Abnormal P50 Suppression in Migraine Patients during the Attack and Interattack Period

Migren Hastalarında Atak sırasında ve Ataklar arasındaki dönemlerde Anormal P50 Baskılanması

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ABSTRACT

Habituation can be defined as an adaptive mechanism that protects the cortex against sensory overload in normal persons. The most common interictal electrophysiological abnormality in migraine is lack of habituation. İnterestingly, habituation is normalized just before and during a migraine attack. It was aimed to provide another perspective on habituation response through P50 suppression (sensory gating) method, used in the evaluation of the pre- attention habituation response, under the cholinergic control.

The study population consisted of 17 migraine patients without aura and 18 healthy volunteers were included as a control group. The method for demonstrating sensory gating is the paired-stimulus P50 paradigm. We compared the initial stimulus (S1), second stimulus (S2) amplitude and latency and the percentage of sensory gating in the ictal and interictal periods with healthy controls.

The percentage of P50 suppression of the migraine group in the attack and interictal periods were significantly reduced compared with those of the control group ($P < 0.05$). This difference was related to significantly lower S1 amplitude in the migraine group compared with the control group ($P < 0.05$). Although, the S1 and S2 amplitudes and percentages of P50 suppression were closer to the control values during an attack, the differentiations between groups was observed still significant ($P < 0.05$).

This conclusion supports the notions of loss of habituation associated with interictal cortical hypoexcitability and the ictal normalization of the loss of habituation. The present study suggests that migraine patients may have a dysfunction in thalamo-cortical excitatory cholinergic activity.

Keywords: Sensory gating, pedinculopontine nucleus, cholinergic insufficiency, migraine

ÖZET

Sönümleme normal kişilerde aşırı duysal yüklenmeye karşı korteksi korumak için bir adaptasyon mekanizması olarak tanımlanabilir. Migrende en sık elektrofizyolojik anormallik sönümlemenin yokluğudur. İlginç olarak bir migren atağından hemen önce ve atak sırasında sönümleme normalize edilmiştir. Bu çalışmada kolinerjik kontrol altında sönümleme yanıtını değerlendirmek için p50 supresyon metoduna (duyusal perdeleme) karşı ortaya çıkan sönümleme yanıtına başka bir bakış açısı sağlamak amaçlanmıştır.

Çalışma 17 aurasız migren ve kontrol grubu olarak 18 sağlıklı gönüllüyü içermekteydi. Yöntem, duyusal perdelemeyi göstermek için p50 uyarı örneği ile eşleştirildi. İlk uyarı (S1), ikinci uyarı (S2), amplitüt, latans ve iktal-interiktal periyotlardaki duyusal perdeleme oranı sağlıklı bireylerle karşılaştırıldı.

Atak ve interiktal peryotlarda migrenli gruptaki p50 süpresyon oranı kontrol grubuna göre belirgin bir şekilde azalma gösterdi ($p < 0.05$). Kontrol grubu ile karşılaştırıldığında farklılık büyük oranda S1 amplitütündeki düşüklük ile ilişkiliydi ($p<0.05$). S1 ve S2 amplitütleri ve p50 supresyon oranı atak sırasında kontrol değerlerine yakın olmasına rağmen gruplar arasında hala büyük farklılıklar görülmektedir ($p < 0.05$).

Sonuç olarak, sönümlemenin kaybı düşüncesi interiktal kortikal hipoeksitabilite ve iktal olarak bunun normalize edilmesi ile ilişkilidir. Dolayısıyla çalışma migren hastalarında talamo-kortikal eksitatör kolinerjik aktivitede bir disfonksiyon olabileceğini önermektedir.

Anahtar Kelimeler: Duyusal perdeleme, pedinkülopontin nucleus, kolinerjik yetmezlik, migren

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INTRODUCTION

Migraine is a neurovascular disorder with the primary dysfunction of brainstem centers that regulate vascular tone and pain sensation (1). Current theories related to migraine pathophysiology include vascular, neurogenic, and hypoxic teories (2). The primary feature of the neural theory is “spreading depression”, which Leao defined as a reduction of the marked spontaneous electrical activity in the cortex (3).

The potential link between cortical spreading depression and headache has been identified, but the mechanism underlying central modulation of migraine is still unclear. Weiller et al. reported that aminergic nuclei (locus ceruleus, raphe nuclei) in the brainstem modify trigeminal pain processing during migraine (4). Using positron emission tomography, brainstem activation has been visualized during spontaneous migraine attacks, even after successful pain-relieving migraine treatment and brainstem nuclei nociceptors that are involved in the central control of pain may be dysfunctional in migraineurs and may have increased tolerance for trigeminal neuronal hyperexcitability (5,6).

Electrophysiological studies showed that interictal period in migraine patients have indicated a habituation defect in visual and auditory evoked potentials formed by repeated stimuli. This was thought to be due to hypofunction of the serotonergic projections from the brainstem to the sensory cortex (7,8). An overview of abnormalities during the interictal period in migraine patients provided evidence of low serotonergic and dopaminergic and high noradrenergic activities as well as abnormal cortical excitability in migraineurs between attacks (8).

Sensory gating is the primary physiological mechanism underlying the filtering of unnecessary stimuli, the selection and removal of stimuli evaluated as trivial, and the protection of the brain from confusion caused by excess stimuli (9). Sensory gating can be measured by determining the P50 suppression rate using the observed changes in amplitude of the auditory evoked potential after repeated auditory stimuli (10,11). Sensory gating, which is associated with brainstem structures (12), is important while the brain is processing information and may be related to the pathophysiology of migraine. In this study, we investigated P50 sensory gating during and between attacks in migraine patients.

MATERIALS AND METHODS

The study population consisted of 17 migraine patients without aura diagnosed according to the criteria of the International Headache Society [13], and 18 healthy volunteers were included as a control group. None of the migraine patients or their first-degree relatives had a history of neurological or psychiatric diseases except for migraine. None of the controls or migraine patients had any other medical condition detectable by history or clinical examination, and none had taken drugs on a regular basis or had taken any drug within 3 days before the recordings. Two P50 recordings were performed in the subject group, one during an attack and the other in the interictal period. In interictal records, patients had not had an attack in the previous 3 days. Recordings in patients who had migraine attacks within 3 days after registering interictal recordings were repeated.

P50 measurement

The method used for electrophysiological recordings was based on previously described protocols (14) with slight modifications as described previously by our group (15).

The electrophysiological examinations were performed at the Laboratory of Clinical Neurophysiology, Department of Neurology, University of Inonu, over a 3-month period. Subjects in both the migraine and control groups refrained from smoking for at least 12 h before the electroencephalogram (EEG) and from tea and coffee on the morning of the EEG. The subjects were seated in a comfortable chair in a sound- and light-attenuated, electrically shielded room.

The subjects were instructed to relax with the eyes open and to fixate on a point straight ahead, to avoid eye motion artifacts. EEG activity, detected with a disk electrode affixed to the vertex (Cz) and referenced to the left mastoid (A2), was recorded in four channels with a MEM-4200K evoked potential recording system (Nihon Kohden, Tokyo, Japan) integrated with an auditory stimulator. The mean signal was registered in two channels and amplified 20,000 times with a band pass filter (1–100 Hz) and a 50Hz notch filter. Impedance was kept at <0. 5 kOhm. EEG data were collected for 1000 ms for each stimulus pair presented. Additional channels were used to record the electro-oculogram (EOG) between the superior orbital and lateral canthus.

Ten minutes of continuous resting-state EEG activity was recorded prior to the auditory double-click paradigm. The test stimulus was a click sound of 0. 1 s duration set 60 dB above the auditory threshold with a rarefaction output phase and was presented binaurally through earphones. The auditory threshold of each subject was measured through earphones 15 min before the recordings. The interval between the first and second clicks (interstimulus interval, ISI) was 500 ms, and the interval between two pairs of clicks was 10 s. The recording system automatically rejected trials that contained artifacts, indicated by a response of ±70 μV over the area of P50 for evoked potentials or EOG recordings. Thirty non-rejected waves were used to give an average signal for analysis. The wave peaks were determined visually, and the latencies and amplitudes were marked manually.

The most positive peak between 40 and 80 ms after the conditioning stimulus was selected as the P50 final latency for the first click (S1), and the wave amplitude was measured relative to the preceding negativity. The wave for the second click (S2) was determined using the peak corresponding to S1 ± 10 ms from the latency of the first conditioning waveform, and its amplitude was also measured relative to the preceding negativity. The S1 and S2 amplitudes were collected in sequence and averaged separately for analysis. The data were collected by one investigator and analyzed by an independent, trained evaluator blind to the state of the subjects.

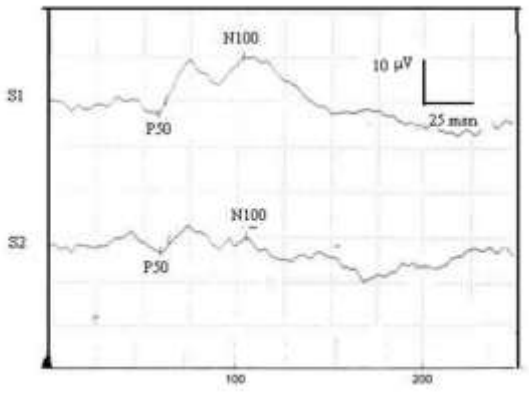

Figure 1: The grand averages of the P50 EPs in attack of migraine patient. Calibration bars indicate 2 SV and 25 ms. S1, conditioning stimulus; S2, test stimulus, the onset of stimulus. Amplitüde measurements were from baseline to peak. One hundred milliseconds increments were marked on the X axis.

Averages with no discernible conditioning P50 waves were excluded from the analysis, and the analysis was repeated in these four subjects. Gating ratios were calculated from the peak-to-peak amplitudes for S1 and S2 (S2/S1). The percentage of P50 suppression was calculated as follows: [1 – (S2 amplitude/S1 amplitude)] × 100 (16) (Figure 1, 2). The results are expressed as mean values ± standard deviation (SD).

Statistical analysis

Statistical analyses were carried out with IBM SPSS Statistics V20 for Mac. P50 values were compared between the migraine and control groups. All results are presented as means ± SD. Student's t-test was used for independent samples, and the Mann–Whitney U test was used for non-normally distributed data, to compare continuous variables between the migraine and control groups. The categorical variable (gender) was analyzed using a chi-square test. P50 amplitudes and latencies, and suppression percentages of amplitudes were compared with controls. In all analyses, $P < 0.05$ was taken to indicate statistical significance.

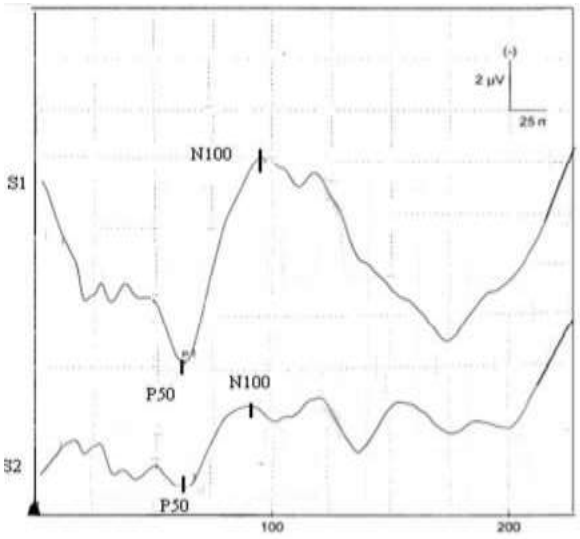

Figure 2: The grand averages of the P50 EPs in interictal period of migraine patient. Calibration bars indicate 10 SV and 25 ms. S1, conditioning stimulus; S2, test stimulus, the onset of stimulus. Amplitude measurements were from baseline to peak. One undred milliseconds increments were marked on the X axis.

RESULTS

Seventeen patients (10 females and 7 males) diagnosed with migraine were included as the subject group, and 18 healthy volunteers (10 females and 8 males) were included as the control group. The mean age was 28. 88 ± 8.54 years for the migraine group and 25.44 ± 3. 36 years for the control group. There was no difference in mean age or gender distribution between the migraine and control groups.

Migraine patients showed no statistically significant difference in percentage of P50 suppression or P50 amplitude between the attack and interictal periods (Table 1).

The percentage of P50 suppression of the migraine group in the attack and interictal periods were significantly reduced compared with those of the control group (P <0.05). This difference was related to significantly lower S1 amplitude in the migraine group compared with the control group (P < 0. 05) (Table 2).

Table 1: Neurophysiological findings of attack and interictal periods in migraine patients

	Attack (n:17)	Interictal	P *
	Mean±Std. Deviation	Mean±Std. Deviation	
P50 first amplitude	2.66±1.44	2.29±1.36	0.17
P50 second amplitude	1.93±1.35	2.40±1.58	0.59
P50 first latency	59.65±5.93	60.24±6.27	0.70
P50 second latency	59.41±4.61	60.71±6.11	0.47
P50 GATE %	24.30±31.87	14.62±21.96	0.27

Mann-Whitney U

Table 2: Neurophysiological findings attack and interictal periods of migraine patients and control groups

	Control (n:16)	Attack	Interictal	P* (C&A)	P* (C&I)
	Mean±Std. Deviation	Mean±Std. Deviation	Mean ± Std. Deviation		
P50 first amplitude	5.40±4.12	2.66±1.44	2.29±1.36	.034	.008
P50 second amplitude	2.26±1.78	1.93±1.35	2.40±1.58	.736	.657
P50 first latency	57.50±10.79	59.65±5.93	60.24±6.27	.287	.195
P50 second latency	56.83±11.16	59.41±4.61	60.71±6.11	.258	.110
P50 GATE %	54.48±30.40	24.30±31.87	14.62±21.96	.017	.001

C: control, A: attack, I: Interictal; * Mann-Whitney U

DISCUSSION

The results of this study indicate decreased amplitude of the P50 potential and reduced suppression of the P50 potential, which are consistent with impairment of sensory gating in migraine patients both in attack and between attacks.

The possible source of the P50 wave could be related to the pedunculopontine nucleus (PPN) that forms the cholinergic component of the ascending reticular system (12). GABAminergic and other inhibitor synapses that induced by the first stimulus cause the response to the second stimulus to be inhibited and it is thought that the P50 suppression (sensory gating). The brain is protected in this way from the interfering effect of the second stimulus (17,18). As drugs increasing GABA activity are beneficial in migraine treatment, it has been suggested that migraine patients have a GABA dysfunction (19).

Sensory gating during the interictal period has been explored in migraine patients, and a reduction in gating of the auditory responses was demonstrated. Compared with healthy controls, migraine patients showed a lower level of inhibition of the P50 cortical response to the second of the two homologous stimuli, and normal P50 amplitude (20). These findings suggested that the sensory gating impairment and loss of habituation to consecutive stimuli in migraine may be related to a dysfunction in the control of incoming information, possibly involving hypofunction of the raphe nucleus during the interictal period (20).

However, patients with migraine show excitation arising from the noradrenergic locus ceruleus in the interictal period and during the migraine prodrome and aura. The pain is the result of the uninhibited increase in the firing rate of the rostral raphe nucleus (21-23), and in these cases, cause an increase in the inhibitory inputs to PPN (24). We found reduced P50 amplitude, which might have resulted from increased inhibitory PPN inputs, in both the interictal and ictal periods.

In addition, sensory gating is related to the sleep cycle and excitability (25). According to the central inhibition theory, which is a variant of the neuronal theory of migraine pathogenesis, an uninhibited increase in firing rate of the serotonergic system in the raphe area is responsible for the pain. The serotonergic neurons in the raphe area are not only responsible for pain but also play a role in the regulation of sleep. These observations suggest that the serotonergic system may participate in sensory gating (26).

In the present study, P50 recordings were performed during the ictal and interictal periods in the migraine group. A decrease in the percentage of P50 suppression was detected in migraine patients, compared with the control group, during the ictal and interictal periods. This decrease was related to reduce of S1 amplitude in the migraine group compared with the control group. The reduced S1 amplitude in the ictal and interictal periods may be related to PPN dysfunction owing to increased PPN inhibitor inputs stemming from the dorsal raphe nucleus and locus ceruleus respectively, therefore, sufficiently suppress the S2 amplitude as a result of GABAminergic dysfunction (18,24).

The findings of the present study suggest that migraine patients may have a dysfunction in PPN that is to say cholinergic dysfuntion. Already, a few studies have also suggested that cholinergic agents may use for treatment of migraine attack and prophylaxis (27). This lack of auditory sensory gating may be due to a hypofunction of PPN. Further neuropshyological, radiological and biochemical studies are needed in this matter.

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