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Blink reflex in migraine headache

Zeynep Unal,[1,5] Fusun Mayda Domac,[2,5] Ece Boylu,[3,5] Abdulkadir Kocer,[4,5] Tulin Tanridag,[5] Onder Us[5]

[1]Neurology Department, Manisa State Hospital for Mental Health and Neurological Disorders, Manisa, Turkey

[2]Neurology Department, Erenköy Training and Research Hospital for Psychiatric and Neurological Disorders, Istanbul, Turkey

[3]Neurology Department, Gelişim University, Istanbul, Turkey

[4]Neurology Department, Medeniyet University Göztepe Training and Research Hospital, Istanbul, Turkey

[5]Neurology Department, Marmara University, Electrodiagnostic Neurology Master Programme, Istanbul, Turkey

ABSTRACT

OBJECTIVE: Activation of trigeminovascular system is thought to play an important role in migraine pathogenesis. Blink reflex (BR) test is an easy method to study the trigeminal system. Latencies recorded in BR test were evaluated to examine neurophysiological changes that occur in migraine patients.

METHODS: A total of 40 patients diagnosed with migraine (9 with aura and 31 without aura) according to the International Headache Society (IHS) International Classification of Headache Disorders, 2nd edition, and 30 healthy control subjects were assessed using BR test. Supraorbital nerve was stimulated on each side, and unilateral early component (R1), and bilateral late component (R2) latencies were evaluated.

RESULTS: Significantly longer latency values were recorded on both right and left sides (RR1 and LR1) as well as both ipsilateral and contralateral R2 on the left side (LR2i and LR2c) in the migraine group compared to the control group. Longer RR1 and LR1 latencies were found in patients with migraine who had an attack at the time of study ($p<0.01$). There was no statistically significant correlation between the location of pain and latencies in the interictal period ($p>0.05$). But significantly longer R1 and R2i latencies were found at the symptomatic side of patients examined during the headache attack ($p=0.037$ and $p=0.028$ respectively). There was no statistically significant correlation between the recorded latencies and gender, attack duration, attack frequency and migraine type ($p>0.05$).

CONCLUSION: Results of BR test in the present study are thought to point to a dysfunction in brainstem and trigeminovascular connections of patients with migraine headache and support the trigeminovascular theory of migraine.

Keywords: Blink reflex; headache; migraine.

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Correspondence: Dr. Fusun Mayda Domac. Erenköy Ruh ve Sinir Hastalıkları EAH, Noroloji Klinigi, Sinan Ercan Cad. No:29, Kozyatagi, Istanbul, Turkey
Tel: +90 216 302 59 59 / 422 e-mail: fusundomac@yahoo.com.tr

As a result of previous studies, theories related to pathophysiology of migraine have become more complex and concentrated on neuronal dysfunction [1]. Important roles played by neurogenic inflammation of meningeal vessels combined with activation of trigeminovascular system, and sensitization of trigeminal nuclei in the brainstem have been demonstrated [2-4]. Sensitization of trigeminovascular system has been thought to be responsible for pain felt during initial phase of migraine, and evidence concerning its potential subclinical continuation during interictal phase is available [1,5-7]. Cutaneous allodynia occurring during migraine attacks has been associated with sensitization of central trigeminal nuclei [2,8]. Association between impairment of central inhibitor mechanisms and sensitization processes developed during and following migraine attacks has been emphasized [8,9]. Chronic pain has also been thought to stem from derangement of inhibitory control mechanisms [9].

Neurophysiological tests, such as transcranial magnetic stimulation, evoked potentials, event-related endogenous potentials, autonomic tests, and blink reflex (BR) have become important tools in the investigation of cerebral excitability, nociceptive systems, central, and peripheral mechanisms in primary headaches [1,10-14]. BR is a noninvasive test to obtain information about peripheral and central neurologic functions and thus far it has been used in the investigation of pathophysiology of various types of headaches [11-15]. Early component of BR (R1) is transmitted via pontine pathway, and it is recorded only by unilateral stimulation. Late component (R2) is a polysynaptic response passing through lateral reticular formation, and is recorded bilaterally [16]. R2 reflects excitability of interneurons in the brainstem, and its synaptic transmission function at this level [17]. Central sensitization of neurons in the spinal trigeminal nuclei induces depolarization of cutaneous trigeminal axons with resultant alterations in R2 responses [9].

In studies of BR, R1 and R2, latency measurements have yielded different data in cases of migraine headache. The aim of this study was to investigate whether latency values from BR test performed on patients with migraine headache differ from those of the control group, and to analyze the role of trigeminovascular system in the pathogenesis of migraine.

MATERIALS AND METHODS

A total of 27 female and 13 male patients diagnosed as having migraine, with or without aura, based on International Classification of Headache Disorders, 2nd edition, criteria published by International Headache Society (IHS) were included in the study. Control group consisted of 30 age-matched (20 female, and 10 male) subjects without any known present or past systemic or neurological disease. Detailed neurological examinations were performed on all participants. Tests to be performed were thoroughly explained to study participants, and consent was obtained. Approval of the study was obtained from the ethics committee of Marmara University Faculty of Medicine.

Migraine patient data on gender, type of migraine (with or without aura), time interval between examination and onset of attack (during, within or 72 hours after onset of the attack), frequency and location of attack were recorded.

Patients who had received prophylactic treatment within the previous 3 months, in whom there was presence of disease that might affect electrophysiological examination or involving trigeminal or facial nerve, or in whom a structural lesion was detected on cranial images, had headaches other than migraine, or aged younger than 18 or older than 60 years were excluded from the study.

Blink Reflex (BR)

BR was measured using 4-channel Medelec electromyography (EMG) device (Becton, Dickinson and Company, Franklin Lakes, NJ, USA) in the Marmara University Department of Neurology electrophysiology laboratory. The examinations were performed at normal room temperature in a noiseless laboratory with patients lying on examination table in supine position with eyes closed. Silver-coated electrodes were used for testing: Active electrodes were placed bilaterally on m.orbicularis oris, and

reference electrodes were placed on nasal wings. Ground electrode was placed between the stimulator and active electrode.

Right and left supraorbital nerves were stimulated successively over the supraorbital foramen. Stimuli were applied for 0.2 milliseconds with 30-second intervals. Responses were elicited 5 times, consecutively from both sides: early component (R1), late component ipsilateral (R2i) and late component contrlateral (R2c). Latency of reflex responses was measured from shortest initial deflection. Average values of R1, R2, and R2c latencies were calculated. Latency values recorded in patients with migraine and in the control group were compared. Correlations between gender of patients, location and frequency of pain, and latency values were assessed.

Statistical Analysis

SPSS software (version 13.0; SPSS Inc., Chicago, IL, USA) was used to evaluate data obtained from patient and control groups. Normality of distribution was tested using Kolmogorov-Smirnov test. Descriptive statistics (mean, standard deviation) were gathered for all groups. Student's-t test was used to compare the 2 groups and chi-square test was used to evaluate categorical variables. For the comparison of more than 2 groups, one-way analysis of variance (ANOVA) test was used. Results were evaluated as statistically significant at a level of $p<0.05$.

RESULTS

Mean age of patients with migraine headache was 37.36±9.67 (19-50) years. Control group consisted of healthy volunteers with a mean age of 36.5±11.68 (20-51) years. Migraine headache group comprised 28 (70%) female and 12 (30%) male patients, while the control group consisted of 20 (66.7%) women and 10 (33.3%) men.

Nine patients (22.5%) met criteria of migraine with aura; 31 (77.5%) were diagnosed as having migraine without aura. More than 4 attacks per month were experienced by 27 patients (67.5%), while 13 patients (32.5%) experienced fewer. Migraine headache was felt on the right by 17 participants (42.5%), on the left by 14 (35%), and on both sides by 9 study participants (22.5%) (Table 1).

A total of 12 (30%) patients were examined during migraine headache attack. Fourteen patients (35%) had experienced their last attack within the

Table 1. Demographic characteristics of migraine and control groups

	Migraine group	Control group
Number of study participants	40	30
Age (years)	37.36±9.67	36.5±11.68
Gender		
Female, n (%)	28 (70)	20 (66.7)
Male, n (%)	12 (30)	10 (33.3)
Frequency of attacks		
<4/month	13 (32.5)	
≥4/month	27 (67.5)	
Location		
Unilateral	31 (77.5)	
Bilateral	9 (22.5)	
Type of migraine		
With aura	9 (22.5)	
Without aura	31 (77.5)	

Table 2. Comparison of latency values obtained in migraine and control groups on eye blink reflex test

Latency	Migraine group Mean±SD	Control group Mean±SD	p
R1 latency (ms)			
Right	11.07±1.42	10.27±1.61	0.004*
Left	11.66±1.3	9.85±1.25	0.000*
R2 latency (ms)			
Right R2i	28.84±3.65	27.82±3.16	0.136
Right R2c	29.02±3.26	28.09±3.17	0.291
Left R2i	30.21±3.23	27.73±2.89	0.018*
Left R2c	30.45±2.80	27.55±3.02	0.001*

R1: Early component; R2i: Ipsilateral late component; R2c: Contralateral late component; SD: Standard deviation; *Statistically significant values.

previous 3 days, and it was significantly longer ago for the remaining 14 (35%).

In the patient group, right and left R1 latency values (0.000 and 0.004, respectively) were found to be significantly longer than the control group. R2i and R2c latency values after stimulation to right side were compared with those of the control group and no significant intergroup difference was found; however, R2i and R2c latency values after stimulation to left side (0.018 and 0.001, respectively) were also significantly longer than those of the control group (Table 2).

R1, R2i, and R2c latency values after right- and left-side stimulation did not have a statistically significant difference between types of migraine ($p>0.05$) (Table 3).

Patients were divided into 3 groups based on time of the attack. LR1 latency values obtained from patients during headache attack were significantly longer than those recorded within or more than 72 hours after attack ($p=0.042$ and $p=0.034$, respectively). RR1 latency values measured during attack were longer relative to other groups without any statistically significant intergroup difference (Table 4).

Table 3. Comparison of latency values obtained on eye blink reflex test in patient groups with migraine

Latency	Migraine with aura Mean±SD	Migraine without aura Mean±SD	p
R1 latency (ms)			
Right	11.01±1.5	11.09±1.43	0.646
Left	10.98±1.4	11.12±1.43	0.252
R2 latency (ms)			
Right R2i	28.37±2.61	28.98±3.95	0.687
Right R2c	29.1±3.28	29±3.32	0.291
Left R2i	29.85±2.53	30.32±3.46	0.159
Left R2c	30.17±3.05	30.23±2.75	0.389

R1: Early component; R2i: Ipsilateral late component; R2c: Contralateral late component; SD: Standard deviation.

Table 4. Comparison of latency values obtained on eye blink reflex test according to time elapsed between onset of examination and last attack

	Ictal	The last 3 days	The last >3 days	p
Right R1 Latency (ms)	11.62±1.5	10.96±1.45	10.89±1.42	0.157
Right R2i Latency (ms)	28.24±2.67	29.11±4.22	29.18±3.68	0.626
Right R2c Latency (ms)	28.74±3.09	28.68±3.6	30.22±3.3	0.318
Left R1 Latency (ms)	12.44±0.69	10.91±1.44	10.59±1.24	0.042*
Left R2i Latency (ms)	31.04±1.61	29.04±3.76	28.05±2.66	0.034*
Left R2c Latency (ms)	29.6±2.66	30.08±2.9	30.44±2.65	0.237

R1: Early component; R2i: Ipsilateral late component; R2c: Contralateral late component; *Statistically significant values.

No statistically significant correlation was found between patient gender, frequency of attacks, or time of onset and latency values (p>0.05) (Tables 4,5,6). In the patient group, R1 and R2i latency values recorded during ictal (headache attack) phase from symptomatic and intact side were found to be statistically significantly correlated (p=0.037, and p=0.028, respectively), while prolongation of latency values of the intact side recorded during interictal phase were independent from symptomatic side.

DISCUSSION

Various functional imaging studies have shown that during migraine headache attack, brainstem is activated and abnormalities are seen in ascending

Table 5. Comparison of latency values obtained on the eye blink reflex test in male and female patients

	Female (n=28)	Male (n=12)	p
Right R1 Latency (ms)	10.98±1.36	11.26±2.02	0.316
Right R2i Latency (ms)	28.95±3.76	28.7±3.03	0.944
Right R2c Latency (ms)	30.3±4.52	29.88±3.17	0.485
Left R1 Latency (ms)	10.99±1.41	11.12±1.48	0.543
Left R2i Latency (ms)	30.06±3.27	30.6±3.1	0.445
Left R2c Latency (ms)	30.25±2.77	30.26±2.93	0.244

R1: Early component; R2i: Ipsilateral late component; R2c: Contralateral late component.

Table 6. Comparison of latency values obtained on eye blink reflex test according to frequency of migraine attacks

Frequency of attacks	<4/month	>4/month	p
Right R1 Latency (ms)	11.27±1.38	10.81±1.41	0.388
Right R2i Latency (ms)	28.69±3.48	29.03±4.1	0.803
Right R2c Latency (ms)	29.38±3.49	28.56±3.01	0.504
Left R1 Latency (ms)	11.27±1.44	10.89±1.39	0.476
Left R2i Latency (ms)	29.63±3.28	30.65±3.23	0.402
Left R2c Latency (ms)	30.04±2.95	30.76±2.73	0.496

R1: Early component; R2i: Ipsilateral late component; R2c: Contralateral late component.

and descending nociceptive pathways during ictal and interictal phases [18,19]. Trigeminal system provides sensory innervation of extracranial and intracranial arteries, as well as afferent fibers of nociceptive transmission. The contribution of trigeminovascular system to pathogenesis of migraine has been detected in experimental animal and human studies [6,7]. In BR studies performed in cases of migraine, data measuring R1 and R2 latencies have demonstrated differences. It has been thought that this discrepancy was related to different methods used, diversities in patients selected, and latency recording time (ictal/interictal) [20].

Aktekin et al. conducted BR tests on migraine patients during interictal phase using standard methods and compared measurements of R1 and R2 latencies, R2 amplitudes, and area with those of control group without finding any significant intergroup difference. They stated that these findings can be considered evidence that migraine-specific trigeminal dysfunction is a transient condition [21,22].

In healthy control participants, headache was induced with electrical stimulation and the effects of central inhibition mechanisms on experimental migraine model were investigated. BR tests were performed before, during and after experimentally triggered headache. It was found that R2 suppressed after pain induced by electrical stimulation normalized during pain-free phases. The authors claimed that the obtained findings demonstrated that inhibition in migraine was not impaired [23]. Sand et al. compared patients who experience migraine-type headaches with control group during interictal phase, and stated that R2 amplitude values were not different [24]. Similar results have also been obtained in other studies [25-28].

In a study by Bank et al., R1 latency values elicited by supraorbital stimulation did not differ significantly from those of the control group, while significantly longer R2 latencies were found in the patient group. However, they did not indicate whether or not this study was performed during patient migraine attack or not. They stated that these findings could be presented as objective evidence of the involvement of trigeminal afferents and/or polysynaptic pathways in the brainstem of patients with migraine headache [29]. In the present study, right- and left-sided R1, as well as R2i and R2c latency values were compared with those of the control group, and significantly longer latencies were detected in the patient group, supporting role of trigeminovascular system in migraine.

R2 was prolonged compared to responses during migraine attack, pain-free phases or controls

[12,25]. This condition is thought to emerge as a response to sensitization of cutaneous nociceptive afferent arch or neurons in the trigeminal nucleus [12]. Yet these findings may be useful to better understanding of the role of trigeminal complex in pathophysiology of headache, follow-up of patients during migraine episodes or evaluation of treatment response [30].

A limitation of the present study is that amplitudes of early and late components elicited during BR test were not investigated or evaluated. When compared with those of the control group, significantly prolonged latency values of early and late components recorded during both ictal (headache attack) and interictal phases suggest that trigeminovascular dysfunction in patients with migraine headache is not a transient phenomenon. Predominant prolongation of latency during ictal phase implies that the brain is passing through different excitability phases and increased sensitization of trigeminal neurons during migraine attack.

The association between location of pain and recorded side of BR has been investigated in various studies. In studies performed during pain-free period, no correlation between location of pain and recorded side was found. [2,25,31]. Despite abnormal responses elicited when stimulation was delivered from both sides, lack of any correlation on the painful side has been thought to be related to widespread suppression of the R2 interneurons at a bulbopontine level [25]. However, prolonged late component latency on the involved side in the BR test, and increase in the area of R3, which uses the same pathways as R2, have been more frequently detected with statistical significance during ictal phase [2,25,26]. In the present study, a statistically significant correlation was found between symptomatic side and R1 and R2i latency values during ictal phase. This finding is thought to reflect sensitization of trigeminal nucleus of the symptomatic side during ictal phase.

In conclusion, the results obtained in BR test demonstrated presence of dysfunctional connections between brainstem and trigeminovascular system in patients with migraine headache and support trigeminovascular hypothesis in migraine.

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