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Original Article

Evaluation of Visual Evoked Potential in Migraine Individuals

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Abstract

Background: Migraine is a multifactorial brain disorder characterized by recurrent disabling attacks of a headache. The migraine patients have visual disturbances during the attack as well as during the interictal period. In addition, even between attacks some aspects of cortical dysfunction are peculiar in migraineurs.

Aim: This study aims for knowing the pathogenesis of migraine in between attacks that lead to migraine disorder.

Materials and Methods: The study was conducted by evaluating the visual evoked potential of 30 migraine patients during the headache-free period and compared with 30 normal persons. The results were interpreted and statistically analyzed.

Results: There was statistically significant increase in amplitude of P100 wave of the migraine patients due to deficient habituation after a period of 15 min stimulation. In normal subjects, there was a decrease in amplitude of P100 wave due to the effect of habituation. The deficient habituation can be due to decreased serotonin levels leading to reduced pre-activation of the cortex.

Conclusion: The migraine patients has attributed to abnormal cortical processing in migraine with interictal hyperactivity leading to heightened responsiveness and lack of habituation and lack of intracortical inhibition.

Key words: Habituation, Migraine, Visual evoked potential

INTRODUCTION

Migraine is a common disabling primary headache disorder with a high prevalence, socio-economic, and personal impacts. The World Health Organization ranks migraine as one of the top 20 leading neurological causes of disability. The headache is a pervasive symptom and the most common problem that the neurologists encounter in their clinical practices. It is estimated that 12% of world's population suffer from migraine and in India, of 1200 million populations, there are 150-200 million migraineurs under treatment. The gender prevalence of migraine is about 20% in females and 6% in males. According to the International Headache Society (IHS), migraine is classified into headache with aura and headache without aura. Migraine is characterized by recurrent headache disorder manifesting in attacks lasting 4-72 h, with typical headache of unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea and/or photophobia and phonophobia. Visual disturbances are well-known clinical features of migraine. The migrainous aura is visual in 82% of cases, with symptoms such as flashes of light, stars, zig-zags, central or paracentral blind spot, and scotoma.[1] The migraine patients are also more sensitive to environmental light stimuli.[2] Apart from this, migraine in some can produce progressive brain damage. Pathophysiological studies in migraine patients and animal models of the migraine headache have identified the trigeminovascular system,[3] brainstem,[4,5] and the cerebral cortex[6-8] as structures which may have primary causative roles. Modern neuroimaging studies[9] have confirmed that migraine with aura symptoms are due to a cortical phenomenon similar to spreading depression. Various methods in electroneurophysiology are particularly

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appropriate for the study of migraine pathophysiology because they are a traumatic and able to detect functional abnormalities.[10] Among the evoked potentials, visual evoked potentials (VEPs) are commonly used and have been extensively studied in migraine during the past 30 years. Studies have shown that migraineurs are characterized by changes in the evoked potentials even during the headache-free period. The excitability of the cerebral cortex in the interictal state of migraine appears to be fundamental in the brain's susceptibility to migraine attacks. Between attacks, the migraine patients are characterized by potentiation instead of habituation of stimulation-evoked cortical responses. The pathogenesis could be due to increased or decreased cortical excitability. Although several studies have been done for the biochemical and neurophysiologic abnormalities that precipitate a migraine attack, the subtle factor that causes migraine disease, which if present should also be detectable in pain-free period, representing underlying dysfunction. This study is indented in knowing about the pathophysiology of migraine by evaluating VEP in migraine patients in between attack and comparing them with normal persons.

MATERIALS AND METHODS

It is a cross-sectional study, conducted in the Institute of Physiology and Experimental Medicine, Madras Medical College, from 2008 to 2011. Ethics Committee approval and Informed consent from patients were obtained. The migraine patients of both gender in the age group between 20 and 50, having the normal vision were selected fulfilling the IHS criteria for headache and were tested during the headache-free interval. The VEP test was performed using EMG, EP-MARK II (Recorders Medicare System) machine. The patients were asked to avoid oil or hair spray after hair wash and patients with refractory error were asked to wear their usual glasses. The FPz reference electrode was kept over the vertex (12 cm from the nasion), the Cz ground electrode over the forehead and Oz active electrode over the occiput (5 cm above the inion). The electrodes were connected to the preamplifier. The filter range was 2-100 Hz with sweep speed, duration, and sensitivity were 350 ms, 50 ms/D, and 2 μV, respectively. The amplification range was 20,000-1,00,000 with the number of epochs were 200 and with the electrode impedance kept below 5 kΩ. Black and white checkerboard of 80% contrast was used with the stimulus type of pattern reversal. The size of the pattern was 8 × 8 min with rate of stimuli 1-2 Hz. Full field was used with black and white. The focus was red with the mean luminance of the central field 50 cd/m^2 and with the background luminance of 20-40 cd/m^2. The visual stimulus was delivered by photo stimulator at frequency of 10 flashes/s. Both the study group and the control group were stimulated continuously for 15 min. This 15 min period was divided into four blocks of 3.8 min each. Each block was an average of 300 epochs. The response obtained was displayed in the monitor and the peak latency, peak to peak amplitude of the positive and negative wave was measured.

RESULTS

There is a very highly significant ($P < 0.0001$) decrease in the amplitude of P100 in the 4th block when compared to the 1st block in both the eyes in the controls (Table 1).

There is a very highly significant ($P < 0.001$) increase in the amplitude of P100 in the 4th block when compared to the 1st block in both the eyes in migraine patients (Table 2).

A very highly significant ($P < 0.001$) increase in the P100 amplitude is seen in the 4th block of migraine patients when compared to the controls (Table 3).

There is a progressive increase in the amplitude in the migraine patients from the first block to the fourth block. There is a progressive decrease in the amplitude from the first block to fourth block in the control group. The amplitude of the first block in migraine patients is lower than the amplitude of the first block in the controls (Table 4).

Tables 5 and 6 show a very highly significant ($P < 0.0001$) decrease in the latency of the N145 wave in the migraine patients when compared to the control group in both the eyes.

Table 1: P100 amplitude (mv) in the control group

Place	Pair	*N*	Mean±SD	*t* value	*P* value
Left eye	1st block versus 4th block	30	6.5643±1.32008	20.186	<0.0001**
		30	3.9127±1.09528		
Right eye	1st block versus 4th block	30	6.6283±1.47342	22.140	<0.0001**
		30	3.7157±1.23378		

SD: Standard deviation, **highly significant

Table 2: P100 amplitude (mv) in the migraine patients

Place	Pair	*N*	Mean±SD	*t* value	*P* value
Left eye	1st block versus 4th block	30	5.6203±2.66406	−7.160	<0.0001**
		30	6.5243±2.68805		
Right eye	1st block versus 4th block	30	5.8203±2.72149	−4.497	<0.0001**
		30	7.0247±2.61677		

SD: Standard deviation, **highly significant

Table 3: Comparison of P100 amplitude (mv) in the 4th block between the migraine patients and controls

Place	Group	*N*	Mean±SD	*t* value	*P* value
Left					
4th block	Migraine patients	30	6.524±2.6880	4.928	<0.0001**
	Controls	30	3.913±1.0953		
Right					
4th block	Migraine patients	30	7.025±2.6168	6.265	<0.0001**
	Controls	30	3.716±1.2338		

SD: Standard deviation, **highly significant

Table 4: Amplitude of P100 wave (mv) from 1st block to 4th block

Place	Mean values	
	Controls	Migraine patients
Left eye		
1st block	6.56	5.62
2nd block	5.56	6.45
3rd block	4.75	6.57
4th block	3.91	6.52
Right eye		
1st block	6.63	5.82
2nd block	5.64	6.25
3rd block	4.71	6.58
4th block	3.72	7.02

Table 5: Comparison of VEP latency (ms) in the left eye

Variable	Group	*N*	Mean±SD	*t* value	*P* value
N75 (ms)	Controls	30	66.435±2.9452	−1.194	0.240
	Migraine patients	30	68.048±6.7846		
P100 (ms)	Controls	30	95.5853±3.46872	1.518	0.136
	Migraine patients	30	93.6697±5.97927		
N145 (ms)	Controls	30	148.283±10.9468	3.925	<0.0001**
	Migraine patients	30	136.688±11.9122		

SD: Standard deviation, VEP: Visual evoked potential, **highly significant

Table 6: Comparison of VEP latency (ms) in the right eye

Variable	Group	*N*	Mean±SD	*t* value	*P* value
N75 (ms)	Controls	30	66.251±3.0018	−0.903	0.371
	Migraine patients	30	67.225±5.0854		
P100 (ms)	Controls	30	95.7847±4.42328	1.701	0.096
	Migraine patients	30	92.9780±7.87919		
N145 (ms)	Controls	30	149.017±10.6557	4.074	<0.0001**
	Migraine patients	30	134.440±16.4475		

SD: Standard deviation, VEP: Visual evoked potential, **highly significant

DISCUSSION

The present study deals with the changes in the VEPs in patients with migraine. The changes are compared with the controls. There was no statistically significant difference in the age, height, weight, and gender between study and the control group. In this study, both the controls and the migraine patients were stimulated continuously for 15 min. This 15 min period was divided into four blocks of 3.8 min each. The data were statistically analyzed, and their significance derived using independent samples *t*-test and paired *t*-test. VEP results were interpreted with respect to their latency and amplitude. Amplitude of the wave denotes the number of fibers recruited. Increase in the amplitude indicates more number of fibers is being recruited. Decrease in the amplitude indicates less number of fibers is being recruited. Latency denotes the time taken for the impulse to travel from the retina to the occipital striate area. In this study, when the P100 amplitude of the first block and the fourth block were compared, there was a very highly significant ($P < 0.001$) decrease in the amplitude of the fourth block (Table 1) in the controls which may be because of habituation, whereas there was a very highly significant ($P < 0.001$) increase in the amplitude of the fourth block of the migraine patients (Table 2) indicating potentiation. When the amplitude of the P100 of the fourth block of the migraine patient was compared with the amplitude of the fourth block of the controls, a very highly significant increase ($P < 0.001$) in the amplitude of the P100 was noted in the migraine patients (Table 3). When all the four blocks were compared, there was a progressive increase in the P100 amplitude from the first block to the fourth block in migraine patients indicating that more and more number of fibers were recruited (potentiation) during the continuous period of stimulation for 15 min. In the controls, there was a progressive decrease in the amplitude from the first block to the fourth block indicating that the fibers recruited were decreasing during continuous period of stimulation probably because of habituation (Table 4). This result was consistent with the study done by Gawel *et al.* (1983),[11] Diener *et al.* (1989),[12] and Khalil (1991),[13] who have said that there was an increase in amplitude of P100 wave in migraine patients on pattern-reversal stimulus. Similarly, Afra *et al.* (1998),[14] found that during repetitive pattern-reversal stimulation lasting 2 min, the amplitude of the P100 wave increased in migraineurs when tested interictally, whereas it decreased in healthy control subjects. Hartner and White (1970), and Peachy *et al.* (1994),[15] said that check size (spatial frequency) influences the components of habituation behavior of pattern-reversal VEP, whereas Oelkers *et al.* (1999),[16] notes that the peak to peak amplitudes were consistently higher in migraineurs

at all spatial frequencies. Dienner *et al.* (1989),[12] found that there was a decrease in P100 amplitude after treatment with Beta-blockers. Contrary to the above studies, Benna *et al.* (1985),[17] Mariani *et al*. (1988),[18] Drake *et al*. (1990),[19] and Tagliati *et al*. (1995),[20] have said that there was no difference in the VEP amplitude between the migraine patients and the normal subjects. However, there was no significant difference in the latency of N75 and P100 between the migraine patients and the controls. This result was similar to the study done by Benna *et al*. (1985),[17] Mariani *et al*. (1988),[18] Drake *et al.* (1990),[19] and Tagliati *et al*. (1995).[20] In another study done by Oelkers *et al*. (1999),[16] migraineurs exhibited longer latencies than healthy controls when small checks were presented, i.e., high spatial frequency. A highly significant decrease ($P < 0.001$) in the latency of N145 wave (Tables 5 and 6) was observed in both the eyes of this study. This may be attributed to the increased excitability of the cerebral cortex in patients with migraine. Thus, habituation "a response decrement as a result of repeated stimulation" in VEP, which appears to be a physiological phenomenon in the visual cortex, is defective in migraineurs as evidenced by an increase in the amplitude of VEP. Habituation in the nervous system is a ubiquitous phenomenon with complex, region, and functional-dependent mechanisms. In cerebral cortex, it is likely to be modulated by excitatory neurons receiving thalamocortical input, intracortical inhibitory interneurons, and subcortical connections of the brainstem involving the neurotransmitters such as serotonin, dopamine, noradrenaline, and histamine that normally protects against cortical overstimulation.[21,22] Serotonin has widespread innervation of sensory cortices and exhibits tonic pacemaker activity and thus plays a modulatory role in cortical information and processing.[23] Since serotonin plays a pivotal role in migraine pathogenesis,[24] low interictal activity in the serotonergic pathway could be responsible for a low pre-activation level of sensory cortices which causes both increased detection thresholds and a wider range of suprathreshold activation before reaching a saturation or "ceiling" effect.[25-27] This leads to deficient habituation. Initial low amplitudes recorded in this study are due to low pre-activation of visual cortex (Table 4). Thus, habituation of the VEP, which appears to be a physiological phenomenon in the visual cortex, is defective in migraine patient's in-between attacks. Defective habituation is not limited to the processing of visual information alone. It has also been demonstrated for cortical auditory evoked responses,[28] event related potentials,[29] as well as for contingent negative variation.[30] Coppola *et al.* (2007),[31] in his study further substantiated that the deficient habituation is purely cortical phenomena, and this is due to abnormal thalamic control. A change in thalamocortical activity due to anatomical and functional disconnection of the thalamus from its controlling inputs (e.g., aminergic brain stem nuclei) can favor hypoactivity at the cortical level causing deficient habituation leading to thalamocortical dysrhythmia syndrome. Another explanation for an interictal habituation deficit might be due to lactate accumulation in sensory cortices during sustained activation. The abnormal cortical information processing in migraine during repetitive photic stimulation may have deleterious consequences on the metabolic homeostasis of the brain parenchyma. As habituation protects the cerebral cortex against sensory overload, repeated photic stimulation causes transient, excess of glycolysis accompanied by a significant rise in lactate levels.[32,33] Sappey-Marinier *et al*. (1992),[34] found that, during pattern-reversal visual stimulation in healthy control subjects, cortical lactate levels began to decrease only after the amplitude of the VEP had diminished by 50% and concluded that the response habituation was an adaptive mechanism prohibiting an excessive increase in cortical lactate levels. If this mechanism is defective, it induces metabolic instability leading to lactate accumulation thus triggering spreading depression (by Lauritzen, 1994[35]) or a similar dysfunctional leading to attack. Such metabolic shifts demonstrated with spectroscopy was seen in the study conducted by Welch *et al*. (1989); Barbiroli *et al*. (1992);[36] Montagna *et al*. (1994);[37] Sangiorgi *et al*. (1994).[38] Recent nuclear magnetic resonance (NMR) spectroscopy study performed interictally in migraine with aura patients disclosed elevated lactate levels in the occipital cortex Watanabe *et al*. (1996).[39]

CONCLUSION

Migraine patients have attributed to abnormal cortical processing in migraine with interictal hyperactivity leading to heightened responsiveness and lack of habituation and lack of intracortical inhibition. Further studies can be done to know the precise relationship between physiological and biochemical abnormalities of the cerebral cortex in migraine. This can be done by combining sensory activation with neurophysiological techniques for functional imaging such as positron emission tomography or NMR. The best insight into the nature of interictal cortical dysfunction will lead to novel therapeutic targets and may allow a better understanding of the mode of action of available therapies.

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