The Event-related Potential P300 in Patients with Migraine

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ABSTRACT

Objective: Recording of event-related potentials by using oddball paradigm of auditory P300 has yielded conflicting results in migraine. The aim of this study was to demonstrate that migraine patients have reduced P300 amplitude and prolonged P300 latency, suggesting alterations of the cognitive-evaluative component. **Methods:** We recruited 29 migraine patients (24 females; median age 40 years) and 29 healthy age- and gender-matched participants. Participants were subjected to the same testing procedures of auditory P300 by discrimination the target auditory stimulus from the frequent stimulus, and analyzing P300 target/frequent stimulus amplitudes, and P300 target/frequent stimulus latencies. **Results:** Patients with migraine don't have prolonged P300 target stimulus latency, but have a longer P300 frequent stimulus latency for 17.5ms. Out of 29 participants with migraine 8 had pathological P300 target stimulus amplitude, and 19 had pathological P300 frequent stimulus amplitude. **Conclusion:** People with migraine have altered the P300 which indicates the presence of cognitive dysfunction in these patients and importance of early diagnosis and intervention to preventing any deterioration in cognitive functions.

Key words: migraine disorders, cognition, event-related potentials, P300.

1. INTRODUCTION

Migraine is a chronic neurovascular headache in which neural events result in the dilatation of blood vessels, which in turn causes pain and further nerve activation (1).

Data from several studies demonstrate that migraine is a risk factor for stroke, and that migraine is associated with an increased prevalence of clinically silent brain lesions, an increased risk for deep white matter lesions and subtle gray matter damage (2-6). The results of these studies suggest that individuals with migraine, due to these structural lesions, have impaired cognitive function (7).

Taking into account that migraine affects 10% of adults in occidental countries (8) and the results of study which show association between migraine and higher risk of dementia (9), it is clear that the relationship between cognitive decline and migraine present a significant public health interest.

Recording of event-related potentials (ERPs), because of its objectivity and noninvasive characteristics, presents one of the most useful tools in investigating neural substrates and cerebral regions involved in specific cognitive function. It implies recording of brain activity during a cognitive task.

Among the components of ERPs, the P300 is undoubtedly the most studied cerebral wave in evaluating cerebral information processing during the course of various neurological diseases because of its easy recording and reliability (10, 11).

The P300 develops if the subject is actively engaged in the task of detecting the targets. The task of the experimental subject is responding to the presence of target stimulus (12). Amplitude of the wave varies with the improbability of the targets and latency with the difficulty of discriminating the target stimulus from the standard stimuli. Typical peak latency in young adult subjects making a simple discrimination is 300±10 ms (13).

P300 latency reflects timing of mental processes and the increase of latency represents prolongation of the processing time. P300 amplitude has

been considered to be more closely related to the intensity of processing and amplitude reduction and abnormal topographic distribution reflect either a failure in the activation of some generators (frontal and parietal cortex, thalamus and temporo-mesial cortex) or a chronodispersion of the information processing (10, 11).

Due to the considerations presented, this study aimed to characterize the P300 in adults with migraine and normal hearing. We hypothesized that migraine patients have the P300 abnormalities, reduced P300 amplitude and a prolonged latency, suggesting alterations of the cognitive-evaluative component.

2. MATERIALS AND METHODS

The patients who attended Split University Hospital Center and who fulfilled the diagnostic criteria of migraine according to the International Classification of Headache Disorder (2nd edition) (14), were initially considered for the present study. The data were collected in the period from January 2014 to June 2014. Patients were drug-free for at least 72 h. We excluded those below 18 and above 70 years of age. All patients underwent clinical neurological examinations by a neurologist. Clinical data included age, gender, the duration of the migraine history, the average number of headaches, taking medications for migraine, and dominant hand (Table 1).

Informed consent was obtained from all individual participants included in the study. Ethics committee of University Hospital Split approved the implementation of the research and the use of medical records.

For the research group, the inclusion criteria were medical diagnosis of migraine, normal hearing thresholds and normal neurological development. The exclusion criteria were: general neurological or psychiatric disease, a history of drug abuse or dependency, including alcohol consumption, a history of other types of headache or mixed headache types, complaints of tinnitus, impaired auditory function, anemia, ulcerative colitis, liver and kidney disease.

Participants in the control group were randomly selected and with no history of headache attacks or drug/alcohol abuse. The inclusion criteria for the control group were: history of normal neurological development, normal hearing thresholds, absence of psychiatric diagnoses, no complaints of tinnitus, and no auditory processing disorders.

Both groups were subjected to the same procedure testing auditory P300. The examination was conducted on the device Medelec Synergy-Oxford Instruments (San Francisco, USA).

Recording was carried out according to standard procedure (15). Each patient's hearing threshold was determined. For conducting the tests we used sound stimuli intensity 70 dB above the hearing threshold. The potentials were recorded using Ag/AgCl surface electrodes placed according to the international 10–20 system at the point Fz, Cz, Pz, C3, C4 and mastoid (16). The P300 was obtained using the auditory oddball paradigm, in which two stimuli (frequent and target) were presented in random order. The ratio of stimuli was 1:4. The participants were required to discriminate the infrequent stimulus (target stimulus) from the frequent stimulus by noting the occurrence of the target by mental counting. Two consecutive, equal records to each respondent to assess the reproducibility and depletion of neurons were performed.

After the examination the length of P300 target/frequent stimulus latency and P300 target/frequent stimulus amplitude were estimated.

P300 targeted/frequent stimulus latencies were expressed numerically within reference value 300 ± 10 ms, and P300 targeted/frequent stimulus amplitudes were expressed as normal (5.6±0.1 μV), lower (5.3±0.1 μV), low (5.0±0.1 μV) and very low (4.6±0.2 μV).

Statistica 7.0 (StatSoft, Inc., Tulsa, USA) was used for the statistical analysis of the clinical data. Quantitative data were presented as mean ± standard deviation or median. Clinical data were statistically analyzed using t-test, $\chi 2$ test, Fisher's exact test, or Pearson correlation coefficient.

3. RESULTS

Twenty nine participants with migraine were recruited (median age 40 years, range between 20 to 66 years; 24 females) and 29 healthy age- and gender-matched participants (median age 38 years, range between 20 to 66 years; 24 females).

	Participants with migraine n=29	
Medications	Analgetics	18 (62)
Triptans	5 (17)	
Analgetics + Triptans	6 (21)	
Dominant hand	Right-handed	27 (93)
	Left-handed	2 (7)
Average number of headaches	1-2 times per year	1 (3,5)
	3-4 times per year	1 (3,5)
	1-2 times per month	12 (41)
	3-4 times per month	7 (24)
	More than 4 times per month	8 (28)
Duration of the migraine history (years)		10 (1-50)

Table 1. Review of number (%) of participants with migraine according to the investigated qualitative variables or median (min-max) of quantitative variables.

The duration of the migraine history less than 4 years had 25% patients, 25% had between 4 and 10 years, 25% between 10 and 15 years, and 25% of them between 15 and 50 years.

Because of the small number of individuals in each groups we grouped lower, low and very low P300 target/frequent stimulus amplitudes in one category named reduced P300 target/ frequent stimulus amplitude.

There was a statistically significant difference between the research and the control group according to the P300 target stimulus amplitude. There were 4 times more participants with migraine than participants in the control group in category reduced P300 target stimulus amplitude, with a significance level of 92% ($\chi 2$=3.0; P=0.082, Table 2).

Participants with normal P300 frequent stimulus amplitude and those with reduced P300 frequent stimulus amplitude were compared. There were 9.5 times more participants with migraine than participants in the control group in category of reduced P300 frequent stimulus amplitude, and 2.7 times more participants in the control group than in the group of participants with migraine in category of normal

		All participants n=58	Participants with migraine n=29	Control group n=29	P
P300 target stimulus amplitude	Normal	48 (83)	21 (73)	27 (93)	
	Lower	9 (15)	7 (24)	2 (7)	0.082
	Low	1 (2)	1 (3)	0	
	Very low	0	0	0	
P300 frequent stimulus amplitude	Normal	37 (64)	10 (35)	27 (93)	
	Lower	7 (12)	5 (17)	2 (7)	<0.001
	Low	9 (15)	9 (31)	0	
	Very low	5 (9)	5 (17)	0	
P300 target stimulus latency (ms)			299.8±11.4 300 (273-327)	300±2.9 300 (295-306)	0.802
P300 frequent stimulus latency (ms)			314.5±14.4 316 (276-345)	297±17 300 (209-305)	<0.001

Table 2. Review of number (%) of participants according to the P300 target stimulus amplitude and P300 frequent stimulus amplitude and mean (standard deviation) and median (min-max) of P300 target stimulus latency and P300 frequent stimulus latency in relation to the test groups.

P300 frequent stimulus amplitude ($\chi 2$ with Yates correction =19.1; $P<0.001$, Table 2).

There was no statistically significant difference in the value of P300 target stimulus latency between the participants with migraine and the control group (t=0.252; $P=0.802$, Table 2).

Mean of P300 frequent stimulus latency was 17.5 ms longer in the group of participants with migraine compared to the control group (t=4.2; $P<0.001$, Table 2).

Seventy two percent of all participants with migraine had some changes of the P300 that suggest possible disturbances of cognitive processing.

There was no statistically significant correlation between the duration of the migraine history and P300 target stimulus latency (Pearson correlation coefficient r=0.11; $P=0.568$), neither between the duration of the migraine history and P300 frequent stimulus latency (Pearson correlation coefficient r=0.0007; $P=0.997$).

There was no statistically significant difference in the distribution of participants according to the average number of headaches in relation to the duration of migraine history ($P=1$, Fisher's exact test, Table 3).

		Duration of the migraine history		P
		≤10 years	>10 years	
Average number of headaches	2 times per month and rarely	8 (28)	6 (20)	1*
	3 times per month and more	8 (28)	7 (24)	
P300 target stimulus amplitude	Normal	13 (45)	8 (28)	0.405*
	Reduced	3 (10)	5 (17)	
P300 frequent stimulus amplitude	Normal	5 (17)	5 (17)	0.714*
	Reduced	11 (38)	8 (28)	
P300 target stimulus latency		299.6±10.5 299.5 (274-315)	300±13 303 (273-327)	0.904**
P300 frequent stimulus latency		315±13.6 312.5 (295-335)	314±16 317 (276-345)	0.835**

Table 3. Rewiev of number (%) of participants with migraine according to the average number of headaches, P300 target and frequent stimulus amplitudes, and median (min-max) of P300 target and frequent stimulus latencies in relation to the duration of the migraine history (≤10 years; >10 years).b, *Fisher´s exact test, **t-test

There was no statistically significant difference in the distribution of participants according to the P300 target stimulus amplitude ($P=0.405$, Fisher's exact test) and P300 frequent stimulus amplitude ($P=0.714$, Fisher's exact test) in relation to the duration of migraine history (Table 3).

We didn't demonstrate statistically significant difference in P300 target stimulus latency (t=0.122, $P=0.904$) or P300 frequent stimulus latency (t=0.210, $P=0.835$) in participants with migraine in relation to duration of migraine history (≤10 years; >10 years) (Table 3).

4. DISCUSSION

Several studies have linked migraine with mild changes in several cognitive domains (17, 18). Neurophysiological tools, such as the P300, have provided valuable information in evaluating cognitive abnormality and pathological changes of the P300 (12). Two principal neurophysiological markers have been considered as an objective index of cognitive processing: latency P300 and amplitude P300 (10).

In this study, auditory oddball paradigm was used, to compare cognitive ERP responses (the P300-wave) between patients with migraine and control subjects. We have shown that patients with migraine don't have prolonged P300 target stimulus latency, but have a longer P300 frequent stimulus latency for 17.5 ms. Out of 29 participants with migraine 8 had pathological P300 target stimulus amplitude, and 19 had pathological P300 frequent stimulus amplitude. According to the above results, we found that 21 participants with migraine have some possible disturbances of cognitive processing.

According to the mentioned facts it could be suggested that migraine sufferers have prolonged frequent stimulus latency of P300 which could represents a prolonged cognitive processing time. On the other hand, amplitude reduction reflects either a failure in the activation of some cerebral generators. Recent studies revealed that the reduction of the P300 amplitude was also evident when using the passive oddball paradigm (19).

A possible explanation of the pattern of abnormalities in migraine sufferers could be due to the main pathophysiological feature of the disease that is the neurovascular disorder. The neurovascular disorders directly influence neural activity and since the ERPs come from complex interactions between cortical and subcortical neural circuits, they cause the disruption of network connections giving origin to conduction slowing or conduction block and cause cognitive processing disturbances. On the other hand the P300 abnormalities can be explained by the fact that some cognitive functions can be modulated by head pain experience. Hence recurrent pain might have produced a constant abnormality of brain and cognitive processing disturbances (20, 21).

Several authors have described the P300 latency and amplitude as neurophysiological markers of cognitive functioning in migraine. Some studies show that the amplitudes of P300 were significantly decreased in patients with migraine in comparison with the healthy controls, but the latencies of P300 didn't show any significant effects (22, 23). Other results show significant elongation of latencies and an increment of P300 amplitudes in the group of migraineurs during headache attacks (24), while some results show that migraine patients had reduced P300 amplitudes and longer P300 latencies (25) what is concordant with our findings. Results are contradictory but we can't compare them completely because some changes are demonstrated in patient with migraine during headache-free period and spontaneous attack (25), and some in interictal migraine without aura (22).

Study carried out on children aged 7-18 years has shown a significantly longer latencies of P300 in the group of all patients with migraine (with and without aura), and no statistically significant correlation between the P300 parameters and illness duration which coincides with our results (26).

Schmitz et al. (27) have demonstrated that individuals with long disease duration compared with those with a short disease duration showed significantly decreased white and gray matter density. Taking into account our results that show that there are no differences in P300 parameters between patients with long duration of the migraine history and patients with short duration of the migraine history we can conclude that, during the short duration of migraine history, abnormalities of the P300 parameters are subtle indicators of cognitive impairment.

Some limitations of the present study require consideration. The small study sample limited the ability to examine the effects of gender and age. Another potential confounding factor is the use of different drugs for treatment of headache attack. We tried to avoid that by interrupting any therapy at least 72 hours before recording the P300.

5. CONCLUSION

Oddball paradigm studies of auditory P300 have yielded conflicting results in migraine. Despite the small sample we have shown that among patients with migraine abnormalities in cognitive potential P300 exist and suggest impairment in cortical regions included in cognitive functions. Taking into consideration association between migraine and cognitive decline we can conclude that early diagnosis and intervention may be important to prevent any deterioration in cognitive functions or migraine chronification and the P300 may represent a valuable aid for the clinicians to explain functional differences in brain activity in patients affected by migraine.

CONFLICT OF INTEREST: NONE DECLARED.

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