Original Article

Randomised, controlled blink reflex in patients with migraine and tension type headache

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Abstract

Objectives: To investigate the latencies, amplitudes of R1, R2i and R2k responses and R2 habituation; to compare the groups with each other and with the placebo group and to demonstrate new evidences on migraine and tension-type headache TTH mechanisms.

Methods: This analytical study was carried out among 40 migraine patients who were admitted to Yuzuncu Yil University, Medical Faculty, Neurology Clinics between May 2009 and December 2009, with or without aura according to the diagnostic criteria of International Headache Society 2004 classification. Forty TTH patients, who were diagnosed with TTH were included, and 40 control group subjects were formed according to the same demographic data. SPSSv13 was used for Chi-square test, one-way ANOVA and Pearson correlation coefficients was used for the determination of the relation between the groups and categorical.

Results: Mean age was 33.04 ± 9.07 years. An average of RR2k latency was significantly high in migraine group comparing with TTH and the control groups, and in TTH group comparing with the control group. Similarly, the average of LR2k latency was found to be significantly higher in migraine group than TTH and the control groups, and significantly higher in TTH group than the control group.

Conclusion: Our findings demonstrated that brainstem and trigeminovascular connections play an important role in migraine pathogenesis and that central mechanisms play a role in TTH and concerning these two diseases.

Keywords: Migraine disorders, Tension-type headache, Trigeminal nuclei, Photophobia, Turkey (JPMA 61:978; 2011).

Introduction

The activation of trigeminal system and sensitization of trigeminal nucleus of the brainstem are considered to play an important role in migraine. In tension-type headache (TTH), central mechanisms are the major factors.[1,2] Blink reflex (BR) is an objective neurophysiologic assessment method for trigeminal system, facial nerve and lateral medulla status.[3,4] Afferent arc of BR is formed by the sensation fibers of trigeminal nerve while efferent arc is formed by motor nerve fibers.[5-8] BR occurs with electrical or mechanical stimulation of supraorbital nerve and includes three responses: Early response is the ipsilateral response to the stimulation (R1), and two late responses are the ipsilateral and contra lateral responses (R2i and R2k).[9] R1 is a cutaneous originated oligosynaptic reflex, which is transported by trigeminal afferent nerve fibers. Trigeminal afferents mainly attain sensorial nucleus in pons, and then they are transmitted to ipsilateral facial nucleus and excite orbicularis oculi motor neurons. R1 reflex occurs on stimulating orbicularis oculi muscle. R2 is transmitted to the spinal tractus in the dorsolateral region of the pons and medulla oblongata before the fibers of the reflex pathway reach the caudal end of spinal trigeminal nuclei, and it is then transmitted to facial nucleus in reticular formation through polysynaptic medullar pathways.[3-12]

The aim of our study was to compare the migraine and TTH patient groups with each other and with the healthy subjects of the control group according to various criteria by evaluating R1, R2i and R2k response latencies of BR, amplitudes and R2 habituations, to present new evidences on the origin of migraine and peripheric trigeminovascular hypothesis and the central mechanisms in TTH.

Patients and Methods

In the analytical study, 40 migraine patients who were admitted to Yuzuncu Yil University, Medical Faculty, Neurology Clinics between May 2009 and December 2009, with or without aura according to the diagnostic criteria of International Headache Society (IHS) 2004 classification (13), and 40 TTH patients, who were diagnosed with TTH were included, and 40 control group subjects were formed according to the same demographic data. Patients with primary headache, other than migraine and TTH, or individuals, who had neurological or physical diseases, causing secondary headache were excluded. Furthermore, among the included patients having migraine and TTH with other neurological and systemic diseases, which can affect BR, were also excluded. Frequency and severity of attacks,

duration of the disease, headache localization, prophylactic drug usage, triptan usage, nausea and/or vomiting and the rate of photophobia-photophobia symptoms were recorded in patients, who were diagnosed with migraine with and without aura. In addition, the achievement of daily living activities and the level of ache were evaluated for these patients by fulfilling the migraine disability assessment scale (MIDAS). The frequency and severity of attacks, duration of the disease and prophylactic drug usage were recorded for the patients, who were diagnosed with TTH as well.

Kimura method and BR protocol were studied in all study groups. An electromyography (EMG) device with a specific habituation test programme was used to elicit and record BR responses and to randomly repeat stimulation at different time intervals so as to induce habituation. Statistical analyse "One-way variance analysis" (One-way ANOVA) was performed in terms of continuous variables to compare the group averages. Following the variance analysis "Duncan multiple comparison test" was used in order to determine the different groups. Pearson correlation coefficients were calculated to determine the relationships between these variables. Chi-square test was used for the determination of the relation between the groups and categorical variables and statistical package for the social sciences (SPSS) (version: 13) programme was used for the calculations.

Approval from the Ethics Committee and written informed consent from all patients and the control group subjects were obtained for the study.

Results

The age range of all groups was between 18-64 years, with a mean age of 33.04 ± 9.07 years. The age range in the migraine group was between 18-51 years; with the mean age being 30.85 ± 8.03 years. The age range in the TTH group was between 19-64 years and the mean age was 34.45 ± 9.42 years. The age range in the control group was between 19-61 years; with a mean of 33.83 ± 9.51 years. There was no statistically significant difference in the mean age of groups.

Migraine group, TTH group and the control group consisted of 18 (45%) males and 22 (55%) females, 22 (55%) males and 18 (45%) females and 21 (52.5%) males and 19 (47.5%) females, respectively. There was no statistically significant difference between the groups on the basis of gender.

Migraine group consisted of 15 (37.5%) migraine patients with aura, 25 (62.5%) migraine patients without aura, and according to the MIDAS questionnaire, 6 (15%) patients were stage I, 15 (37.5%) patients were stage II, 14 (35%) patients were stage III and 5 (12.5%) patients were stage IV. In the migraine group, 5 (12.5%) patients had mild, 16 (40%) patients had moderate, 19 (47.5%) patients had severe pain, while in TTH group 9 (22.5%) patients had mild, 28 (70%) patients had moderate and 3 (7.5%) patients had severe pain. The difference between the groups was statistically significant on the basis of intensity of pain. Intensity of pain in the

Table-1: Comparison of GKR latency and amplitude in migraine group patients with and without habituation.

Habituation		N	Average	p
sagr1 lat	Pozitive	32	9,9750	0,214
	Negative	7	9,7929	
sagr1 amp	Positive	33	201,9697	0,095
	Negative	7	289,1429	
Sagri2 lat	Positive	33	37,7545	0,387
	Negative	7	36,9286	
sagr2i amp	Positive	33	267,0303	0,920
	Negative	7	274,2857	
sagr2k lat	Positive	33	38,4788	0,264
	Negative	7	37,4000	
sagr2k amp	Positive	33	268,2727	0,972
	Negative	7	270,8571	
solr1 lat	Positive	33	9,9667	0,300
	Negative	7	9,8071	
solr1 amp	Positive	33	250,6061	0,012
	Negative	7	487,1429	
solr2i lat	Positive	33	36,9682	0,780
	Negative	7	36,4071	
solr2i amp	Positive	33	238,3030	0,158
	Negative	7	332,7143	
solr2k lat	Positive	33	38,5106	0,144
	Negative	7	36,9786	
solr2k amp	Positive	33	240,6667	0,720
	Negative	7	263,7143	

Table-2: Definitive statistics and comparison results in TTH group in terms of habituation.

		N	Average	p
sagr1 lat	Positive	32	10,0484	0.018
	Negative	8	9,6500	
sagr1 amp	Positive	32	215,6563	0.520
	Negative	8	251,6250	
sagr2i lat	Positive	32	36,1656	0.590
	Negative	8	35,7250	
sagr2i amp	Positive	32	240,1250	0.107
	Negative	8	351,1250	
sagr2k lat	Positive	32	37,0344	0.973
	Negative	8	37,0625	
sagr2k amp	Positive	32	205,9375	0.140
	Negative	8	293,1250	
solr1 lat	Positive	32	10,0953	0.133
	Negative	8	9,9313	
solr1 amp	Positive	32	231,7500	0.320
	Negative	8	283,2500	
solr2i lat	Positive	32	36,1578	0.601
	Negative	8	36,7063	
solr2i amp	Positive	32	232,2188	0.071
	Negative	8	354,2500	
solr2k lat	Positive	32	37,0469	0.541
	Negative	8	37,7000	
solr2k amp	Positive	32	227,5313	0.065
	Negative	8	390,0000	

Table-3: Definitive statistics of migraine, TTH and the control groups in terms of GKR habituation.

			Group		
			Migraine	TTH	Control
Habituation	Positive	Number	33	32	36
		%	82,5%	80,0%	90,0%
	Negative	Number	7	8	4
		%	17,5%	20,0%	10,0%

migraine group was more severe (p = 0.001). While habituation was not seen in 7 (17.5%) of the patients in the migraine group, 33 patients (82.5%) demonstrated habituation Table-1. Similarly, habituation was not seen in 8 (20%) of the patients in the TTH group, but 32 (80%) patients had habituation Table-2. In the control group, 4 (10%) patients did not have habituation, but it was observed in 36 (90%) patients. Definitive statistics of migraine, TTH and the control groups in the terms of GKR habituation are demonstrated in Table-3. There was no statistically significant difference between the groups in the BR habituation.

In terms of photophobia, the difference between the groups was statistically significant. Photophobia was higher in the migraine patients than TTH patients ($p<0.05$).

Right R2 (RR2) average latency was significantly higher in migraine group than TTH group and it was higher in TTH group comparing with the control group. RR2k average latency was significantly higher in migraine group than TTH group and it was higher in TTH group compared with the control group. Furthermore left R2k (LR2k) average latency was significantly higher in migraine group than TTH group and it was higher in TTH group compared with the control group. LR2 average latency was not much different between migraine and TTH groups, however, it was significantly higher in both the groups compared with the control group ($p=0.001$). No significant difference was found between the groups in terms of other latency and amplitude values.

Although there was a statistically significant increase in RR2i, RR2k and LR2i, LR2k latencies depending on the age ($p<0.05$), no statistically significant increase was observed in BR latencies of migraine and TTH groups with increasing age.

When migraine group patients were divided into two groups as with- and without- aura, RR2 amplitude value was found significantly higher in the group with aura than without aura ($p<0.05$). When migraine group patients were separated into two groups in the terms of phonophobia, LR2i latency values were found to be significantly higher in the group with phonophobia than the other group without phonophobia, in the comparison of both sides (right and left) latency and amplitude values of BR ($p<0.05$). When migraine group patients were separated into two groups in terms of habituation, LR1 amplitude values were found to be significantly higher in the group with habituation than the other group without habituation, in the comparison of both side (right and left) latency and amplitude values of BR ($p<0.05$).

When TTH group patients were separated into two groups in the terms of level of pain, LR2 amplitude values were found to be significantly lower in the group with severe pain than the other group with mild pain, in comparison to both sides (right and left) latency and amplitude values of BR ($p<0.05$). When TTH group patients were separated into two groups in terms of prophylactic treatment, RR1 amplitude values were found to be higher and LR1 latency values were found to be shorter in the group, receiving prophylactic treatment, than the other group without prophylactic treatment in comparison to both sides (right and left) latency and amplitude values of BR ($p<0.05$). When TTH group patients were separated into two groups in terms of habituation, RR1 latency values were found to be significantly longer in the group with habituation than the other group without habituation in comparison of both sides (right and left) latency and amplitude values of BR ($p<0.05$). When TTH group patients were separated into two groups in the terms of photophobia, LR2i latency values were found to be significantly longer in the group with photophobia than the other group without photophobia, in the comparison of both sides (right and left) latency and amplitude values of BR ($p<0.05$). When TTH group patients were separated into two groups in terms of phonophobia, LR2i and LR2k latency values were found to be significantly longer in the group with phonophobia than the other group without phonophobia in comparison of both side (right and left) latency and amplitude values of GKR, ($p<0.05$).

Discussion

Today, headache is one of the most common complaints faced both in general medicine and neurological practice. The fact that "migraine headache is more common in female adult population" was known since years and verified in all publications, and this situation was also the same in our study: 55% of migraine patients were female. However, 45% of TTH patients were female. In recent studies, it was suggested that migraine incidence was becoming lower after the age of 40 years.[14,15] We found that the mean age of our patients was 30.85, which was consistent with the literature data. TTH was frequent in middle age group and the mean age was found as 34.45, which is also consistent with the literature.

Attacks with aura occur in 10% of migraine patients.[13] In our study, the proportion of migraine with aura was found to be 32,5%, and this situation may depend on the special selection of the patients, for better statistical signification of other parameters in migraine with aura. Symptoms consistant with cortical or brainstem dysfunction emerge during the

period of aura.[16,17]

Several studies have been published on chronic TTH. Normal R1, R2i and R2k latency values were reported.[1,18] Avramidis et al. worked with BR in the episodic type TTH and they obtained R2i and R2k within normal amplitudes and sizes in their study. The authors reported that BR value is normal, and the interneuron in the trigeminal and the facial nerve and the BR arc were intact in TTH patients.[19] However, some authors stated that central mechanisms in pathogenesis of episodic type headache could not be ignored.[1,2] In our study, the comparison of TTH group and the control group showed a statistically significant latency extension of R2i and R2k values in favour of TTH patients. This supports the idea that central mechanisms in TTH pathogenesis cannot be ignored.

In another study, comparing the ipsilateral R1 latency of migraine patients with the control group was reported to be significantly longer (p=0,025). In this study, it was supported that brainstem and trigeminovascular connections had an important role in pathogenesis of migraine.[20] According to our study results, there was statistically significant extension between RR2i, RR2k latency and LR2i, LR2k latency of the migraine group patients. Our finding is also pointing to the importance of trigeminovascular connections and brainstem localization in migraine.

The study of Di Clemente et al.[21] investigated nosiceptive BR with stimulation of right supraorbital region in 16 migraine patients with aura, 15 healthy subjects and 14 healthy subjects with family history of migraine in their first degree relatives. The most significant habituation impairment was found in healthy subjects with family history of migraine. Second one was the migraine patient without aura, inversely correlated with the frequency of attacks, nociceptive-specific BR habituation was interictally insufficient and it was thought to occur due to trigeminal sensitization. Insufficient nociceptive-specific BR habituation is an individual marker of genetic predisposition.[21]

In previous studies, important impairment in habituation of R2 component of BR was observed in prodromal phase of migraine attack in subgroup of migraine patients. De Marinis et al. reported that dopaminergic mechanisms have a role in brainstem BR pathway activation in these patients.[22] In another study, De Marinis et al. investigated the BR and its habituation in patients with chronic migraine, outside and during a spontaneous attack, and 35 control subjects. The R1 and R2 latencies, amplitudes and areas of the basal blink reflex were similar in patients studied both outside and during an attack as well as in control subjects, whereas the blink reflex habituation responses were markedly reduced in patients studied outside an attack. The percent changes in the R2 areas from the baseline values, obtained when stimuli were delivered at time intervals of 10, 5, 4, 3, 2 and 1s, were statistically different ($p<0.01$-$p<0.001$) from those of the same patients studied during a migraine attack and of those of control subjects. There was a significant correlation between decreased habituation of the blink reflex and a higher frequency of attacks. The stimulus intensities of the blink reflex (multiples of the detection threshold intensities) were significantly lower ($p<0.001$) on the side affected, or more severely affected, by headache in patients studied during a migraine attack. The decreased habituation of the blink reflex outside an attack reflects abnormal excitability in "chronic migraine", which normalizes during the attacks. Central sensitisation mechanisms (allodynia) may explain the lower detection thresholds observed on the side affected by headache in patients during the attacks. The blink reflex and its habituation may help shed light on the subtle neurophysiological changes that occur in migraine patients between and during attacks.[23] In our study, during the assessment of BR habituation in migraine, TTH and the control groups each consisting of 40 patients, habituation loss was observed in the rates of 17.5%, 20% and 10%, respectively, and it was not statistically significant.

Conclusion

Our findings demonstrated that brainstem and trigeminovascular connections play an important role in migraine pathogenesis (trigeminal system activation, the sensitization of brainstem trigeminal nucleus, abnormal synaptic transmission, suppression of brainstem interneuron region), and that central mechanisms play a role in TTH and concerning these two diseases.

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