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Original scientific paper

Effects of Trigeminal Nerve Dysfunction in Various Types of Headaches

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ABSTRACT

Headaches are one of the most common ailments in modern society, leading to severe diminishing of general activities and they result in significant impact on the patient's quality of life. Blink reflex is an objective neurophysiological method for determining the status of the trigeminal system, facial nerve and the lateral part of medulla oblongata. The aim of this study was to examine the connection between trigeminal nerve dysfunction and various types of headaches using functional electrophysiological assessment of blink reflex tests in patients and controls. The sample comprised 60 subjects with headache attacks, 44 females, and 16 males). The control group consisted of 30 healthy subjects (19 females, and 11 males) who did not suffer from headaches. The age of subjects ranged from 20 years to 76 years with the mean of 42.81 years. Trigeminal nerve function was assessed by using blink reflex tests in patients suffering from headaches and in controls, applying the standard procedure described by Kimura et al. Pathological findings of blink reflex were observed in 58.3 % of patients suffering from headaches and in only 20 % of cases in the control group. The application of Yates' χ^2 test showed a significant correlation between pathological blink reflex and headache occurrence ($\chi^2 = 10.354$; $P = 0.001$). Normal blink reflex was found in 41.7 % of patients suffering from headaches and in 80 % of control group subjects. Females with pathological blink reflex have 4 times higher risk for headaches than controls (OR = 4.107; 95% CI = 1.036 – 17.565). Males with pathological blink reflex have a considerably higher risk for headaches, and it was 13 times higher than in controls (OR = 13.500; 95% CI = 1.555 – 153.646). There is a strong correlation between pathological blink reflex and the occurrence of headaches in both genders, indicating significant association of trigeminal nerve dysfunction with the occurrence of headaches. The use of blink reflex testing could be of help to detect patients with an increased risk for headaches.

Key words: *headaches, blink reflex, trigeminal nerve dysfunction*

Introduction

Present knowledge about the pathophysiology of migraine headache and tension-type headache is incomplete, as well as their connection with trigeminal nerve disorder. The concept of neurogenically induced migraine dates back to 1960 when Chapman and his associates found a polypeptide responsible for vasodilation and hypotension similar to substance P, named neurokinin, in the aspirate of the fluid from the aching part of the head, only during migraine headache,[1,2].

The issue of central, peripheral or combined mechanism of the occurrence of migraine and tension-type headache remains unresolved. Clinical occurrences such as increased skin sensitivity, hyperalgesia and allodynia in primary headaches point to modified trigeminocervical nociceptive system in terms of facilitation or sensitization of central nociceptive neurons[3,4].

Some research suggests that rostroventral division of periaqueductal grey matter has a special role in trigeminal nociception. Another argument in favour of central point of inception is a study in which the implantation of stimulating electrodes into periaqueductal grey matter (PAG) caused a headache similar to migraine and a report on the existence of multiple sclerosis plaque in PAG, which had the same effect[5,6]. It is possible that in migraine patients there is a dysfunction of periaqueductal grey matter resulting in ipsilateral and contralateral disinhibition or inadequate inhibition of trigeminovascular afferent nociceptive information and consequent pain[7].

Sensitivity to head movement during a migraine attack and cranial sensitivity could also originate from central

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trigeminal pathways with PAG dysfunction as the cause[8-10].

Although the trigeminal nerve innervates meninges and probably plays a part in migraine occurrence, the initial triggering mechanism for migraines is still not understood well. Some research of migraine headache with visual aura points to the key role of expanding cortical depression, which is considered to be responsible for the creation of visual aura [11]. It is believed that cortical depression activates trigeminovascular afferent signals and causes a series of cortical, meningeal events and events in the area of brain stem, which correspond to the occurrence of migraine headache. As a consequence of cortical depression, there is an increase in blood circulation in the middle cerebral artery due to combined trigeminal and parasympathetic activity. Trigeminal axons projecting to meninges contain vasoactive neuropeptides, which stimulate the leakage of plasma proteins and vasodilatation in the area of dura mater, which are the characteristics of neurogenic inflammation. Research on animal model showed that cortical depression also causes the activation of ipsilateral trigeminal nucleus caudalis, i.e. central trigeminal projection associated with nociception[12]. Both events are blocked by trigeminal denervation[12]. Based on animal models it is believed that cortical depression might be a trigger in the cerebral cortex sufficient to activate the trigeminal system, occurrence of headache and meningeal vasodilation reflex[12].

The pathophysiology of tension-type headache is also incompletely clarified and based on clinical trials it is believed that peripheral mechanisms would have a more important role in episodic tension headache, while in chronic tension headache central mechanisms of occurrence would be primary. However, it is believed that peripheral mechanisms would be crucial for the onset of tension-type headache, while central mechanisms would be more important for its continuation[13].

Blink reflex is an objective neurophysiological method for determining the status of trigeminal system, facial nerve and lateral medulla. Blink reflex tests in migraine patients and control group without migraine showed uncertain results. However, since it is believed that spinal trigeminal nucleus plays a part in the pathophysiology of migraine, R2 and R2' latencies that are anatomically connected to spinal trigeminal nucleus are more important[14]. In some research no significant difference was found in these late blink reflex responses, while in others insignificant shortening of R2 latency was confirmed in the group of patients suffering from migraine without aura[14]. The abnormal latency of late R2 response could be the result of the sensitisation of brainstem interneuron, which could be involved in the pathophysiology of trigeminovascular disorder in migraine.

Another research established that blink reflex habituation in chronic migraine patients was significantly reduced between attacks, and that there is a correlation between decreased habituation and increased frequency of attacks[15]. The intensity of stimuli during an attack was considerably lower on the side of the head (more) affected by headache. Reduced habituation points to abnormal irritability in chronic migraine, while lower intensity of stimulus points to the presence of central sensitisation mechanism.

The research, which tested blink reflex in chronic tension-type headache, mostly showed regular R1, R2 and R2' latencies which would point to intact interneurons of the trigeminal and facial nerve, as well as the reflex arc of blink reflex[16]. However, some authors still don't rule out the role of a central mechanism in the pathophysiology of episodic tension-type headache (research identified statistically significant prolonged values of R2 and R2' latencies)[17].

The objective of this research is to examine the presence of a disorder in trigeminal nerve function as a part of the pathophysiological mechanism in the occurrence of headache. An analysis of the trigeminal nerve function was conducted via blink reflex in patients suffering from headaches and control group subjects not suffering from headaches.

Test subjects and methods

Test subjects in this research were divided into two groups: the 1st group of patients with severe headaches and the 2nd control group of individuals not suffering from headaches.

The group of patients suffering from headaches was made up of individuals, which were determined to have headaches according to the questionnaire on headaches, while the control group was made up of individuals not suffering from headache. 60 subjects suffering from headaches (44 females and 16 males) and 30 individuals not suffering from headaches (19 females and 11 males (Table 1) were analysed.

The age of test subjects was distributed evenly and it ranged from 20 to 76 years with an average of 42.81 years (Table 2). Test subjects suffering from headaches and control group subjects were of approximately the same age.

TABLE 1

SAMPLE STRUCTURE BY GENDER

GROUP	FEMALES		MALES		TOTAL
	N	%	N	%	N
Subjects with headache	44	73	16	27	60
Control	19	63	11	37	30
Total	63		27		90

TABLE 2

SAMPLE STRUCTURE BY AGE

GROUP	N	MEAN	SD	MIN	MAX
Subjects with headache	60	42.90	12.99	20	76
Control	30	42.63	11.7	25	72
Total	90	42.81	12.5	20	76

The average age of subjects suffering from headaches was 42.90 years, and in the control group it was 42.63 years.

Blink reflex as an objective neurophysiological method was used to determine the status of trigeminal system, facial nerve and lateral medulla in subjects suffering from headaches and control group subjects. In testing blink reflex, supraorbital nerve stimulation procedure was used according to the method described by Kimura et al.[18], which is considered to be a standard procedure today.

To test the significance of the correlation of blink reflex findings with headache χ^2-test with Yates' correction was used. In statistical tests no differentiation was made between the blink reflex being modified ipsilaterally or bilaterally, rather the existence of a pathological finding was recorded only. Probability ratio was also calculated as an estimate of the relative risk for the occurrence of headache in case of pathological blink reflex findings.

Results

Pathological finding of blink reflex was observed in 58.3% patients suffering from headaches, while in the control group of individuals not suffering from headaches it was detected in only 20% of cases (Table 3). Using the calculation of Yates' corrected χ^2 test it was established that there is a significant correlation between the pathological blink reflex finding and the occurrence of headache ($\chi^2 = 10.354$; P = 0.001). Individuals with headaches have a regular blink reflex in 41.7%, and individuals from the control group in 80% of the cases.

Calculation of the relative risk for headache occurrence showed that individuals with pathological blink reflex finding are at a 5.6 times higher risk for the occurrence of headache than individuals with normal blink reflex finding (OR = 5.600; 95% CI = 1.817 – 18.038) (Table 3).

The graphic also shows a clear connection between the pathological blink reflex finding and the occurrence of headache (Figure 1.). While headaches are frequent in individuals with pathological blink reflex finding (in 58% of cases), normal blink reflex finding is present in 80% of cases in the control group.

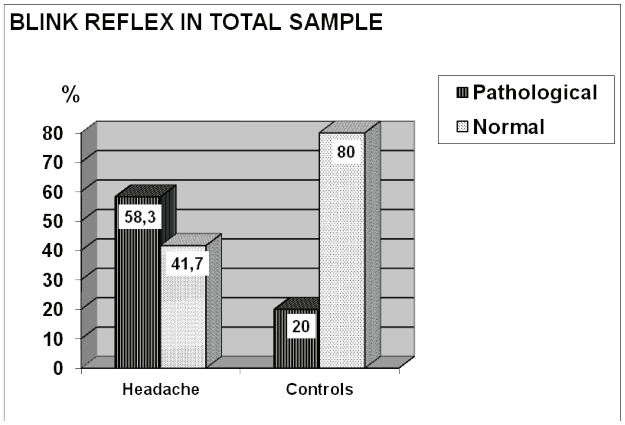

Fig. 1. *Correlation between pathological blink reflex and headache occurrence in total sample: individuals with headaches have a pathological blink reflex finding in 58% cases, and individuals without headaches only in 20 % of the cases.*

TABLE 3

DIFFERENCES IN FREQUENCIES OF PATHOLOGICAL BLINK REFLEX BETWEEN PATIENTS WITH HEADACHE AND CONTROLS (BOTH SEXES COMBINED)

Blink reflex	Group				Total	
	Headache		Controls			
	n	%	n	%	n	%
Pathological	35	58.3	6	20.0	41	100.0
Normal	25	41.7	24	80.0	49	100.0
Total	60		30		90	
$\chi^2 = 10.354$		df = 1			P = 0.001***	
OR = 5.600		95% CI = 1.817 – 18.038				

Yates' corrected $\chi 2$ test

TABLE 4

DIFFERENCES IN FREQUENCIES OF PATHOLOGICAL BLINK REFLEX BETWEEN FEMALES WITH HEADACHE AND CONTROLS

Blink reflex	Group				Total	
	Headache		Controls			
	n	%	n	%	n	%
Pathological	23	52.3	4	21.0	27	100.0
Normal	21	47.7	15	79.0	36	100.0
Total	44		19		63	
$\chi^2 = 4.084$		df = 1			P = 0.05*	
OR = 4.107		95% CI = 1.036 – 17.565				

Yates corrected χ^2 test

Pathological blink reflex finding was observed in 52.3% of females suffering from headaches and only in 21% of controls (Table 4). Using the calculation of Yates' corrected χ^2 test, it was determined that there is an important correlation between pathological blink reflex finding and headache occurrence in women ($\chi^2 = 4.084$; P = 0.05). Individuals suffering from headaches have a regular blink reflex in 47.7%, and controls in 79% of cases.

The calculation of relative risk for headache occurrence showed that individuals with pathological blink reflex finding have a 4 times higher risk for the occurrence of headache than individuals with normal blink reflex finding (OR = 4.107; 95% CI = 1.036 – 17.565) (Table 4).

The graphic shows a clear correlation between the pathological blink reflex finding and the occurrence of headache (Figure 2.). While headaches are very highly represented in individuals with pathological blink reflex finding (in 52.3% of the cases), in the control group normal blink reflex finding appears in 79% of the cases.

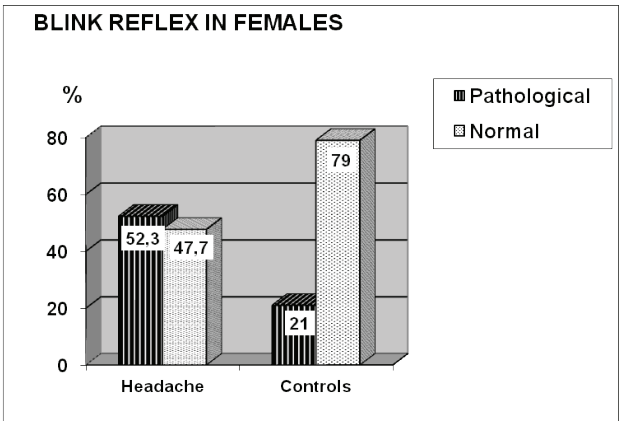

***Fig. 2**. Correlation between pathological blink reflex and headaches in females: pathological blink reflex in females with headaches was observed in 52.3% of cases, and only in 21% of controls.*

TABLE 5

DIFFERENCES IN FREQUENCIES OF PATHOLOGICAL BLINK REFLEX BETWEEN MALES WITH HEADACHE AND CONTROLS

Blink reflex	Group				Total	
	Headache		Controls			
	n	%	n	%	n	%
Pathological	12	75	2	18.2	14	100.0
Normal	4	25	9	81.8	13	100.0
Total	16		11		27	
$\chi^2 = 6.307$		df = 1			P = 0.012**	
OR = 13.500		95% CI = 1.555 – 153.646				

Yates' corrected χ^2 test

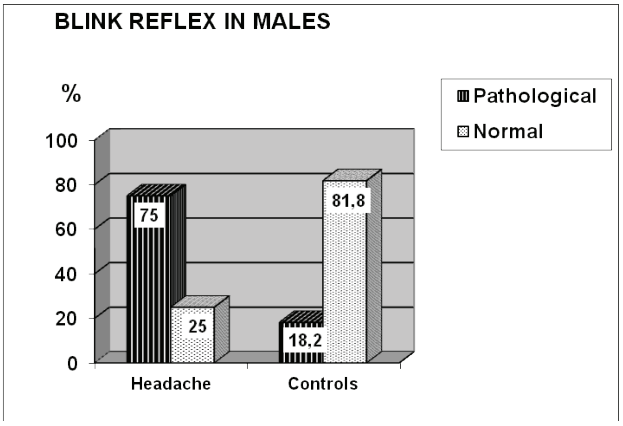

***Fig. 3**. Correlation between pathological blink reflex and the occurrence of headaches: pathological blink reflex in males with headaches was observed in 75% of cases, and among males without headaches only in 18.2% cases. Normal blink reflex is present in only 25 % of males with headaches, while in males without headaches it was observed in 81.8% of cases*

The pathological finding of blink reflex was determined in 75% of males with headaches, while in the control group of males without headaches it was identified in only 18.2% of cases (Table 5). By using the calculation of Yates' corrected χ^2 test, it was found that there is a clear correlation between pathological blink reflex finding and the occurrence of headache in males ($\chi^2 = 6.307$; P = 0.012). Males suffering from headaches have a regular reflex in only 25%, and men from the control group only in 81.1% of cases.

The calculation of relative risk for the occurrence of headache showed that males with pathological blink reflex finding have 13.5 times higher risk for the occurrence of headache than men with normal blink reflex finding (OR = 13.500; 95% CI = 1.555 – 153.646) (Table 5.). Compared to the finding for females, the risk for headache occurrence in males with pathological blink reflex finding is several times higher than in females with a disorder of this reflex. (13.5:4.1).

The graphic also shows a clear correlation between the pathological blink reflex finding and the occurrence of headache in males (Figure 3.). While headaches are highly represented in males with pathological blink reflex finding (in 75% of cases), in the control group normal blink reflex finding occurs in 81.8% of cases.

Discussion

Headache can affect the daily functioning of an individual in all segments, but also all segments of society. Therefore, the World Health Organization placed headaches among the top conditions causing significant decrease in general ability and working ability. It is believed that capacity for work is considerably lowered during a migraine attack[9].

This research included 90 subjects, 60 of which had primary migraine or tension-type headaches, and 30 subjects represented a control group (cervical or lumbosacral syndrome). The existing knowledge about the pathophysiology of migraine headache and tension-type headache are incomplete, but each study points to potential or certain correlation with trigeminal nerve disorder. The concept of neurogenically induced migraine dates back to 1960[1,2]. The question of central, peripheral or combined mechanism of the occurrence of migraine or tension-type headache remains unresolved. Clinical occurrences such as increased skin sensitivity, hyperalgesia and allodynia in primary headaches point to modified trigeminocervical nociceptive system in terms of facilitation or sensitization of central nociceptive neurons[3,4].

The role of peripheral mechanisms in migraine is supported by the research of ultrastructural appearance and protein expression of zygomaticotemporal branch of the trigeminal nerve (liquid chromatography analysis/mass spectrometry), which identified various proteins and molecular networks in migraine patients[20].

The pathophysiology of tension-type headache is also not completely clarified and, based on clinical trials, it is

believed that peripheral mechanisms would have a more important role in episodic tension headache, while in chronic tension headache, central mechanisms of occurrence would be primary. However, it is believed that peripheral mechanisms would be crucial for the onset of tension-type headache, while central mechanisms would be more important for its continuation[13]. It is considered that due to certain conditions, painful stimuli from myofascial pericranial tissue may be prolonged or more intense than usual.

In this research, about 50% of subjects were 30 to 50 years old with the median of approximately 44 years, which corresponds to the data presented earlier. Quantitative and qualitative characteristics of headaches change with advancing age, so the representative quality of the study was extremely important. The findings showed that the study included 63 women and 27 men (2.3:1 ratio), which speaks of the greater number of women with pain syndromes. Many epidemiological studies showed higher prevalence of pain syndromes in women than in men, as well as the fact that women perceive pain for longer periods than men[21, 22].

Migraine diagnosis is made based on the clinical picture that must meet the criteria of the International Headache Society[23]. When choosing subjects for the study, apart from diagnostic examination, which excluded secondary headaches, symptoms were evaluated and subjects were included in the testing based on clinical diagnosis and in accordance with the aforementioned criteria. The sensation of pain, and consequently certain types of primary headaches, is also influenced by different socioeconomic and cultural factors besides gender, including ethnic and religious affiliation, economic status, profession, employment status, marital status, degree of education, lifestyle.

Blink reflex is an objective neurophysiological method for determining the status of trigeminal system, facial nerve and lateral part of medulla oblongata. Blink reflex testing in migraine patients and control group without migraine presented uncertain results. Some research identified a significant difference in R1 latencies: statistically considerably shorter[14] or longer[24] in the group of migraine patients. However, since it is considered that spinal trigeminal nucleus plays a part in migraine pathophysiology, R2 and R2' latencies that are anatomically connected to spinal trigeminal nucleus are more important[14]. In some research no significant difference was found in these late blink reflex responses, while in others insignificant shortening of R2 latency was confirmed in the group of patients suffering from migraine without aura[14]. The abnormal latency of late R2 response could be the result of the sensitisation of brainstem interneuron, which could be involved in the pathophysiology of trigeminovascular disorder in migraine.

Interictal testing of blink reflex habituation in migraine patients determined that it is most affected in healthy individuals with family history of migraine, then in patients suffering from migraine without aura in which it is inversely proportional to the frequency of attacks and it is probably a consequence of trigeminal sensitization[25]. Another research established that blink reflex habituation in chronic migraine patients was significantly reduced between attacks and that there is a correlation between decreased habituation and increased frequency of attacks[15].

The research, which tested blink reflex in chronic tension-type headache, mostly showed regular R1, R2 and R2' latencies which would point to intact interneurons of the trigeminal and facial nerve, as well as the reflex arc of blink reflex[16,26]. However, some authors still don't rule out the role of a central mechanism in the pathophysiology of episodic tension-type headache[17, 27].

This research proved that in the group of patients suffering from headache, out of the total number of 60 subjects, 58.3% had a modified blink reflex, while in the control group of a total of 30 subjects, only 20% had a modified blink reflex. Results show that in subjects with severe headache the frequency of modified blink reflex is significantly higher than in control group subjects. Pathological blink reflex is present in 58.3% of patients suffering from headache and in only 20% of individuals without headache (Table 3). Results also showed that there is a considerable statistical correlation between patients with severe headache and pathological blink reflex finding for both sexes viewed together (χ^2 = 10.354; P= 0.001). Persons with pathological blink reflex finding have a 5.6 times higher risk for the occurrence of headache than individuals with normal blink reflex.

Research showed that pathological blink reflex was present in 52.3% of females with headaches, and in 75% of cases of males with headaches (Figure 2 and Figure 3). Hence, the relative risk for headache occurrence in females with pathological blink reflex is 4.1, while males with pathological blink reflex have a 13.5 higher risk for headache occurrence than those with normal blink reflex (Table 5). The existence of a strong correlation between pathological blink reflex and the occurrence of headaches in females (Table 4) and males (Table 5) was established.

A great role in pain evaluation is certainly played by blink reflex since it enables us to assess the function of trigeminal complex in suffering patients in a non-invasive and affordable way compared to the results of other diagnostic tests and pain assessment scales[14, 15, 24, 25]. In this research, as well as many earlier ones, blink reflex proved effective in demonstrating peripheral and central dysfunction of trigeminal complex.

In future research, it would be interesting to correlate blink reflex assessment and clinical picture with graphic functional methods in order to connect the potential pathomorphological substrate with the functional deficit depicted on blink reflex[26].

Based on the results of these studies it can be concluded that in the evaluation of patients with primary headache types blink reflex plays a large part and it can help objectivize the suffering. The results obtained in this study confirmed the results of some earlier studies describing the activation of trigeminal complex in primary types of headache.

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UTJECAJ POREMEĆAJA FUNKCIJE TRIGEMINALNOG ŽIVCA U RAZLIČITIM OBLICIMA GLAVOBOLJE

S A Ž E T A K

Glavobolja je vrlo česta bolest modernog društva koja dovodi do ozbiljnog smanjenja općih i radnih životnih aktivnosti u pacijenata za vrijeme njenog trajanja sa značajnim utjecajem na kvalitetu života. Refleks treptaja je objektivna neurofiziološka metoda za utvrđivanje statusa trigeminalnog sustava, facijalnog živca i lateralnog dijela produžene moždine. Cilj ovog istraživanja je da se pomoću funkcijskih elektrofizioloških i radioloških metoda prikaza pokuša dokazati povezanost disfunkcije trigeminalnog živca u različitim vrstama glavobolja. U skupini bolesnika sa glavoboljom ima 60 ispitanika, 44 žene i 16 muškaraca. Kontrolna skupina sastoji se od 30 zdravih ispitanika koji ne boluju od glavobolje. Starosna dob kompletnog uzorka je od 20 do 76 godina sa prosječnom dobi ispitanika od 42,81 godina. Za testiranje funkcije trigeminalnog živca, kod bolesnika koji imaju glavobolju i u ispitanika kontrolne skupine, korištena je standardna metoda koju je opisao Kimura sa suradnicima. Patološki nalaz refleksa treptaja utvrđen u 58,3 % pacijenata s glavoboljama, dok je u kontrolnoj skupini osoba bez glavobolje nađen u svega 20 % slučajeva. Izračunavanjem Yatesovog korigiranog χ^2 testa utvrđeno da postoji značajna povezanost nalaza patološkog refleksa treptaja i pojave glavobolje ($\chi^2 = 10,354$; $P = 0,001$). Osobe s glavoboljama imaju uredan refleks treptaja u 41,7 %, a osobe kontrolne skupine imaju ga u 80 % slučajeva. Žene s patološkim nalazom refleksa treptaja imaju 4,1 puta veći rizik za pojavu glavobolje od žena s normalnim nalazom refleksa treptaja (OR = 4,107; 95 % CI = 1,036 – 17,565). Muškarci s patološkim nalazom refleksa treptaja imaju 13,5 puta veći rizik za pojavu glavobolje od muškaraca s normalnim nalazom refleksa treptaja (OR = 13,500; 95% CI = 1,555 – 153,646). Postoji jaka povezanost između nalaza patološkog refleksa treptaja i pojavnosti glavobolje, neovisno o dobi i spolu pacijenata, što ukazuje da postoji statistički značajna povezanost između pojavnosti glavobolja i poremećaja funkcije trigeminalnog živca. Testiranje refleksa treptaja može biti od pomoći pri detekciji bolesnika sa povećanim rizikom od glavobolje.