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Habituation of P300 in migraineurs tension-type headache subjects during inter-ictal period as compared to control group

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ABSTRACT

Background: Habituation of P300 in the migraineurs has been studied in a number of studies, but not very often in tension type headache patients. Moreover, most of the studies have used only single montage. This study assesses the habituation in migraineurs and tension type headache subjects during inter-ictal period with the help of three scalp montages., **Aims and objectives:** To find out if the habituation of P3 differ between the migraineurs, tension type headache subjects and controls during inter-ictal period., **Methods:** Study sample comprised of three groups - migraineurs, tension type headache subjects as well as a healthy control group. Fifty subjects in each group were included after screening for the respective inclusion criteria and exclusion criteria. None of the subjects were blood relatives of each other. Habituation of P3 was assessed using the frontal, central and parietal electrodes using odd-ball paradigm for target stimuli., **Statistical Analysis:** Data was analyzed with the help of SPSS V11.0 for Windows. Paired sample t test and one way ANOVA with post-hoc tukey (wherever required) were performed., **Results:** P3 did not show habituation or the potentiation after successive trials in any of the group. Similarly, amplitude or latency of any of these waves was not significantly different among groups. These results were consistent among all the three scalp montages., **Conclusion:** In between the headache episodes, event related potentials do not habituate or potentiate, thus confirming the true episodic nature of the headache episodes.

Key Words: Migraine, tension type headache, habituation, P300

INTRODUCTION

Habituation in migraine is often seen as a basic pathophysiological process and is impaired in patients, days before the headache thus representing the increased susceptibility of brain to provoking agents as well as a genetically determined abnormality that determines the risk of migraine attack.[1-4]

Sinistchkin et al[5] conducted an experiment using odd ball auditory paradigm with the hypothesis that migraineurs should show habituation to both target as well as non target stimuli since it is dependent upon the mitochondrial metabolism abnormality and noradrenergic or serotonergic abnormality.[6,7] They found that migraine patients are characterized by reduced short term habituation of P50 on non-target tones only, or the sensory gating deficit. They proposed that it was not the result of abnormal refractory period, but was secondary to the inability to filter irrelevant stimuli resulting in the stimulus overload in the brain. It may lead to migraine attack under disturbed brain energy metabolism and abnormal cortical excitability.[8,9] Attentional demands increase the amplitude of target P50 and lead to increased T/C ratio. However, this effect is not apparent in subjects with sensory gating deficit and hence was seen in healthy controls only.[5]

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In long term habituation, only the P300 for target stimulus was different between migraineurs and controls. P300 is related to evaluation of cognitive characteristic of the stimulus and fails to habituate if the subject has to provide attention to each stimulus. Stimulus discrimination required allocation of attentional resources while maintaining the signal value of the stimulus. Abnormal habituation on target conditions only, in migraineurs suggests that they fail to discriminate the stimuli.[5]

All of these studies show two basic problems in migraineurs- (i) increased amplitudes of averages of large number of trials and (ii) lack of habituation in successive trial blocks. However, this data should be interpreted with caution. Increased amplitude, however, indicates cortical hyperexcitability, but this happened only with large number of trials! In other words, it could be understood as reduced ability of cortex to habituate to a given stimuli, or that greater response was generated with successive suprathreshold stimuli.

The studies of P300 in the TTH are scarce. One study shows that P3 latency or amplitude was not affected by the ictal or inter-ictal state in episodic TTH sufferers and it was not different from healthy controls or migraine without aura.[10,11] Loss of habituation was not observed in episodic TTH patients.[12,13]

In short, there is paucity of literature addressing the P300 habituation among migraineurs and furthermore in tension type headache subjects. This is an important area as it may show the underlying neurobiological activity and may be helpful in understanding the functional neurophysiology.

METHOD

Fifty subjects suffering from migraine, fifty subjects of tension type headache and fifty controls were recruited from the headache clinic of a teaching hospital according to convenient sampling. The study was approved by the institutional ethics committee and informed consent was obtained from all the study subjects. Migraine and TTH were diagnosed according to the International Classification of Headache Disorders (ICHD-2) criteria[14]. The control group consisted of subjects who never had recurrent primary headaches and in whom family history was negative for primary headaches. All the participants were belonging to the same ethnic group and had comparable socio-economic status. None of the subjects were genetically related to the other subjects included in the study.

All the subjects were screened for the exclusion criteria and if present, then that subject was excluded from the study. Subjects with major neurological disorders e.g., epilepsy, space occupying lesions, neurodegenerative disorders, those with chronic daily headache (undiagnosed or mixed type), substance use disorders (except tobacco), taking prophylactic drugs for migraine or tension type headache for more than three weeks, with co-morbid other primary headache, co-morbid psychiatric disorder, consuming anti-oxidants or multivitamins for more than a week were excluded from the study.

Patient's history of headache was taken in detail, followed by the clinical examination and wherever required, appropriate laboratory investigation to rule out secondary headache. Parallel information was also collected from a reliable family member regarding headaches of the sufferer. All the information was recorded on a semi-structured Performa.

NEUROPHYSIOLOGICAL EXAMINATION

All the subjects were called on a separate day for the neurophysiological testing. This day was chosen by the patients so that at least three days have elapsed from their last headache. They were explained the procedure of the neurophysiological testing before starting the test. As per our prior instructions, subjects came to the laboratory after washing their scalp with shampoo and none of the

subject had applied the oil on the scalp on the day of testing.

The event related potentials were recorded with the help of Nihon-Kohden MEB 9100 machine. In an electrically shielded sound proof room with comfortable ambience subjects were asked to sit on a resting chair. Their scalp was further cleaned with the alcohol to improve the electrode contact and silver disc electrodes were applied with the help of electrode-gel on their scalp in fronto-central (Fz), central-vertx (Cz) and parietal-central (Pz) positions according to international 10-20 system. A1 and A2 Reference electrode was placed on the auricles and FPz was used as ground electrode. Skin electrode contact impedance was kept below 5KÙ. Subjects were asked to keep their eyes closed to avoid blink artefacts.

Auditory ERP was recorded using oddball paradigm. Tones of 100 msec duration with a rise and fall time of 10 msec were delivered binaurally. 1 KHz frequency non target tones had sound pressure of 60dB and 2 KHz target tones were delivered at 60 dB SPL. The target and non target tones comprised of 20% and 80% stimuli, respectively. Subjects were asked to press a button in response to the target stimulus. The responses were filtered with a band pass of 0.1-50Hz and averaged for thirty responses. The experiment consisted of four blocks of stimuli presented with five minutes intervals between each block.

The instrument removed the artefact automatically and amplified signals were digitalized over 1000 msec epoch; 100 msec before and 900 msec after the stimulus.

Evoked responses were analyzed in terms of latencies and peak amplitude. Event related potentials of target stimuli were considered for the present study and potentials for standard stimuli were ignored. Peak amplitude for each wave was measured from the baseline. N1 was designated as any negative wave occurring between 50-150 msec after the stimulus. P2 was measured as a positive wave between 125 to 230 msec post-stumulus. N2 was identified as most negative wave occurring 140-275 msec after the stimulus and P3 was marked as a positive wave following N2, representing itself 160 msec to 370 msec after the stimulus.

For the present study, only the first and fourth blocks were taken into consideration.

STATISTICAL ANALYSIS

SPSS v 11.0.0 for Windows was used for the statistical analysis. Paired t test was used to compare the change in values of first block and fourth block. One way ANOVA was used to compare the values among three groups.

RESULTS

Three groups were identical with respect to average age (27.66 years among migraineurs; TTH group 27.6 years; control group 25.18 years). Both the headache groups had preponderance of females as compared to control group (82% among migraineurs; 100% in TTH group; 25% in control group X^2= 70.59, P<0.001). BMI was not different among groups and none of subjects fell into the category of "obese" (Migraine=23.4; TTH 22.7; Control 23.9 P>0.05).

When other illness related factors were analyzed, it was found that migraine and tension type headache group did not differ in regards to total duration of illness, duration since the illness has become disabling and duration of individual headache episode. However, migraineurs had more less frequent headaches per month (10 episodes versus 22 episodes of TTH; P<0.05) but headache took more time to reach the maximal severity (1.36 hours versus 0.30 hour in TTH patients; P<0.05). Chronic TTH was present in 56% and chronic migraine in 14% subjects.

P3 did not show habituation or the potentiation after successive trials in any of the group. Similarly, amplitude or latency of any of these waves were not significantly different among groups. These results were

Table 1: Paired Sample t test in the study group showing difference in latency across trials (trial 1 vs trial 4)

Montage	95% CI		t	P
	Lower	Upper		
Migraineurs				
Latency P3 Fz - Latency P3 Fz 4	-13.7671	61.7671	2.022	.136
Latency P3 Cz - Latency P3 Cz 4	-45.8127	64.8127	.547	.623
Latency P3 Pz - Latency P3 Pz 4	-82.8870	6.3870	-2.727	.072
Tension Type Headache				
Latency P3 Fz - Latency P3 Fz 4	-31.6638	49.9495	.548	.603
Latency P3 Cz - Latency P3 Cz 4	-34.5936	24.8793	-.400	.703
Latency P3 Pz - Latency P3 Pz 4	-34.5133	5.6561	-1.758	.129
Control group				
Latency P3 Fz-Latency P3 Fz 4	-85.0905	72.5905	-.252	.817
Latency P3 Cz - Latency P3 Cz 4	-20.9103	48.9103	1.276	.292
Latency P3 Pz - Latency P3 Pz 4	-29.5353	59.5353	1.072	.362

Table 2: Paired Sample t test in the study group showing difference in amplitude across trials (trial 1 vs trial 4)

Montage	95% CI		t	P
	Lower	Upper		
Migraineurs				
Amplitude P3 Fz - Amplitude P3 Fz 4	-4.2226	1.4326	-1.570	.214
Amplitude P3 Cz - Amplitude P3 Cz 4	-9.4483	11.5283	.316	.773
Amplitude P3 Pz - Amplitude P3 Pz 4	-7.3684	9.6084	.420	.703
Tension Type Headache				
Amplitude P3 Fz - Amplitude P3 Fz 4	-4.4159	5.9359	.377	.721
Amplitude P3 Cz - Amplitude P3 Cz 4	-3.4993	4.3026	.265	.802
Amplitude P3 Pz - Amplitude P3 Pz 4	-3.5535	2.7835	-.312	.767
Control group				
Amplitude P3 Fz - Amplitude P3 Fz 4	-4.0866	7.0616	.849	.458
Amplitude P3 Cz - Amplitude P3 Cz 4	-3.1993	2.3193	-.507	.647
Amplitude P3 Pz - Amplitude P3 Pz 4	-16.6041	9.4574	-1.180	.359

Table 3: One way ANOVA test in the sample showing difference in latency and amplitude of P3 (First Block)

					95% CI		F	P
Montage	Group	Mean	SD	SE	Lower	Upper		
Latency P3 Fz	Control	356.3333	30.07768	12.27916	324.7687	387.8979	.199	.821
	Migraine	344.2857	29.92610	11.31100	316.6087	371.9627		
	TTH	343.5000	60.22458	30.11229	247.6693	439.3307		
Latency P3 Cz	Control	346.8333	28.89579	11.79666	316.5091	377.1576	.480	.629
	Migraine	324.0000	42.26898	15.97617	284.9077	363.0923		
	TTH	339.7500	60.23496	30.11748	243.9027	435.5973		
Latency P3 Pz	Control	332.8333	35.56075	14.51761	295.5146	370.1520	.050	.951
	Migraine	341.2857	56.63543	21.40618	288.9067	393.6647		
	TTH	341.2500	66.22877	33.11439	235.8652	446.6348		
Amplitude P3 Fz	Control	9.4440	7.58044	3.39008	.0316	18.8564	.442	.653
	Migraine	6.8917	3.49736	1.42779	3.2214	10.5619		
	TTH	10.6950	8.72019	4.36010	-3.1808	24.5708		
Amplitude P3 Cz	Control	11.3640	6.57703	2.94134	3.1975	19.5305	1.162	.346
	Migraine	6.2117	4.27400	1.74485	1.7264	10.6970		
	TTH	10.5175	7.48226	3.74113	-1.3884	22.4234		
Amplitude P3 Pz	Control	12.3520	11.50948	5.14720	-1.9389	26.6429	.237	.793
	Migraine	9.2150	6.17267	2.51998	2.7372	15.6928		
	TTH	12.1975	6.81279	3.40639	1.3568	23.0382		

Table 4: One way ANOVA test in the sample showing difference in latency and amplitude of P3 (Fourth Block)

					95% CI		F	P
Montage	Group	Mean	SD	SE	Lower	Upper		
Latency P3 Fz 4	Control	337.5000	28.05352	14.02676	292.8606	382.1394	.124	.884
	Migraine	335.1429	42.29038	15.98426	296.0308	374.2549		
	TTH	349.7500	69.24534	34.62267	239.5652	459.9348		
Latency P3 Cz 4	Control	341.7500	11.58663	5.79332	323.3131	360.1869	.205	.817
	Migraine	328.8571	43.79280	16.55212	288.3556	369.3587		
	TTH	325.7500	43.41563	21.70781	256.6660	394.8340		
Latency P3 Pz 4	Control	361.7500	21.40677	10.70339	327.6870	395.8130	.851	.451
	Migraine	355.7143	47.98164	18.13536	311.3387	400.0899		
	TTH	326.2500	45.48535	22.74267	253.8727	398.6273		
Amplitude P3 Fz 4	Control	9.3600	8.75990	4.37995	-4.5790	23.2990	.421	.666
	Migraine	6.1317	4.74459	1.93697	1.1525	11.1108		
	TTH	9.2075	5.84174	2.92087	-.0880	18.5030		
Amplitude P3 Cz 4	Control	8.9975	7.71262	3.85631	-3.2750	21.2700	.800	.474
	Migraine	5.8100	4.75343	1.94058	.8216	10.7984		
	TTH	10.9575	7.54218	3.77109	-1.0438	22.9588		
Amplitude P3 Pz 4	Control	11.0725	11.39533	5.69766	-7.0600	29.2050	.404	.678
	Migraine	9.6000	5.85763	2.39137	3.4528	15.7472		
	TTH	15.6933	13.57725	7.83883	-18.0344	49.4211		

consistent among all the three scalp montages (Table 1 to Table 4).

DISCUSSION

Functional significance of ERP data has been debated since a long time and a number of theories have been proposed regarding underlying psychopysiological processes. However, here we are mainly concerned with the neur-anatomical as well as functional significance. These waves show the activity of the brain which temporally corresponds the activity of individual brain regions.[15] Hence it can be an excellent tool to study the underlying functional neurological mechanisms.

This is perhaps for the first time when a study has employed all three montages to compare the habituation of these waves, and

to best of our knowledge, first time it is studied among tension type headache subjects.

Functionally, P3a activity corresponds the increase in activity of the brainstem (particularly, LC-NE area) and somato-sensory cortex thus showing the process of internal decision making. [15,16]

Habituation is characterized by reduction in the amplitude of the cortical response when a sustained stimulus of equal intensity is presented. Hence, the normal habituation shows the adaptability of the cortex to overstimulation and lactate accumulation.[17,18] Kandel[19] demonstrated that habituation is dependent upon the serotonergic neurons in *Aplysia* during gill-withdrawal reflex. There are few arguments that show habituation in humans is also depends upon serotonin. Selective serotonin reuptake inhibitors increase the serotonin in the synapse and fluoxetine has been shown to normalize the interictal habituation (which is otherwise deficient) in migraineurs.[20] This could be possible reason behind the effectiveness of these drugs in migarine. Sequential analysis of ERP data from migraine free period to migraine attack shows that P3 latency gradually decreases as the migraine attack comes closer and then increases during attacks[21]. Similarly, P3 latency is greater among migraineurs as compared to control group, however P3 amplitude do not show any difference.[2] It has been demonstrated that the latency of the event-related visual P300 response varies inversely with platelet serotonin content. In particular, it augments, i.e. normalizes, during the attack in parallel with a decrease in platelet serotonin. Others people have also reported that during migraine attack, latency of P3 increases and amplitude decreases, while reverse was seen in these studies during headache free interval.[21,22]

Normalization of amplitude habituation during the attack was also found for VEPs and contingent negative variation.[21,23] Interestingly, on the basis of biochemical studies in peripheral blood, migraine is thought to be characterized between attacks by a low serotonin disposition, which partially reverses during the attack.[24-26] In short, the available data suggests that migraineurs show the deficit of serotonergic transmission in the brain between attacks and this deficiency improves during the attack, thus normalizing habituation.

However, this theory has received many criticisms. Wang et al[27] found that ERP potentiation was secondary to the low cortical serotonergic transmission. On the other hand, Evers et al[2] concluded that serotnergic transmission is not important for habituation. The debate does not ends here, other studies suggest that cortex is hyperexcitable in migraineurs and this predisposes them to have more attack and it is responsible for the lack of habituation in between attacks. But a recent review suggested that 'hyper-excitability' of cortex is misleading term in the available literature.[28]

This study did not show habituation in the control group, migraineurs as well as tension type headache patients in the target P3 amplitude as well as latencies at any of the cortical sites. At the same time, we even did not find the potentiation even when the recordings were made outside acute attack in both symptomatic groups, contrary to the findings of Wang and Schoenen.[27] However, they analyzed only Cz electrode and measured peak to peak amplitudes, while we measured the amplitudes from the baseline to peaks. However, this study has some methodological limitations. Firstly, strict inclusion criteria in this study precludes from generalizing the results as subjects with such isolated illness are not very common in the clinical populations. Hence, results must be applied with caution in the general population. Second, sample size of the study is small relative to the prevalence of the illnesses in question owing to few technical factors. We suggest inclusion of a larger sample in the future studies. Thirdly, the results of the study represent only cross sectional examination during a specified period of illness. In future, sequential measurement may be made at different phases of the illness to elucidate the underlying pathophysiology in all the three subgroups included in this study.

In short, this study showed that in between the headache episodes, event related potentials do not habituate or potentiate, thus confirming the true episodic nature of the headache episodes.

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