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Blink Reflex study in Patients with Migraine

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Abstract

Background The pathogenesis of migraine is thought to include activation of the trigeminovascular system. The blink reflex (BR) test is a well-known method of studying the trigeminal system.

Objective To look into the differences in BR response in migraine patients using the standard approach and to compare the results with matched control subjects, looking for a possible difference in BR ictally and interictally, and clarify whether migraineurs with aura differ from those without aura.

Methods A case-control study of 80 subjects; 40 patients were diagnosed with migraine, with or without aura, and 40 matched healthy volunteers. Disease duration ranges from 2 to 82 months. Both groups were submitted to medical history, clinical neurological examination, and binocular BR study of both eyes.

Results BR data were not different between male and female patients. Right cR2 latency and left iR2 were prolonged in the migraineurs group patients. Right iR2 and cR2 latencies recorded interictally were longer than those obtained ictally. No difference was observed between those with and without aura. The pain location side is not associated with the stimulation side.

Conclusion Patients suffering from episodic migraine may have altered interneuronal brainstem circuits. BR data would not change whether migraine was with or without aura. Interictal changes in BR suggest trigeminovascular dysfunction in migraineurs patients is not a transient phenomenon.

Keywords Migraine, Blink Reflex

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List of abbreviations: BR = Blink reflex

Introduction

It is widely recognized that migraine implicates activation and sensitization of trigeminovascular pathways, as well as trigeminal nuclei in the brain stem, which play an important role in its pathophysiology [1,2].

It has been proposed that migraine may be considered a brain state of altered excitability (overactive nociceptive and antinociceptive systems) both ictally and interictally [3,4]. In chronic migraine, studies have found a loss of inhibition in pain transmission regulation and an anomaly in cortical pain control [5,6].

The blink reflex (BR) is an electrophysiological test that is achieved by electrically stimulating the supraorbital nerve and is used to evaluate the trigeminovascular system [7].

The ocular branch of the trigeminal nerve serves as an afferent conduit for BR, whereas the facial nerve serves as an efferent pathway [8,9]. Upon stimulation, two responses are recorded; an early ipsilateral (R1) response with an onset latency of 9-12 ms designated, and two late bilateral ipsi- and contralateral responses with a latency of 25-35 ms designated iR2 and cR2, respectively [10].

According to research, the R2 component is influenced by segmental and suprasegmental

pathways. As a result, R2 recordings can be used to examine the excitability of brainstem reticular formation and corticoreticular pathways. Furthermore, changes in R2 latency are caused by aberrant synaptic transmission in the brainstem and interneuronal excitability; thus, changes in R2 latency have been largely related to changes in the control of higher central structures [9,11].

The purpose of this study was to look into the differences in BR response in migraine patients using the standard approach and to compare the results with matched control subjects, looking for a possible difference in BR ictally and interictally, and clarify whether migraineurs with aura differ from those without aura.

Methods

This is case-control research that was conducted at the Neurophysiology Department of Al-Imamein Al-Kadhimein Medical City in Baghdad from October 2019 to September 2020. The Iraqi Board of Medical Specialization approved the study (order no. 931; date: 1/3/2020). All the participants were informed about the technique and the aim of the study and informed consent was obtained from them.

Subjects

There were seventy-seven subjects investigated. According to the International Classification of Headache Disorders, forty individuals (28 females and 10 men) were diagnosed with a migraine, with or without aura [12]. The age range was 22 to 54 years (35.5±7.82 years).

Patients who had received prophylactic treatment within the previous 3 months, had a disease that could affect electrophysiological examination or involved the trigeminal or facial nerve, had a structural lesion detected on cranial images, had headaches other than migraine, or were younger than 18 or older than 60 years old were excluded from the study.

Another 39 age- and sex-matched healthy subjects comprised of 25 females and 15 males served as the control group.

Methods

History and clinical examination

After a brief medical history was taken from each patient, data on gender, type of migraine (with or without aura), the time interval between examination and onset of attack (during, within, or 72 hours after onset of the attack), associated and relieving symptoms, frequency, and location of the attack were recorded by a senior neurologist.

Electrophysiological assessments

Keypoint (Medtronic functional diagnosis A/S - DK-2740 Skovlunde, Denmark) EMG machine was used throughout the study. The room temperature was monitored between (25-28°C) during the test procedure and skin temperature between (32-34°C) was ensured using a skin thermometer.

Preston and Shapiro's approved approach was used to examine the BR [13]. Surface recording electrodes were placed over the inferior orbicularis oculi muscles bilaterally for recording the compound muscle action potential from the orbicularis oculi muscle. The active recording electrode is best placed below the eyes just lateral and inferior to the pupil mid–position. The corresponding reference electrode is placed lateral to the outer canthus bilaterally. A ground electrode was placed at the forehead or chin using a special paste and fixed with plaster, to ensure good electrical conduction.

A bipolar surface stimulating electrode was used to stimulate the supraorbital nerve ipsilaterally.

An electrical pulse with a duration of 100 ms is used. The current was increased in modest increments (3-5 mA) from zero mA to supramaximal stimulation, resulting in a response with the shortest latency and largest amplitude potential. A modest current can easily excite the nerve. Supramaximal

stimulation requires no more than 15 to 25 mA.

Because the BR is a multisynaptic route, there is some fluctuation between subsequent supraorbital nerve activations (particularly the R2), and at least 8-10 responses should be induced. Following the completion of one side's investigation, the contralateral side is stimulated and responses are recorded. The shortest latency of the Rl, iR2, and cR2 components was measured.

The electromyography settings were 5 or 10 ms per division sweep speed, the bandwidth of 10 Hz - 10 kHz, and the sensitivity of 100 or 200 µV per division.

Statistical analysis

All statistical analyses were performed using statistical package for social sciences (SPSS), version 25 (IBM Corporation, USA). Quantitative variables were presented as mean ± standard deviation (SD) and analyzed with an independent student t-test. Categorical variables were expressed as counts and percentages and analyzed with a chi-square test. For all tests, a significant level of statistics was considered when $p<0.05$.

Results

No significant difference was noticed in the age and gender between the migraine and control groups (Table 1).

Table 1. Demographic characteristics of migraine and control groups

Variables		Migraine group	Control group	P-value
Number of participants		38	39	
Age (years)	Mean±SD	35.5±7.82	39.31±9.77	0.065
Gender	Males, n (%) Females, n (%)	10 (26.3%) 28 (73.7%)	14 (35.8%) 25 (64.2%)	0.364
Disease duration (months)	Range	2-82		
Location	Unilateral, n (%) Bilateral, n (%)	17 (44.7%) 21 (55.3%)		
Type of migraine	With aura, n (%) Without aura, n (%)	17 (44.7%) 21 (55.3%)		

Table 2 illustrates the data of BR components in migraine and control groups. The right cR2 latency and the left iR2 were significantly prolonged in the patients versus the controls ($p = 0.024$; $p = 0.019$, respectively). Other BR components were not different between the two groups.

Dividing the patients with migraine into those with and without aura, none of the BR components were different between the two subgroups (Table 3).

Based on the time of the attack, patients were divided into two groups (Table 4). The right iR2 and cR2 latency values acquired from patients following 2 days of the headache attack were substantially longer than those obtained from patients during the headache attack ($p = 0.002$; $p < 0.001$, respectively).

Table 2. Comparison of blink reflex latency values in migraine and control groups

Variables		Migraine group N=38 Mean±SD	Control group N=39 Mean±SD	P-value
iR1 latency (ms)	Right	10.48±1.66	9.71±2.76	0.144
	Left	10.43±2.84	9.55±1.93	0.116
R2 latency (ms)	Right iR2	33.25±6.36	33.31±5.02	0.969
	Right cR2	35.53±6.26	32.27±6.19	0.024
	Left iR2	36.73±7.21	33.13±5.81	0.019
	Left cR2	36.1±6.77	36.33±7.31	0.887

R1: Early component; iR2: Ipsilateral late component; cR2: Contralateral late component; SD: Standard deviation

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

Variables		Migraine without aura N=17 Mean±SD	Migraine with aura N=21 Mean±SD	P-value
iR1 latency (ms)	Right	10.75±1.31	10.14±2.0	0.269
	Left	11.14±3.14	9.54±2.18	0.085
R2 latency (ms)	Right iR2	33.7±6.1	32.7±6.82	0.637
	Right cR2	36.38±6.25	34.48±6.3	0.362
	Left iR2	33.22±5.3	33.02±6.56	0.918
	Left cR2	35.68±7.45	36.1±6.77	0.671

R1: Early component; iR2: Ipsilateral late component; cR2: Contralateral late component; SD: Standard deviation

Table 4. Comparison of blink reflex latency values according to the time passed between the start of the examination and the last attack

Variables		Ictal N=16 Mean±SD	The last 2 days N=22 Mean±SD	P-value
iR1 latency (ms)	Right	9.98±1.98	10.8±1.66	0.137
	Left	9.64±2.23	10.94±3.11	0.17
R2 latency (ms)	Right iR2	29.41±6.47	35.75±5.0	0.002
	Right cR2	30.72±5.06	38.67±4.85	<0.001
	Left iR2	31.55±6.78	34.42±4.82	0.090
	Left cR2	35.19±7.22	36.7±6.55	0.510

R1: Early component; iR2: Ipsilateral late component; cR2: Contralateral late component; SD: Standard deviation

Discussion

In this study, significantly longer right cR2 and left iR2 latencies were recorded in the migraineurs independent of stimulation. These changes could be the result of aberrant synaptic transmission in the brainstem and interneuronal excitability. This idea is

supported by neural networks mediated by the R2 component of BR, which include the trigeminal caudal nucleus, excitatory interneurons of the bulbopontine lateral reticular formation, and pontine facial nuclei innervating orbicularis oculi. Furthermore, because R2 response is controlled by segmental and suprasegmental mechanisms, it assesses the excitability of brainstem reticular formation and corticoreticular circuits [9,11].

Imaging investigations on migraine sufferers revealed increased brainstem activity, implying that the brainstem may be a migraine generator [14]. During ictal and interictal migraine headache attacks, these imaging tests revealed anomalies in the ascending and descending nociceptive pathways [15,16].

Several investigations comparing the latencies of R1, iR2, and cR2 waves in migraine sufferers and controls (Table 5) yielded diverse results. Unal et al. [17] discovered significantly longer R1 latency values on both the right and left sides, as well as both the left iR2i and cR2, in the migraine group compared to the control group in their investigation.

Patients who experienced an episode at the time of the research showed longer R1 and R2 latencies [17]. Their findings corroborate the trigeminovascular theory of migraine by pointing to abnormalities in the brainstem and trigeminovascular connections of migraine patients.

Table 5: Main published studies about the blink reflex in migraine

Authors	N	Diagnosis	Age Mean±SD	Timing of recording	Significant findings
Present study	38	21 MO, 17 MA	35.5±7.82	1-3 days after the attack	R2 latency prolongation
Avramidis et al. (2017) [21]	55			Ictal	Reduced R2 amplitude and area
Uygunoglu et al. (2017) [29]	20	6 MO, 14 CM	37.5±8.9	Within 48 h after the attack	No difference
Unal et al. (2016) [17]	40	31 MO, 9 MA	37.36±9.67	During the attack	R2 latency prolongation
Brooks and Fragoso (2013) [28]	160	CM	50.8±18.2	NA	No difference
Zduńska et al. (2013) [27]	29			NA	No difference
Yildirim et al. (2011) [18]	40	25 MO, 15 MA	30.85±8.03	Interictal	R2 latency prolongation
De Marinis et al. (2007) [11]	35	CM	37.0±6.0	>72 hours after the attack; <3 hours before the next attack	No difference
Sand et al. (2006) [26]	23	13 MO, 10 MA	33.9±12.5	NA	No difference
De Marinis et al. (2003) [25]	30	MO	33.0±8.0	>72 hours after the attack	No difference
de Tommaso et al. (2002) [5]	70	50 MO, 20 MA		during different cognitive situations	Altered cR2 amplitude and latency
Aktekin et al. (2001) [24]	34	24 MO, 10 MA	32.7±8.5	Interictal	No difference
Avramidis et al. (1998) [20]	19	MO	37.5	Ictal	Reduced R2 amplitude
Sand and Zwarts (1994) [23]	15	10 MO, 5 MA	19.0±12.0	NA	No difference
Bánk et al. (1992) [19]	43	33 MO, 10 MA	31.1±9.6	> 14 days after the attack	Prolonged R2 latency

MO = Migraine without aura; MA = Migraine with aura; CM = Chronic migraine

When a 40-migraineur group was compared to a control group, there was a statistically significant increase in bilateral R2 latencies [18]. They confirm that migraineurs have functionally defective brainstem and trigeminovascular connections, as evidenced by trigeminal system activation, sensitization of the brainstem trigeminal nucleus, aberrant synaptic transmission, and suppression of brainstem interneuron areas.

Furthermore, significantly prolonged R2 but similar R1 latencies in the migraine group were found in the patient group [19] harmonizing the results of this study. These data suggest that in migraine, the trigeminal afferent and/or polysynaptic pathways in the brainstem may be functionally changed.

Avramidis et al. [20,21] observed reduced R2 amplitude ictally and proposed that the brain stem interneuron part of the BR arc may be diffusely suppressed in migraine, with an abnormality in the R2 component only during the attack phase of migraine and that this dysfunction returned to normal thereafter. Other investigations have found that migraineurs have a lack of habituation to pain stimuli [11,22].

On the reverse, many studies found no difference between controls and migraineurs [11,23-29]. They believed BR to be a primitive reflex or relatively basic reflex that is not impaired unless there is considerable brainstem damage; others stated that this is proof that migraine-specific trigeminal dysfunction is a temporary disorder.This disparity in results was attributed to different methodologies utilized, differences in patient selection, latency recording time (ictal/interictal), a lower sample size, or incorrect designation of individuals as migraine sufferers. Furthermore, methodological discrepancies between research may cause disagreement when comparing the results. On the other hand, no single approach or gold standard is advised for BR research in migraine or other primary headaches.

When dividing patients according to the type of migraine, 55.3% were without aura and 44.7% with aura. Although the discrepancy is likely due to the limited sample size, studies show a decreased prevalence of migraine with aura compared to the most frequent migraine without aura [30].

In this study, no significant difference was noticed between migraineurs with and without aura regarding BR latencies. This is in harmony with the findings of other groups of researchers [17]. Meanwhile, the right R2 amplitude value was found significantly higher in the group with aura than without aura as noticed by another group [18].

While dividing the patients into two subgroups based on whether the testing is done ictally or intericately, the right iR2 and cR2 latencies were prolonged interictally than those obtained ictally. This shows that trigeminovascular dysfunction in migraine patients is not a transient phase. This finding was in harmony with the results of other researchers [18,19], but in contradiction to those of Unal et al. [17]. This situation may depend on the special selection of the patients.

This study, as well as other ictal and interictal investigations, looked into the relationship between the pain localization site and the recorded side of BR. There was no correlation discovered between the area of pain and the recorded side [11]. The current study's findings are most likely because BR measurements were taken while some of the patients were pain-free. However, another study showed a significant correlation between the symptomatic side and prolong R1 and R2i latency values during the ictal phase [17]. The latter authors interpret their findings as a result of trigeminal nucleus sensitization on the symptomatic side during an ictal phase. Another group of researchers found an increase in the area-under-the-curve of R2 on the affected side during migraine attacks [28].

In conclusions, patients suffering from episodic migraine may have altered interneuronal

brainstem circuits. BR data would not change whether migraine was with or without aura. Interictal changes in BR suggest trigeminovascular dysfunction in migraineurs patients is not a transient phenomenon.

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Author contribution

Both authors contributed directly to the creation of this paper and approved the final version that was submitted. The electrodiagnostic tests were performed by both authors. Likewise for the manuscript. Also, the study was conceptualized, designed, and interpreted by both authors. Similarly, the final manuscript has been read and approved by both authors.

Conflict of interest

The authors declare no conflict of interest.

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