±14.5, 98.6±11.5/98.7±10.8, 115.5±16.3/118.3±6.2 ms, respectively. The latencies of P100, P2, N3, and P3 waves in migraine group were higher than those in TTH and control groups ($p<0.05$).

Conclusion: This study showed that migraine patients had higher VEP latencies than controls and episodic TTH patients. These findings may indicate that central mechanisms as well as peripheral mechanisms play a role in the pathophysiology of migraine and that episodic TTH originates from peripheral tissues.

Keywords: Migraine, Tension-type headache, Visual evoked potential

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INTRODUCTION

Migraine and tension-type headache (TTH) are the most common primary headaches and the diagnosis is made by clinical findings (1, 2). There is no imaging method or electrophysiolo-gical test that can diagnose these two headaches or make the differential diagnosis of these two headaches. Visual evoked potential (VEP) is a neurophysiologic test that reflects the physiology of the visual pathways. Abnormalities in VEPs in patients with migraine have been shown in many studies (3-5). Conditions such as delay in P100 wave latency, absence of habituation of VEP amplitude are among these abnormalities (3-6). VEP and other neurophysiologic studies in migraine show that central mechanisms as well as peripheral mechanisms may play a role in the pathophysiology of migraine (1-6). Pattern reversal VEP (PrVEP) was used as a method in most of the migraine studies (3-5), and flash VEP (FVEP) was applied to migraine patients in some studies (7, 8). Although studies have been conducted on PrVEP – TTH (9-11), they are less in number than migraine -VEP studies. In addition, the number of studies in which FVEP was applied in patients with TTH was few (7). It was aimed to obtain information about the pathophysiology of migraine and TTH by using PrVEP and FVEP.

MATERIAL AND METHODS

Subjects

This prospective study was conducted in Clinical Neurophysiology Laboratory of Adana City Training and Research Hospital (ACTRH) between November 2018 and December 2019. Individuals with one of the following conditions were excluded from the study: disease that could cause neuropathy, such as diabetes mellitus; neurodegenerative disease; eye disorders such as cataracts and glaucoma. Individuals with headaches such as migraine and TTH were not included in the control group. Episodic migraine and episodic TTH were considered in individuals meeting the recommended criteria (12). Migraine and TTH patients were required to have no headache within 5 days prior to the VEP study. Patients with migraine and TTH using drugs such as antidepressants for headache prophylaxis were not included in the study. Considering the previous studies on migraine and TTH, it was decided that there should be a minimum of twenty-seven patients in each group (95% confidence interval, level 0.05 type 1 error) (4-6, 11). The mean headache severity of the patients during the last three months was analyzed using the visual analogue scale (VAS) (13). The procedures applied to all human participants were in accordance with ethical standards of the ACTRH ethics committee and the 1964 Helsinki declaration and its later amendments. Ethics committee approval was received from ACTRH Ethics Committee (number: 25/336). Written consent was obtained from all participants.

VEP study

VEP study was performed with Cadwell Sierra Summit EMG unit (Cadwell Laboratories, Kennewick, Washington, USA). PrVEP and FVEP were performed as recommended (14). Silver cup electrodes were used for recording. The high pass and low pass filters were 1 Hz and 100 Hz, respectively. Sensitivity and sweep rate were set at 5 μV / division and 25 ms / division, respectively. Oz and Fz points were marked as recommended in the international 10-20 electroencephalography system. The active electrode was placed at Oz and the reference electrode at Fz. VEP test was performed when impedances were <5 kΩ for all electrodes. CBOX 18.5" LED monitor and Cadwell LED Goggles were used for PrVEP and FVEP, respectively. The stimulus rate was 1 Hz for both PrVEP and FVEP. A black and white checkerboard was used for PrVEP. The point in the middle of the screen was red. The distance between the LED monitor and eyes of the participants was 100 cm, and check size was 41 min of arc (8x8 checkerboard was used). The contrast difference between black and white checks was 90% and the mean luminance is 240 cd m-2. The software program allowed the calculation of the interval between the time when the stimulus was delivered and the time when the checkerboards were seen on the LED monitor, which was 56 ms. PrVEP latencies have been corrected by the program considering this delay time. Two hundred VEP potentials were averaged for both PrVEP and FVEP, and this was done twice for each eye. N175, P100, N145 waves obtained by PrVEP and N1, P1, N2, P2, N3, P3 waves obtained by FVEP were analyzed. The latencies and P100 amplitudes (measured from N75 wave to P100 wave), and P2 amplitudes (measured from N2 wave to P2 wave) of these waves were calculated.

Statistical Analysis

The Shapiro-Wilk test was used to determine the distribution of the data. Pearson's Chi-squared test was used to analyze categorical variables. Kruskal Wallis and Mann-Whitney U tests were used in group comparisons. Bonferroni correction was used for post hoc analysis and multiple comparisons. Mean ± standard deviation (SD) and mean were calculated for descriptive statistics. Upper limits of VEP latencies obtained from controls were calculated as mean ± 2 SD. If p value was <0.05, it was considered statistically significant. Statistical Package for the Social Sciences (SPSS IBM Corp; Armonk, NY, USA) 22.0 was used to perform the statistical analysis.

RESULTS

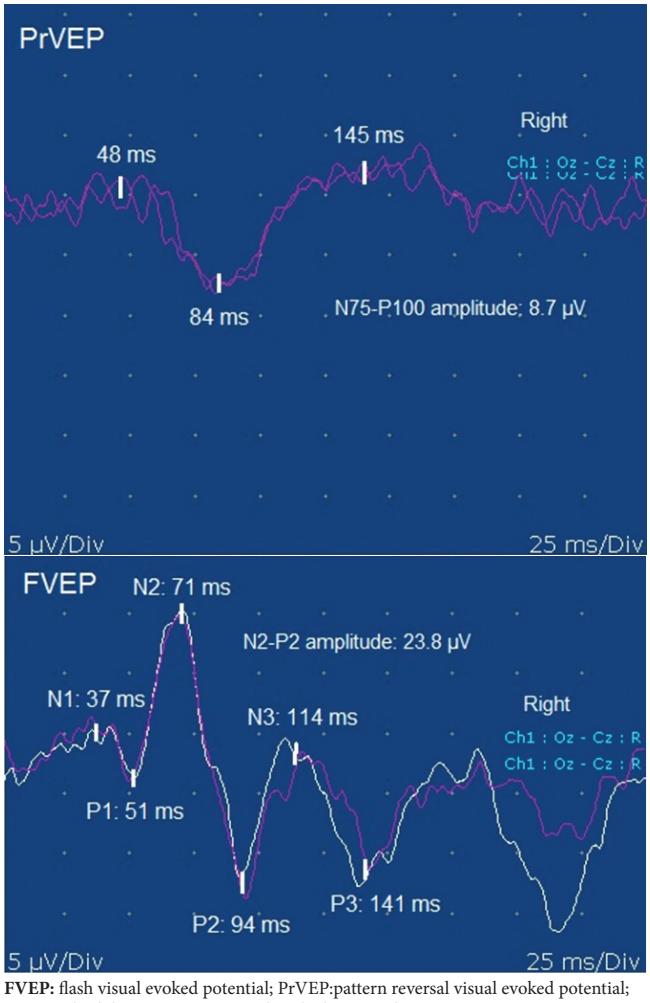
Thirty-one healthy individuals, 31 migraine and 27 TTH patients were included in the study. **Table 1** shows the demographic data of the participants. Age and gender were not different between the groups (p>0.05, **Table 1**). The VAS score of migraine patients was significantly higher than the VAS score of TTH patients (p<0.001, **Table 1**). The clinical characteristics of migraine patients are shown in **Table 2**.

An example of PrVEP and FVEP of a TTH patient is shown in **Figure 1. Table 3** shows the comparison of VEP parameters between groups. There was no significant difference between VEP parameters of the right and left eyes (p>0.05). While N75, P100, N145, N2, P2 were obtained from all pa-

Tablo 1. Descriptive features of the individuals

Clinical feature	Controls (n=31)	Tension-type headache patients (n=27)	Migraine patients (n=31)	P value
Age (years)	34.1 ± 8.9 (19-54)	32.9 ± 9.9 (18-59)	32.4 ± 11.6 (18-57)	0.705
Gender: Male (%)	7 (22.6)	4 (14.8)	5 (16.1)	0.613
Duration of the disorder (median) (years)	-	3.7 ± 2.9 (2)	7.6 ± 8.3 (4)	0.078
VAS score (median)	-	6.5 ± 1.1 (7)	8.0 ± 1.2 (8)	**<0.001**

tients, other VEP parameters were obtained from some patients **(Table 3)**. P100, P2, N3, P3 wave latencies were higher in migraine patients compared to controls and TTH patients ($p<0.05$, **Table 3**). In addition, N75 wave latency was higher in migraine patients compared to controls ($p<0.05$, **Table 3**). **Figure 2** shows the right P2 wave latency among the groups. Upper reference limits for right and left P100 latencies were calculated as 104.8 ms and 103.4 ms, respectively. Upper reference limits for right and left P2 latencies were 136.5 ms and 133.8 ms, respectively. The number of migraine patients with abnormal P100 and P2 wave latency in the right or left eye was 7 (22.6%) and 4 (12.9%), respectively. P100 wave and P2 wave latencies were normal in patients with TTH.



FVEP: flash visual evoked potential; PrVEP:pattern reversal visual evoked potential; **SD:** standard deviation; VEP: visual evoked potential.

Figure 1. An example of VEP of a patient with tension-type headache

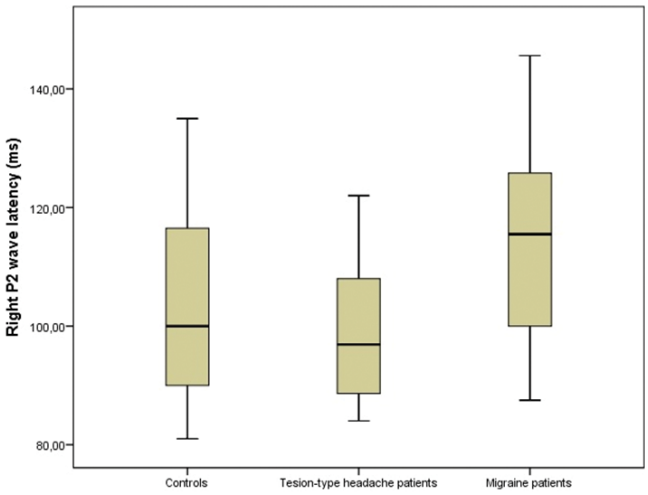


Figure 2. Right P2 wave latency among groups

DISCUSSION

Migraine and TTH are the two most common headaches that can cause limitations in daily life activities (1, 2, 15). They can negatively affect work life as well as daily life activities. It is known that migraine is more common in women (1, 2). TTH is also seen at a slightly higher rate in women, as the age increases, the frequency of TTH in men and women converges (1, 2, 16). The fact that the number of female in this study was higher than the number of male was consistent with the literature (1, 2, 16). Similar to previous studies, nausea / vomiting was seen in most patients in this study (1, 2, 17). Aura is seen in approximately one third of migraine patients (1, 2). The rate found in our study was consistent with this.

Headache severity is mostly moderate-severe in migraine, while it is mild-moderate in TTH (15, 16). The fact that the VAS scores found in this study are higher in migraine patients compared to TTH patients supports this situation. Since the treatments for these two headaches are different, it is important to differentiate them (1, 2). Clinical diagnostic criteria can differentiate the two diseases, but unfortunately migraine and TTH cannot be distinguished by laboratory tests or imaging methods. Although VEP parameters are found to be different in migraine and TTH patients in studies (10, 11), the use of neurophysiologic tests is limited in the diagnosis of these two headaches (18). The low number of mig-

Table 3. PrVEP and FVEP parameters among groups

VEP parameter	Controls Mean ± SD		Tension-type headache patients Mean ± SD		Migraine patients Mean ± SD		P value	
	Right	Left	Right	Left	Right	Left	Right	Left
PrVEP								
N75 latency (ms)	57.2 ± 6.5 (n=31)	57.2 ± 6.3 (n=31)	60.5 ± 5.9 (n=31)	59.9 ± 5.9 (n=31)	63.4 ± 5.5 (n=31)	61.8 ± 6.1 (n=31)	0.001*	0.022*
P100 latency (ms)	89.8 ± 7.5 (n=31)	91.0 ± 6.2 (n=31)	91.0 ± 4.9 (n=31)	91.3 ± 5.2 (n=31)	97.6 ± 8.1 (n=31)	97.1 ± 7.5 (n=31)	0.002*	<0.001*
N135 latency (ms)	134.3 ± 13.8	132.8 ± 12.4 (n=31)	134.8 ± 11.4 (n=31)	135.9 ± 11.4 (n=31)	144.9 ± 19.5 (n=31)	144.3 ± 19.5 (n=31)	0.071	0.056
P100 amplitude (μV)	9.5 ± 3.5 (n=31)	9.2 ± 3.4 (n=31)	10.0 ± 3.8 (n=31)	10.2 ± 4.3 (n=31)	10.1 ± 4.5 (n=31)	10.2 ± 4.3(n=31)	0.823	0.574
FVEP								
N1 latency (ms)	46.5 ± 10.1 (n=24)	47.6 ± 10.4 (n=24)	41.3 ± 4.7 (n=23)	40.5 ± 3.9 (n=22)	47.5 ± 11.7 (n=25)	46.9 ± 10.5 (n=25)	0.075	0.058
P1 latency (ms)	62.0 ± 12.1 (n=30)	63.1 ± 12.4 (n=25)	56.8 ± 6.9 (n=27)	57.3 ± 6.2 (n=23)	63.2 ± 14.4 (n=31)	64.3 ± 11.9 (n=27)	0.263	0.078
N2 latency(ms)	78.9 ± 13.2 (n=31)	80.4 ± 12.2 (n=31)	76.5 ± 8.4 (n=31)	76.6 ± 8.1 (n=31)	81.2 ± 13.5 (n=31)	83.3 ± 12.5 (n=31)	0.453	0.158
P2 latency (ms)	104.7 ± 15.9 (n=31)	104.8 ± 14.5 (n=31)	98.6 ± 11.5 (n=31)	98.7 ± 10.8 (n=31)	115.5 ± 16.3 (n=31)	118.3 ± 16.2 (n=31)	<0.001*	<0.001*
N3 latency (ms)	119.8 ± 18.7 (n=24)	121.8 ± 18.2 (n=26)	116.3 ± 15.9 (n=24)	108.6 ± 26.8 (n=21)	139.7 ± 24.2 (n=23)	139.0 ± 21.8 (n=26)	0.001*	<0.001*
P3 latency (ms)	143.5 ± 17.2 (n=24)	142.6 ± 15.7 (n=26)	139.5 ± 19.7 (n=24)	139.1 ± 21.1 (n=21)	165.7 ± 25.2 (n=23)	162.8 ± 22.8 (n=26)	0.001*	0.001*
P2 amplitude (μV)	14.7 ± 7.1	14.6 ± 7.5	11.8 ± 5.2	15.2 ± 24.2	15.2 ± 7.3	15.6 ± 7.3	0.195	0.052

Kruskal Wallis test was used in group comparisons. Bonferroni correction was used for post hoc analysis. If p value was <0.05, it was considered statistically significant. *: Right and left N75 latency was higher in migraine patients compared to the controls (p = 0.001, p=0.017); Right P100 / Left P100 / Right P2 / Left P2 / Right N3 / Left N3 / Right P3 / Left P3 latency was higher in migraine patients compared to the control and tension-type headache patients (p < 0.001, p=0.009 / p = 0.006, p=0.012 / p=0.039, p<0.001 / p=0.003, p<0.001 / p=0.009, p=0.003 / p=0.015, p<0.001 / p=0.015, p=0.003 / p=0.009, p<0.001); FVEP, flash visual evoked potential; PrVEP, pattern reversal visual evoked potential; SD, standard deviation; VEP, visual evoked potential.

raine patients with P100 and P2 wave latency abnormalities found in our study supports this situation. The presence of abnormalities in VEP parameters in migraine patients compared to TTH patients may indicate that the pathophysiology of migraine and TTH are different. The pathophysiology of migraine and TTH has not been clearly elucidated. Peripheral pain mechanisms such as decreased relaxation of myofascial muscles are thought to play a role in episodic TTH (2, 16). On the contrary, the increase in the sensitivity of pain pathways in the central nervous system may explain the pathophysiology of chronic TTH (2, 16). There are many evidences showing that both peripheral and central mechanisms contribute to the pathophysiology of migraine (1, 2, 19). Activation of the trigeminal pathways, peripheral and central sensitizations are mechanisms that are thought to have a role in the pathophysiology of migraine (19). It is known that cerebral hyperexcitability is increased in patients with migraine, as shown by neurophysiologic studies such as VEP and auditory evoked potentials (18-20). VEP abnormalities found in episodic migraine patients in this study support this situation. Since the patients in this study were taken during the interictal period, our findings may indicate that migraine may have an effect on the brain (21). On the contrary, the findings in this study suggest that peripheral pain mechanisms play a role in the pathophysiology of episodic TTH.

Although the origin of VEP waves is not known, there are studies showing that the P100 wave originates from the striate cortex. The N75 wave may be the initial response of the striate cortex. The N145 wave can originate from both the striate and the extrastriate cortex. In FVEP, unlike PrVEP, a large part of the retina is stimulated and therefore the response occurs over a large area of the cerebral cortex (14). VEP abnormalities in migraine patients found in this study were present in most VEP waves. This may indicate that a large area of the cerebral cortex is affected in migraine patients.

There were some limitations in this study. First, migraine patients were not divided into subgroups as those with aura and those without aura. The second limitation is that only patients with episodic TTH were included in this study. We

think that studies on VEP in episodic and chronic TTH patients will be very interesting.

In conclusion, this study showed that patients with migraine have VEP abnormalities, indicating increased cerebral hyperexcitability in migraine. Finding that the VEP parameters of episodic TTH patients in this study were not different from the controls may indicate that episodic TTH originates from peripheral structures.

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