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A CASE CONTROL STUDY OF EVENT RELATED POTENTIAL P300 WAVE IN HEADACHE FREE PERIOD OF MIGRAINE PATIENTS AND HEALTHY CONTROL SUBJECT

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ABSTRACT

Background: Chronic migraine patients sometimes complain regarding attention and memory during their long course of disease process. Migraine has a modifying impact sub - clinically on cognitive skills that have been evaluated by a battery of psychological questionnaire based investigative tools both in clinical settings and community. The purpose of this study is to evaluate neurocognitive functions in migraineurs in terms of neural dynamics of endogenous P300 wave ERP (Event Related Potential) component through assessing the amplitude and latency of P300 wave by auditory oddball task. This study establishes the potential role of P300 wave-form as an independent neuropsychological tool for a better appreciation of subclinical reduced cognitive profile with underlying dysfunctional neural dynamics in migraine patients.

Material and Methods: 30 migraine patients in age group of 18-35 year and 30 healthy sex and age matched healthy control subjects were recruited in this study. EEG was recorded to obtain time locked ERPs at Cz, Pz, C3, C4, T3 and T4 electrode sites using 10-20 international system and deploying auditory oddball paradigm during active counting task in migraineurs without aura during headache free period and healthy control subjects. The amplitudes and latencies of P300 wave during active counting task were compared in migraine patients and healthy control subjects using student's t-test.

Result: The amplitude of P300 was observed to be lower in migraineurs indicating the subclinical reduced cognitive processing.

Conclusion: There is subclinical altered cognitive processing in migraine patients in interictal pain free period that might be related to subtle changes in biochemical, structural and/or functional activity in brain during course of disease process.

KEYWORDS : Migraine, ERP, P300 wave

Introduction

Migraine is a headache disorder caused by activation of pathophysiological mechanisms deep within the brain that leads to the release of pain producing inflammatory substances around the nerves and blood vessels of the brain tissue[1]. Migraine typically starts in childhood or puberty and becomes more prevalent between the ages of 22 to 55 years, affecting females more often with a high prevalence among school/college going students and urban residents[2, 3]. Migraine is a chronic headache disorder characterized by recurrent attacks with a time – span of around 4 – 72 hours, has a pulsating quality, is moderate or severely intense in nature that is aggravated by routine physical activity and is commonly associated with nausea, vomiting, photophobia or phonophobia[4]. Migraine may be associated with aura (transient focal neurological symptoms) whose origin is believed to involve the brain stem, and cortex. Migraine is proposed as a neurovascular headache in which dilatation of blood vessels occur due to neural events that aggravate pain resulting in further neural activation[5].

Event Related Potentials (ERPs) are those potentials of electroencephalography (EEG) that are evoked by preparation or perception for events[6]. ERPs give characteristic features of information processing in terms of latency and amplitude in the Central Nervous System[7, 8]. P300/P3 wave is the stimulus and time locked third positive waveform with wide acceptance due to its associated psychological processing, that peaks about 300-600 ms after stimulus onset, with maximal amplitude at midline central or parietal recording sites at scalp[9, 6]. P3 wave is electro-physiological correlate of a steady revision of representation of an environment in the phase – space of the stochastic trajectory of working memory[10]. P3 latency period has been reported to be related to stimulus evaluation time[11] or the time taken to allocate resources and engage memory updation[12] and the speed of the underlying cognitive processing of the stimulus – locked mental task[13]. P300 amplitude gives information on amount of attention resources allocated to stimulus, working memory and task's complexity[14] and is related to decision making and memory processing[15,13].

Material and methods

The present study was conducted in the Department of Physiology in collaboration with Department of Neurology, S.M.S Medical college and hospital, Jaipur (Rajasthan) after receiving the desired clearance from institutional ethical committee in 30 migraine patients without aura (duration of disease Mean ± SD = 4.25 ± 1.16, ranging from 2 to 7 years) already diagnosed by neurologist following the standard diagnostic criteria (International Classification of Headache Disorder)[16] in age range of 18 to 35 years and 30 age and sex matched healthy controls. Informed written consent was obtained from all the enrolled subjects.

Inclusion criteria: 1) age range of 18 – 35 years 2) Normal hearing 3) Subjects who gave written consent

Exclusion criteria: 1) Any other neurological or psychiatric disease 2) History of drug abuse, chronic smoking or/and alcohol intake 3) History of other types of headache or mixed type headache 4) History of any acute or chronic illness 5) Non-cooperative subjects.

It was ensured that the subjects were headache free for at least 24 hours before the commencement of EEG recording. However prophylactic use of anti – Migraine drugs in Migraineurs and intermittent use of analgesics, such as non- steroidal anti – inflammatory drugs (NSAIDs) were not excluded.

EEG and ERP Recording, Analysis and Quantification

The participants were seated on an ergonomic wooden chair in a sound attenuated, dimly lit air – conditioned room. The room temperature was maintained at around 25°C. The EEG was recorded using saline soaked Ag/AgCl surface electrodes. Electrodes were placed at centrocentral (Cz), parietocentral (Pz), left temporal (T3), right temporal (T4), left central (C3) and right central (C4) regions of the scalp according to the International 10 – 20 System. EEG electrode lead pairs of Cz, Pz, T3, T4, C3 and C4 have been paired individually with reference electrode of mastoid and ground electrode of forehead.

Raw EEG was recorded using Brain Electro Scan System (BESS) version 4.0 (Axxonet Systems Technologies Ltd, India). The electrode impedance was kept below 5 Ω and electrical activities were amplified using an amplifier. A band pass filter of 0.5 to 70 Hz and notch filters of 50 Hz and 60 Hz with a delta of 6 were applied in order to remove the electrical line noise. The raw EEG recordings were digitized at a sampling rate of 512 Hz.

Stimulus Protocol

With intensity of 60 dB two types of auditory stimuli i.e. a high

frequency tone (1200 Hz) and a low frequency tone (600 Hz) were used in a pseudo randomized sequence in form of an auditory oddball paradigm. High tone was used as frequent/standard tone (80% probability of presentation) and low tone was used as non – frequent/target tone (20% probability of presentation). A variable inter – stimulus interval of 1500 ms (with a variance of 20) was used with an analysis time of 1000 ms. Every participant was subjected to active counting task. During Active Counting task participants were instructed to carefully count the low tones quietly in mind and tell their number to researcher at the end of experiment. Total 100 auditory stimuli in oddball paradigm were presented to every participant.

Statistical Analysis

Statistical analysis was performed with the SPSS, version 21 for Windows statistical software package (SPSS inc., Chicago, IL, USA). The Categorical data was presented as numbers (percent) and were compared among groups using Chi square test. The quantitative data was presented as mean and standard deviation and were compared by student's t-test

Observations

Table 1: age distribution of the study population

Age Group (Years)	Migraine Patients (Case)	Control
18-24	6	8
25-30	15	14
31-35	9	8
Total	30	30
Mean ± SD	28.03±3.61	27.07±3.97
P value	0.328	

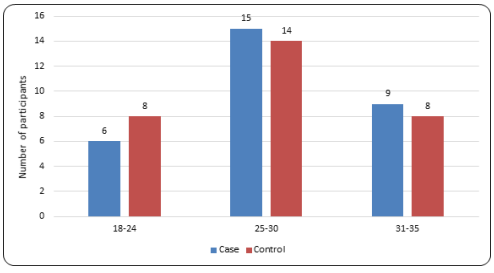

Figure1: Age (years) Distribution of Study Population

Table 2: Gender distribution

Sex	Migraine Patients (Case)	Control
Male	12	12
Female	18	18
Total	30	30

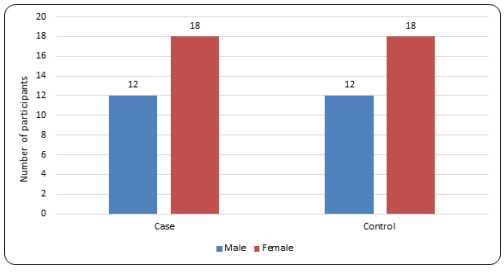

Figure 2: Gender Distribution in Study Population

Table 3: P300 wave amplitude (microvolts) in response to low tone (target stimuli) during active counting task

	Amplitude				
	Migraine Patients (Case)		Control		P value
	Mean	SD	Mean	SD+	
CZ	7.20	5.87	8.35	2.64	0.085
T3	5.87	2.97	7.86	2.71	0.008**
T4	5.92	3.06	7.80	3.63	0.034*
Pz	7.24	2.71	9.31	3.32	0.010*
C3	6.58	2.55	7.92	2.98	0.067
C4	6.25	3.08	8.45	3.40	0.011*

*Significant P value (P < 0.05) ** highly significant P value (P < 0.01)

Table 4: P300 wave latency (milliseconds) in response to low tone (target stimuli) during active counting task.

	Latency				
	Migraine Patients (Case)		Control		P value
	Mean	SD	Mean	SD	
CZ	410.96	55.41	396.63	106.01	0.514
T3	450.49	97.64	460.70	87.90	0.671
T4	423.83	96.93	412.06	106.05	0.655
Pz	420.22	62.52	396.39	97.78	0.265
C3	425.99	56.62	413.09	97.64	0.533
C4	434.40	56.94	405.00	108.65	0.194

Results

Amplitude of P300 wave (in microvolts) came out to be significantly lower in Migraine patients across EEG lead pairs T3, T4, Pz and C4 in response to low tone (target stimuli) during active counting task (table 3). Latency period of P300 wave (milliseconds) do not differ significantly (P>0.05) in Migraineurs and healthy control population in all EEG lead pairs under evaluation in response to low tone during active counting task (table 4).

Discussion

The disease process of Migraine is beset by the interplay of neurological, physiological and psychological factors involving dysfunctional information processing that is most likely modulated by changes in electrical properties of cortical neurons that seem to affect the phase(s) preceding activation of the respective neuronal pools[17]. The present study was undertaken to evaluate the cognitive profile in migraineurs through neural dynamics of P300 wave, in terms of latency and amplitude. The most frequently reported cognitive changes in migraineurs are impaired visual and verbal memory, reduced information processing speed, executive dysfunction, and attention deficit. The presence of cognitive impairment in Migraineurs reinforces the complexity of this disease that is not exclusively associated with pain symptoms[18]. Migraine patients exhibit a deficit in cortical function involved in automatic attention switching[19].

In the present study, during active counting task, the amplitude of P300 wave to target stimulus came out to be significantly reduced (P < 0.05) in EEG electrodes pairs of T3, T4, Pz, C4 and the latency period of P300 wave to target stimulus was not statically significantly increased (P > 0.05). Singh et al[20] (2015) and Huang et al[21] (2017) have documented significantly increased values of latency periods of P300 wave during active task. Singh et al (2015) used auditory oddball paradigm in migraine patients in the age range of 10 – 40 years during the pain free interictal period and active task was used wherein the subjects were asked to to raise the index finger, a task that differed from that of the present study (mental counting of low frequency tone). They had observed significantly long latency (P < 0.05) across Fz, Cz, and Pz EEG electrode pairs. Huang et al (2017) had also documented significantly long latency periods of P300 wave (P < 0.05) and no statically significantly decreased P300 wave amplitude in migraineurs with aura in the age range of 20 – 55 years at Fz, Cz and Pz EEG electrode pairs when visual stimuli were used and active task was to press the button.

Migraine has been proposed as a risk factor for subclinical brain lesions[22]. A positron emission tomography (PET) study of spontaneous migraine demonstrated a spreading bilateral cerebral oligemia in migraine sufferers[23]. Anatomically, diffusion tensor imaging studies in migraine patients have revealed gray matter volume loss in superior temporal gyrus, inferior frontal gyrus, anterior cingulate cortex, amygdale, parietal operculum, and bilateral insula[24, 25]. Anterior cingulate gyrus seems to be particularly sensitive to operations involved in target detection[26]. Subjects with migraine show a significantly higher risk of periventricular white matter lesions[27]. Subcortical white matter lesions have often been associated with deficits in executive functions i.e. high order cognitive processes that include planning, initiation, cognitive flexibility, decision making, regulation, judgement, and feedback utilization[28,29].

In the present study reduced amplitude of P300 wave in migraineurs during task activity in headache free period indicates decreased cognitive processing at subclinical level. Subclinical reduced cognitive processing in migraineurs that is reflection of dysfunctional neural dynamics of P300 wave may plausibly be explained on the

molecular level by slow progressive and relentless alterations in biochemical, structural and functional domain within cortical and subcortical brain areas of migraineurs. Decreased number of recruited neuronal pools or out of sync or out of rhythm of recruited neuronal pool within temporo-parietal region in cerebral cortex may be hypothesized as a cause of disturbances in neural dynamics of P300 wave in Migraineurs**.**

Conclusion

Migraine is associated with subtle changes and transmutations in neural cognitive processing that might be related to structural and/or functional changes within the human brain during the course of disease. P300 wave could be utilized as an addendum to the ongoing management protocol of migraineurs prognosticating the disease profile during course of disease and could provide a window to the clinician reflecting the ongoing dysfunctional neural dynamics that is latent and not manifested clinically.

Limitation

Migraine comorbidities, such as depression and anxiety can influence P300 wave in migraine patients[30, 31]. NSAIDs and prophylactic drugs for migraine may be potential confounding factor. Small cohort may also limit the ability to examine the effects of gender and age in study.

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