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Variability of the blink reflex in patients with migraine

Zmienność odruchu mrugania u chorych na migrenę

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Abstract

Background and purpose: Sensitization of brainstem trigeminal nuclei and activation of the trigeminovascular system are thought to play an important role in migraine. The blink reflex has become a valuable tool for investigating trigeminal nerve function. The aim of the study was to assess the differences in electrophysiological examinations of the trigeminal nerve (blink reflex) in a group of patients with migraine in comparison with a healthy control group.

Material and methods: The examination was conducted among 58 patients. Patients were diagnosed in the Polyclinic or hospitalized in the Department of Neurology of Warsaw Medical University in Bielański Hospital. The study group included 29 patients suffering from migraine (diagnosed according to the International Classification of Headache Disorders, 2nd edition) and 29 patients without headaches served as controls. All patients underwent neurological examination and magnetic resonance imaging to identify organic disorders. The blink reflex was tested among all patients in accordance with electrophysiological laboratory standards.

Results: The latency of the R1 response was significantly shorter among patients with migraine. The latency of R2 and R2' responses was similar in patients and controls. A significant inverse correlation was observed between latency of R2 and R2' responses and frequency of migraine attacks.

Conclusions: The inverse correlation between the frequency of attacks and the latency of R2 and R2' responses of the blink reflex confirms the abnormal eaxcitability induced by the high frequency of migraine attacks.

Key words: blink reflex, migraine, electrophysiological tests.

Streszczenie

Wstęp i cel pracy: W patofizjologii migreny istotną rolę odgrywają nadpobudliwość jądra rdzeniowego nerwu V i aktywacja układu trójdzielno-naczyniowego. Odruch mrugania pozostaje najbardziej wartościową metodą oceny funkcji nerwu trójdzielnego. Celem pracy jest ocena występowania różnic w badaniu odruchu mrugania u chorych na migrenę w porównaniu z grupą kontrolną osób bez bólów głowy.

Materiał i metody: Badanie przeprowadzono u 58 osób. Wszyscy pacjenci byli diagnozowani w ramach Przychodni Przyszpitalnej Szpitala Bielańskiego w Warszawie oraz Kliniki Neurologii II WL WUM. Do grupy badanej włączono 29 chorych na migrenę rozpoznaną zgodnie z Międzynarodową Klasyfikacją Bólów Głowy (wydanie II). Do grupy kontrolnej zakwalifikowano 29 osób, u których nie występowały bóle głowy. U wszystkich pacjentów przeprowadzono badanie neurologiczne oraz wykonano rezonans magnetyczny mózgu w celu wykluczenia zmian organicznych w ośrodkowym układzie nerwowym. Badania odruchu mrugania przeprowadzono w Pracowni Elektromiografii i Potencjałów Wywołanych Kliniki Neurologii II WL WUM w Szpitalu Bielańskim zgodnie z obowiązującymi standardami.

Wyniki: W grupie badanej latencja odpowiedzi R1 była istotnie krótsza w porównaniu z grupą kontrolną. Nie wykazano istotnych różnic pomiędzy latencjami odpowiedzi R2 i R2' w grupie badanej i kontrolnej. Ponadto wykazano istotne korelacje ujemne między wartością latencji odpowiedzi R2 i R2' oraz częstością napadów migreny.

Wnioski: Wykazana ujemna korelacja między częstością napadów i latencją odpowiedzi późnych może świadczyć o nadmiernej pobudliwości jądra rdzeniowego nerwu trójdzielnego indukowanej zwiększoną częstością napadów migreny.

Słowa kluczowe: odruch mrugania, migrena, badania elektrofizjologiczne.

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Introduction

Cerebral vessels, the trigeminal nerve and its brain stem nuclei, as well as some cortical centers are all involved in the pathogenesis of migraine attack. Pain-sensitive cranial structures (large vessels, pia mater vessels, dura mater and venous sinuses) are innervated mostly by the first branch of the trigeminal nerve. In case of trigemino-vascular system activation, impulses are transmitted centrally to the spinal trigeminal nucleus and then they reach the cerebral cortex via the thalamus. Apart from that central transmission of pain, neurotransmitters are also released from the trigeminal nerve endings located around the vessels. Sensory fiber endings of the trigeminal nerve release calcitonin gene-related peptide (CGRP), P substance (SP), neurokinin A, and nitric oxide (NO). All those compounds are involved in the neurogenic inflammation that may activate nociceptive fibers, leading to the central transmission of the pain impulses. According to the predominant recent views, excessive discharges within the spinal nucleus of the trigeminal nerve are considered the primary cause of headache in migraine. As the result of that stimulation, neurogenic inflammation ensues, as well as secondary vascular changes related to the release of inflammatory mediators [1-5].

Electrophysiological studies, including blink reflex studies, remain the most valuable method of assessment of trigeminal nerve function. The blink reflex constitutes bilateral electromyographic reaction of the orbicularis oculi muscle in response to unilateral electrical stimulation of the supraorbital nerve, which is a branch of the trigeminal nerve. The blink reflex consists of two responses: an early response (R1) which is exclusively ipsilateral to the side of stimulation, and a late bilateral response, which is ipsilateral (R2) or contralateral (R2') to the side of stimulation. The reflex arc of R1 passes through the pons: stimulation from sensory fibers is transmitted to the sensory nucleus of the trigeminal nerve in the pons and then reaches the motor neuron of cranial nerve VII via the short interneuronal pathway. In the case of R2 and R2', the reflex arc passes through the medulla oblongata: stimulation from sensory fibers is transmitted to the nucleus tractus spinalis of the trigeminal nerve, and then travels through the polysynaptic uncrossed (R2) or crossed (R2') neuronal pathway of the reticular formation to the motor nucleus of the facial nerve – the ipsilateral (R2) or contralateral (R2') one [6,7].

The aim of the study was to assess the differences in blink reflex observations (including R1, R2, and R2' responses) between a group of patients with migraine and healthy controls without headaches.

Material and methods

This study involved 58 subjects (48 women and 10 men). The study group included 29 patients (24 women and 5 men) aged between 19 and 50 years (mean: 34 years; standard deviation: 8.8) who were diagnosed with migraine according to the International Classification of Headache Disorders, 2nd edition (ICHD-2) and were subjected to a medical interview, neurological examination, magnetic resonance of the head and basic biochemical studies. The majority of patients (62%) were diagnosed with migraine without aura, while the remaining 38% had migraine with visual aura. All patients were diagnosed in the outpatient clinic of the Bielański Hospital in Warsaw and in the Department of Neurology within the Second Faculty of Medicine, Medical University of Warsaw, between January 2009 and July 2011. The control group consisted of 29 subjects (24 women and 5 men; mean age: 31 years; standard deviation: 8.5, range: 22-53 years) who had no headaches. The study and control group did not differ regarding sex or age.

Blink reflex testing was performed in the Laboratory of Electromyography and Evoked Potentials within the Department of Neurology, Second Faculty of Medicine, Medical University of Warsaw at the Bielański Hospital, according to the standard methods. All tests were performed between migraine attacks.

The blink reflex consists of two responses – an early one, i.e. R1, which is unilateral and ipsilateral to the side of stimulation and appears about 10 ms after the stimulation, as well as late responses that appear about 30-40 ms after the stimulation: R2, which is bilateral and ipsilateral to the side of the stimulation, and R2', which is bilateral and contralateral to the side of the stimulation [6,8-10].

During blink reflex testing, patients were lying down. Recording plate electrodes were mounted bilaterally over the lateral part of the orbicularis oculi muscle at the lower eyelid. Reference electrodes were positioned more medially, at the region of the nasal base. Supraorbital nerve stimulation was performed at the site of its exit from the supraorbital foramen. A single pulse (5-10 mA) lasting 0.1 ms was delivered with unequal intervals to avoid habituation. Four to six stimulations on both sides were performed in each subject. The following parameters were calculated: mean latency, duration of R1, R2 and R2' response, as well as the diffe-

rence of their latencies between sides. The particular parameters were compared between the study and control group [6,8-10].

The protocol of the study was approved by the bioethical committee affiliated with the Medical University of Warsaw. All participants were informed about the aim of the study and the methods used and provided written consent to participate.

Statistical analysis was performed using SAS 9.2 software. Quantitative variables were characterized with typical descriptive characteristics: means, standard deviations, medians and ranges. Wilcoxon test for independent samples was used to compare quantitative variables between two groups due to the skewed distribution of the variables. Wilcoxon test for paired samples was used to compare blink reflex parameters between the right and the left side. Correlations between qualitative variables were assessed with Spearman rank correlation coefficient (due to the skewed distribution of the variables). A p-value of < 0.05 was considered statistically significant.

Results

All parameters of the tests performed in the study and control group were within the normal range established in the Laboratory of Electromyography and Evoked Potentials within the Department of Neurology, Second Faculty of Medicine, Medical University of Warsaw at the Bielański Hospital.

R1 latencies differed significantly between the study and control group ($p < 0.05$, Wilcoxon test). No difference was found in R2 or R2' latencies between the study and control group (Wilcoxon test). No difference was noted in particular parameters assessed in blink reflex testing regarding the side of the stimulation (right or left) (Wilcoxon test). The detailed results as well as their comparison are provided in Table 1.

Correlations (Spearman rank correlation coefficients) were tested between parameters of the blink reflex and the frequency of headaches in the study group. An inverse correlation was noted between R2 latency and frequency of migraine attacks ($r = –0.42, p = 0.02$) as well as between R2 latency and the number of days with migraine headache within the last four weeks ($r = –0.61$, $p = 0.0004$). Similar correlations ($r = –0.33, p = 0.07$, and $r = –0.55, p = 0.002$, respectively) were noted for R2' latency.

When subgroups of migraineurs with or without aura were compared, R2 and R2' latencies were shorter in patients with migraine without aura ($p < 0.05$, Wilcoxon test). The detailed results as well as their comparison between patients with migraine with or without aura are shown in Table 2.

While the differences between R2 and R2' were found, patients with migraine without aura had higher frequency of migraine attacks (Fig. 1). Results obtained in patients with migraine without aura probably affected the revelation of the above-mentioned correlation between R2 latency and the frequency of migraine attacks but did not affect the statistical significance as an absolute value.

Discussion

The study reported here revealed significant differences between patients and controls regarding R1 latency (it was shorter in patients with migraine than in con-

Table 1. Comparison of blink reflex parameters between patients with migraine and controls*

Latencies [ms]; median (range)	Study group (n = 29)	Controls (n = 29)	P-value
R1 – left	9.6 (7.9-11.1)	10 (8.4-11.3)	0.0460
R1 – right	9.2 (7.6-11.5)	10 (8.6-12.3)	0.0379
R2 – left	28.9 (21.7-38.7)	29.1 (24.7-33.5)	0.6097
R2 – right	28.7 (21.4-35.8)	28.8 (23.5-34.9)	0.5619
R2' – left	28.9 (22.3-38.5)	28.9 (24.1-33.8)	0.5776
R2' – right	28.6 (21.1-36.0)	28.6 (23.7-35.1)	0.5936

**Data presented as median (range)*

Table 2. Comparison of R2 and R2′ responses of blink reflex between migrainous patients with or without aura*

Latencies [ms]; median (range)	Patients with migraine without aura (n = 18)	Patients with migraine with aura (n = 11)	P-value
R2 – left	28 (21.7-30.1)	30.7 (25.1-38.7)	0.0436
R2 – right	27.4 (21.4-32.6)	30 (27.8-35.8)	0.0033
R2' – left	28 (22.3-30.1)	29.6 (24.9-38.5)	0.0693
R2' – right	27.4 (21.1-32.7)	29.5 (28-36)	0.0076

**Data presented as median (range)*

trols). Perhaps patients with migraine tend to activate the interneurons in the pons faster than controls and that is why the conduction is faster in those subjects. It is the spinal trigeminal nucleus, however, that plays the most important role in development of a migraine attack – according to one of the theories dealing with migraine pathophysiology, this nucleus exhibits increased activation during a migraine attack. The spinal trigeminal nucleus is connected with the thalamus, reticular formation and, indirectly, with cortical centers involved in pain perception. Late responses of the blink reflex (R2 and R2') are anatomically related to the spinal trigeminal nucleus [1,6,11]. Our study did not reveal, however, any significant differences between patients and controls regarding R2 and R2' latencies (median R2 latency was non-significantly shorter in patients with migraine).

Avramidis *et al*. [12] assessed blink reflex parameters in migraineurs during and between attacks. They did not find any difference in R2 and R2' latencies among migraineurs during and between attacks or in controls without headaches. Also, De Tomasso *et al*. [13] did not find any significant differences in R2 and R2' latencies among patients during a migraine attack, after the ingestion of triptan and in controls. Aktekin *et al.* [14] did not find any differences in those latencies among patients with migraine, patients with tension-type headache and controls. De Marinis *et al.* [15] assessed the blink reflex in patients with chronic migraine and did not reveal any differences in latencies or amplitudes of R1 and R2 between patients (during and between attacks) and controls (without headaches). Similar conclusions were drawn in several other studies [16].

On the other hand, Di Clemente *et al.* [17] reported in 2005 the results of studies on the blink reflex and visual evoked potentials in patients with migraine without aura which showed that, similarly to the present study, R2 latency was insignificantly shorter among patients with migraine without aura when compared to controls [17]. Our results and the vast majority of other studies

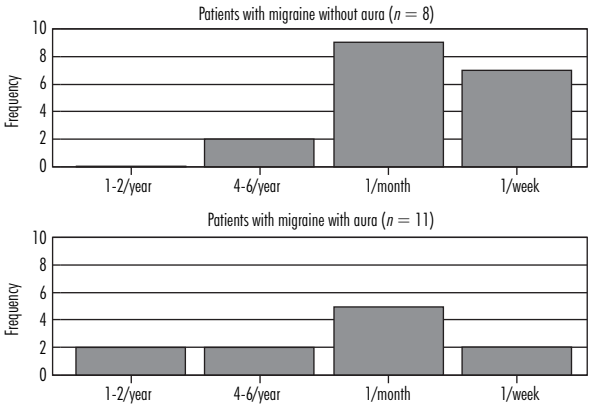

Fig. 1. Frequency of migraine attacks

confirm that R2 and R2' latencies of the blink reflex do not change in patients with migraine. At most, it might be concluded that there is a trend towards a shorter R2 latency in patients with migraine, which was shown in our study and in the study performed by Di Clemente *et al.* Abnormal latency of the late R2 response in the blink reflex might result from sensitization of the brainstem interneurons, which is probably the reason for the trigemino-vascular system disorder in patients with migraine. Perhaps the replication of the study in a much larger sample might confirm those suggestions.

We have also shown that inverse correlations exist among R2 or R2' latencies and the frequency of migraine attacks or the number of days with migrainous headache within the 4 weeks preceding the study. The association between frequency of migraine attacks and shortening of latencies within late responses may point to excessive activation of the spinal trigeminal nucleus and interneurons of the reticular formation induced by the increased frequency of migraine attacks. It is the increased frequency of migraine attacks that probably leads to the increased activation of interneurons and, finally, trigeminal nerve neurons as well as multisynaptic connections within the reticular formation of the brainstem.

Available studies showed the shortening of R2 latency after exposure to compounds provoking a migraine attack. In 2009, Di Clemente *et al.* [18] studied blink reflex parameters before nitroglycerine intake, as well as at one and four hours after this intake in healthy volunteers. Shorter R2 latency was registered after nitroglycerine, but not after placebo. It was concluded that sublingual administration of nitroglycerine provoking a migraine attack induces changes in the blink reflex among healthy volunteers.

Conclusions

1. Assessment of the blink reflex may reveal subtle neurophysiological alterations in patients with migraine, especially those related to the R2 response. Further studies are required to explain the nature of those changes and possible factors affecting those processes.
2. The association between frequency of migraine headaches and the shortening of the late responses might suggest excessive activation of the spinal trigeminal nucleus and interneurons of the reticular formation, induced by the increased frequency of migraine attacks.

Disclosure

Authors report no conflict of interest.

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