Original Article

Central cognitive processing assessed by P300 in migraine, tension-type headache, and cluster headache

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Abstract

Background and Aim: Patients with primary headaches are increasingly recognized to have impairments in various neuropsychological functions. However, there is a paucity of data on the cognitive functions of patients with primary headaches, especially during a headache-free period in Indian population. Therefore, the aim of the present study was to evaluate a cohort of primary headache patients and healthy controls using an auditory P300.

Methods: There were 75 patients including 51 migraine, 16 tension-type headache, and 8 cluster headache patients. They were subjected to a thorough neurological evaluation, following which they were evaluated with an auditory P300 using the oddball paradigm.

Results: Significantly, prolonged latencies ($P < 0.001$) were seen at Fz, Cz, and Pz in all cases as compared to controls. Further, comparison of all three groups with control and comparison of individual group with controls yielded similar results.

Conclusion: Abnormal P300 observed in these patients even during the interictal period suggests the presence cognitive abnormalities in patients with a primary headache.

Key words: Event-related potentials, migraine, P300, primary headache

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INTRODUCTION

The endogenous or event-related potentials (ERPs) are believed to be related to some aspects of cognitive processing and are elicited in conditions where a subject is required to distinguish a target from nontarget stimuli. The P300 cognitive evoked potential, induced by selective attention to a stimulus, is the most widely used endogenous ERP and is useful for studying mechanisms of cognitive processing such as attention, information processing, and executive functions such as processing speed, classification of stimuli, ability to establish goals, controlling innate impulses, decision-making, and goal-directed organizing and planning.[1-3] P300 is a long-latency ERP recorded over the centroparietal area. It indicates recognition of the stimulus, so if the stimulus is perceived but not recognized, then the initial short latency evoked potentials are generated but P300 is not generated.[4] It has drawn an increasing attention as a parameter reflecting the cognitive function of the brain, especially in the field of psychology, psychiatry, and neurology.[5] The latency of P300 depends on the distractibility of the frequent and infrequent stimuli while the amplitude varies with the probability of the target stimuli.[6] The latency of P300 is a measure of the stimulus evaluation time which is supposed to reflect the brain activity as a whole. Patients with a migraine and other

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primary headaches are increasingly being recognized to have impairments in various neuropsychological domains such as visual memory, verbal memory, information processing speed, attention, and executive functions. Abnormalities in the P300 with prolonged latency, reduced amplitudes, and reduced long-term habituation reported in previous studies have helped in the better understanding of the pathophysiology of a headache. However, there is a paucity of data on the loss of cognitive habituation in primary headache disorders from our country. Therefore, in the present study, we have evaluated P300 latencies in a cohort consisting of 75 patients and 70 controls attending the neurology outpatient department and/or admitted to the neurology ward of a tertiary care referral center during a headache-free period.

MATERIALS AND METHODS

The present study was carried out at a tertiary care center and aimed to evaluate the cognitive processing in patients with a primary headache (migraine, cluster, and tension-type headache [TTH]) using a P300 study. This study was approved by the Institute Ethics Committee, and an informed written consent was taken from all patients prior to participation in the study. All patients aged 10 years or above fulfilling the International Classification of Headache Disorders, 3rd edition (beta version) Cephalalgia 2013 33(9) 629-808 International Headache Society diagnostic criteria for a migraine, TTH, and cluster headache (CH) were included in the study. The study participants were divided into four groups; controls (group I), migraine (group II), TTH (group III), and CH (group IV). Patients with a history of head injury, stroke, drug/alcohol abuse, and major psychiatric disorder were excluded. A detailed history was taken in all patients followed by a thorough neurological examination including oculi fundi were carried out in all patients. The subjects were allowed to continue their medication during the study period. Patients were then subjected to a P300 study using an auditory oddball paradigm. These evaluations were performed during a headache-free period.

Event-related potential P300 (auditory event-related potential)

P300 was recorded on Medelec Synergy Electrophysiology/EMG machine. The test was carried out in a quiet, air-conditioned room with the subject lying comfortably on a couch. The auditory oddball paradigm was used and pure tone stimuli were applied binaurally at an intensity of 70 dB SPL at a rate of 0.5 Hz. The target tone (20%) was 2000 Hz and nontarget (80%) 1000 Hz and the order of occurrence were pseudo-random. The rise time and fall time of the tones were 10 ms while plateau time was 100 ms. The test procedure was explained to the subject, and he was familiarized with the frequently occurring nontarget and the rare target stimuli. The subject was asked to respond only to the infrequently presented rare target stimuli by lifting the right index finger to indicate his response. Electrode placement was done at Fz and Cz and Pz (recording sites), ear lobes A1 and A2 (linked reference), and on the forehead at Fpz (ground) according to the International 10–-20 system as per the IFCN guidelines.

The subject was asked to look up straight in front of him with eyes closed. Experimenter observed the subject to ensure that he/she does not go off to sleep and detected the targets correctly. Correct detections were counted. The accuracy of the subject's response was checked by noting the difference between the number of target stimuli actually presented and those to which the subject responded by lifting his right index finger. A correct detection rate of 80% or more was considered adequate.

P300 was recorded by averaging the electrophysiological response to the infrequently placed target stimuli. It occurred as a positive wave after about 300 ms of the stimulus and was recorded from midline Fz, Cz, and Pz electrode. P300 peak was recognized as the positive wave after N1 P2-N2 complex and between 265 and 600 ms and is followed by a slow negative wave. The latency measurements were done by placing cursors on the screen.

Statistical analysis of data

Statistical analysis was done by computing the mean and standard deviation. The comparison between the control group and the primary headache patients was done using Student's *t*-test and among all the four groups were done using one-way ANOVA. A $P < 0.05$ was considered significant.

RESULTS

A total of 75 patients and 70 controls were included in the study. Of 75 patients, 51 patients were with migraine (group II), 16 were with episodic TTH (group III), and 8 with CH (group IV). Age of the patients ranged from 10 to 40 years with maximum patients being in the 21–30 years age group.

There were 37 males and 38 female patients in the patient group, while in the control group there were 38 males and 32 females. Vast majority of patients comprised students (41.3%), followed by businessperson (16%), farmers and homemakers (14.7%), and service class (13.3), while in the control group, students (42%), farmers (10%), homemakers (9%), business class (6%), and service class (3%).

Auditory ERP P300 latency on surface recording electrodes Fz in case group was 374.77 ± 46.807 ms and in control group was 306.93 ± 42.647 ms, which was found to be significant ($P < 0.001$); similarly on Cz in case group P300 latency was 381.83 ± 49.737 ms and in control group was 313.54 ± 36.178 ms, and Pz electrode latency in case was 388.44 ± 76.063 ms and in control group was 309.50 ± 39.152 ms, which was also found to be significant ($P < 0.001$) [Table 1].

Latency comparison between group 1 (Controls), group II (migraine), group III (TTH), and group IV (CH) revealed a significant latency prolongation in all patients as compared to controls ($P < 0.001$) [Table 2]. A comparison of each individual group with the control (I vs. II, I vs. III, and I vs. IV) also yielded a significantly prolonged latency in all the three groups [Table 2].

DISCUSSION

Migraine is a chronic neurovascular disorder causing a disruption between various cortical and subcortical circuits, thus leading to slowing in cognitive processing. P300 is a useful neuropsychological tool because it is noninvasive and easy to administer. Previous studies with P300 have shown that migraine patients had reduced P300 amplitude and longer P300 latency.[7] Migraine patients fail to discriminate stimuli and have an abnormal habituation. This could be attributed to a hyperexcitable cortex in migraine patients and also possibly in TTH.[8] Several authors have reported abnormalities in the ERPs in a migraine and other primary headaches both during headache period and headache-free period with abnormalities seen more during the headache phase.[9-12] In our study also, the auditory ERP P300 latency was significantly prolonged in all headache patients at Fz, Cz, and Pz as compared to the control group. Further, similar results were seen on comparing all the three groups with control and individual comparison of each group with the controls. However, all our patients were evaluated during the headache-free periods, and they were all symptomatically well controlled on medication. Thus, in our study, prolonged latencies were present even during the interictal period. Migraine is a chronic disorder and various studies have shown increased white matter lesion and impaired cognitive functions in a migraine.[13,14] In addition it has been reported that duration of headache is positively associated with brain abnormalities.[15] Probably, the central nervous system abnormalities persist throughout the life of a migraine patient with more abnormalities during the headache phase.

Prolonged P300 latencies in CH patients during the cluster period was demonstrated by Evers *et al*.[11,16] and because P300 latency is an indicator of cognitive performance, the authors concluded that CH has a central origin.[17] Similarly, evidence of dysfunction in the cognitive processing of CH patients was demonstrated in a study by Wang *et al*.[18] in which the authors found a significantly reduced P300 amplitudes in patients as compared to controls with no significant difference between the side of pain and the contralateral side. The authors hypothesized that there was a dysfunction of the supraspinal control of pain in CH and possibly supported by an abnormal hypothalamic function with abnormal amplitudes seen equally on both affected and nonaffected sides. Since all our patients were on medication and were symptomatically controlled, we demonstrated abnormalities even during the headache-free periods thus highlighting the fact that the central nervous system abnormalities are present throughout in patients with CH. However, in future, studies should be conducted in a larger population for understanding the pathophysiology associated with the different types of primary headache.

Limitations of the study

Comparison of the latencies in patients with or without drugs would have yielded a better insight into the pathophysiology since the antimigraine drugs are known to influence the habituation of the ERPs. Further, we did not take into account the disease duration as all our patients were evaluated during the interictal period.

CONCLUSION

Impairments in certain neuropsychological domains such as visual memory, verbal memory, information

Table 1: Latency comparison between control and study group subjects

Variables	Control (*n*=70)	Study (*n*=75)	*P*
Fz	306.93±42.647	374.77±46.807	<0.001
Cz	313.54±36.178	381.83±49.737	<0.001
Pz	309.50±39.152	388.44±76.063	<0.001

Data are expressed as mean±SD. Statistical analysis of data was done by using Student's *t*-test. *P*<0.001 was considered statistically significant. SD: Standard deviation

Table 2: Comparison of latency between healthy subjects, migraine, tension type headache and cluster headache patients

Variables	Group I (*n*=70)	Group II (*n*=51)	Group III (*n*=16)	Group IV (*n*=8)	*P*
Fz	306.93±42.647	374.33±51.534***	362.88±28.444***	401.38±36.383***	<0.001
Cz	313.54±36.178	381.80±56.108***	370.88±29.888***	403.88±30.352***	<0.001
Pz	309.50±39.152	390.10±88.751***	374.88±33.057**	405.00±42.467***	<0.001

Data are expressed as mean±SD. Group I: Controls; Group II: Migraine; Group III: Tension type headache; Group IV: Cluster headache. Statistical analysis of data was done by using one-way ANOVA. Comparison with Group I; **P<0.01; ***P<0.001. SD: Standard deviation

processing speed, attention, and executive functions are increasingly recognized in migraine patients. ERPs, especially the P300, have shown potential usefulness for evaluating certain aspects of cognition in various studies with reduced P300 amplitude, longer P300 latency, and reduced long-term habituation compared to healthy controls predominantly not only in a migraine but also in other primary headaches. The present study also revealed prolonged P300 latencies during the interictal period suggesting the presence of abnormal cognitive processing even in an interictal period in patients with primary headache disorders.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Idiazábal MA, Palencia-Taboada AB, Sangorrin J, Espadaler-Gamissans JM. Cognitive evoked potentials in the disorder attention deficit hyperactivity disorder. Rev Neurol (Barcelona) 2002;34:301-5.
2. Schochat E, Scheuer CI, Andrade ER. ABR and auditory P300 findings in children with ADHD. Arq Neuropsiquiatr 2002;60:742-7.
3. Farias LS, Toniolo IF, Cóser PL. P300: Electrophysiological avaliation of hearing in children who have never repeated and who have repeated at school. Rev Bras Otorrinolaringol 2004;70:194-9.
4. Sutton S, Braren M, Zubin J, John ER. Evoked-potential correlates of stimulus uncertainty. Science 1965;150:1187-8.
5. Picton TW, Stuss DT, Marshall KC. Attention and the brain. In: Friedman SL, Klivington KA, Patterson RW, editors. The Brain, Cognition and Education. New York: Academic Press; 1986. p. 19-79.
6. Fein G, Turetsky B. P300 latency variability in normal elderly: Effects of paradigm and measurement technique. Electroencephalogr Clin Neurophysiol 1989;72:384-94.
7. Drake ME Jr., Pakalnis A, Padamadan H. Long-latency auditory event related potentials in migraine. Headache 1989;29:239-41.
8. Siniatchkin M, Kropp P, Gerber WD. What kind of habituation is impaired in migraine patients? Cephalalgia 2003;23:511-8.
9. Mazzotta G, Alberti A, Santucci A, Gallai V. The event-related potential P300 during headache-free period and spontaneous attack in adult headache sufferers. Headache 1995;35:210-5.
10. Evers S, Bauer B, Grotemeyer KH, Kurlemann G, Husstedt IW. Event-related potentials (P300) in primary headache in childhood and adolescence. J Child Neurol 1998;13:322-6.
11. Evers S, Bauer B, Suhr B, Husstedt IW, Grotemeyer KH. Cognitive processing in primary headache: A study on event-related potentials. Neurology 1997;48:108-13.
12. Buodo G, Palomba D, Sarlo M, Naccarella C, Battistella PA. Auditory event-related potentials and reaction times in migraine children. Cephalalgia 2004;24:554-63.
13. Rocca MA, Ceccarelli A, Falini A, Tortorella P, Colombo B, Pagani E, *et al.* Diffusion tensor magnetic resonance imaging at 3.0 tesla shows subtle cerebral grey matter abnormalities in patients with migraine. J Neurol Neurosurg Psychiatry 2006;77:686-9.
14. Kelman L. The postdrome of the acute migraine attack. Cephalalgia 2006;26:214-20.
15. Schmitz N, Admiraal-Behloul F, Arkink EB, Kruit MC, Schoonman GG, Ferrari MD, *et al.* Attack frequency and disease duration as indicators for brain damage in migraine. Headache 2008;48:1044-55.
16. Evers S, Bauer B, Suhr B, Voss H, Frese A, Husstedt IW. Cognitive processing is involved in cluster headache but not in chronic paroxysmal hemicrania. Neurology 1999;53:357-63.
17. Braverman ER, Blum K. P300 (latency) event-related potential: An accurate predictor of memory impairment. Clin Electroencephalogr 2003;34:124-39.
18. Wang R, Dong Z, Chen X, Liu R, Zhang M, Wu J, *et al.* Cognitive processing of cluster headache patients: Evidence from event-related potentials. J Headache Pain 2014;15:66.