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Assessment of visual evoked potentials in migraineurs: A cross-sectional study

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Abstract

Background & Objective: Many studies demonstrated that migraine patients have an interictal habituation and deficit of visual evoked potentials. Controversially, other studies could not reproduce similar finding. Hence, there is a dilemma regarding what should be the ultimate conclusions. The purpose of this study was to compare amplitude and habituation of pattern reversal visual evoked potentials in migraine with aura patients and healthy volunteers. *Methods:* A total of 40 migraine with aura patients and 40 controls were prospectively enrolled in this cross-sectional study. Using the pattern reversal stimuli, visual evoked potential were estimated in all the participants and abnormalities were noted. *Results:* In migraine with aura patients, there was a statistically significant increase in the amplitude of the P100 wave due to deficient habituation after 15 min stimulation. In normal subjects, there was a decrease in the amplitude of the P100 wave due to the effect of habituation. The deficient habituation can be because of decreased serotonin levels resulting in reduced pre-activation of the cortex. *Conclusion:* Migraine with aura patients show evidence of abnormal cortical processing with interictal hyperactivity seen in heightened responsiveness and lack of habituation to visual evoked responses.

Keywords: Habituation, migraine with aura, visual evoked potential

INTRODUCTION

Migraine is a common disabling primary headache disorder with a tremendous impact not only on professional, social and family lives but also on the economy. The prevalence of migraine is accounting for 12% of the total world's population and, in India, of 1200 million inhabitants; 150-200 million migraine patients are under treatment. The prevalence of migraine is outnumbered in female compared to men (20% vs 6%).[1] In today's scenario, migraine is the most common neurological problem encountered by neurologists in their day to day clinical practices. It is a primary headache disorder characterized by recurrent headaches that are moderate to severe. Typically, the headache of unilateral location is pulsating in nature and persists from a few hours to three days. The pain is usually made worse by routine physical activity. Associated symptoms may include nausea, vomiting, and/or photophobia and phonophobia. Visual disturbances are most common clinical characteristics of migraine. According to the International Classification of Headache Disorders (ICHD), it is classified into two types: headache with aura and headache without aura. In 82% of cases where an aura is present, symptoms of flashes of light, stars, zig-zags, central or paracentral blind spot, and scotoma is observed.[2] Migraine patients are also much susceptible to environmental light stimuli. In the etiopathogenesis of migraine, trigeminovascular system[3], brainstems[4,5], and cerebral cortex[6-8] have assumed to play a significant role. Modern neuroimaging studies[9] have established the association of migraine with aura symptoms with a cortical phenomenon similar to spreading depression.

Many studies proposed that people suffer from migraine are well characterized between attacks by a habituation deficit of visual evoked potentials (VEPs).[10-13] A few studies have been performed over the years focused on this topic.

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Controversially, some studies have been argued against this verdict, which was tentatively due to methodological issues[12,13] or variations in migraine phenotypes.[14] The present study intended to evaluate VEPs changes in migraine patients between attacks compared to healthy volunteers. By this way, we wish to present our observations regarding the conflicting outcome of VEPs changes in migraine with aura by evidence-based practice.

METHODS

The study was a prospective, comparative study with a control group conducted in the tertiary care hospital and teaching centre, south India between June 2017 to June 2018. The study protocol was approved by the institutional ethics committee and informed consent was obtained from patients before enrollment.

The inclusion criteria were patient with age between 18-65 years, who fulfilled the International Headache Society Classification ICHD-3 Beta criteria for migraine with aura and, attack-free for at least 3 days before and after the recording sessions and not taken any prophylaxis drugs were included in the study.

The following cases were excluded from the study: 1. History of first-degree relatives having a migraine with aura for the control group; 2. Failure to reach a best-corrected visual acuity of >6/18; 3. History of other neurological diseases; 4. History of systemic hypertension, diabetes or other metabolic disorders such as chronic kidney disease, chronic liver disease, connective or autoimmune diseases; 5. Regular medication intake (i.e. Analgesics, antibiotics, corticosteroids, antidepressants, benzodiazepines, prophylactic migraine drugs, antiepileptic, medications interfering with magnesium metabolism)

The sample size calculation was by using below mentioned formula, the total sample size was found to be 40 in each group.

$n=2\sigma 2(Z\beta+Z\alpha/2)2/d2$
Samσ =combined SD= (SD12+SD22)/2=2.662+1.3822=4.49
Zβ=0.84 for 80% power
Zα/2=1.96
n with standard deviation in the case group is 2.6, the control group is 1.32, (Madras Medical college group)[15] with 80% power, 95% confidence interval and acceptable clinical difference of mean as 3 and adding 10% non-response error.

METHODS

After completing the consent process, in total, 40 patients who visited the outpatient headache clinic of the neurology department were recruited into the migraine with aura group (case) as per previously mentioned inclusion and exclusion criteria. Forty healthy volunteers (demographically matched) served as a control group. Patients were subjected to a detailed medical history, thorough clinical examination and investigations as per working pro forma. The VEPs test was performed using EP/EMG NEUROPACK-M1 machine. It was recorded by the pattern-reversal stimulation format. The subjects were advised to avoid oil or hair spray after hair wash and, subjects with errors of refraction were asked to use their usual glasses. The FPz reference electrode was placed 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 attached to the preamplifier. The filter range was 2-100 Hz with sweep speed, duration, and sensitivity of 350ms, 50ms/D, and 2μV, 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/m2 and with the background luminance of 20-40 cd/m2. Photo stimulator delivered the visual stimulus at a frequency of 10 flashes/s. Both the study group and the control group were stimulated continuously for 15 min. This 15 min period was split into four blocks of 3.8 min each. Each block contained an average of 300 epochs. The resulting response was shown in the monitor and, the peak latency, peak to peak amplitude of the positive and negative wave were estimated.

Statistical analysis

The extracted data was coded into Microsoft Excel spreadsheet software and entered into a statistical package for social sciences (IBM 21, Armonk, NY, USA). Quantitative values were presented as mean±standard deviation and, categorical data were expressed as frequency (percentage). For comparison across the group, independent sample 'T' test was used. Paired T-test was used to compare two variables that are separated by time in the same subject. The *P*-value of <0.05 was considered as statistically significant.

Table 1: Demographics and clinical characteristics of involved participants

Characteristics	Controls (n=40)	Cases (n=40)	*P*-value
Mean age (years)	33.43±8.50	32.58±9.40	0.673
Age group, n(%)			
11-20	0	2	0.372
21-30	19	20	0.910
31-40	13	10	0.676
41-50	7	7	1.000
51-60	1	1	1.000
Gender, n(%)			
Male	20	19	0.910
Female	20	21	0.912
Duration of disease (years)	–	9.13±1.32	–
Days since the last attack	–	6.83±3.73	–

† Values are mean±SD for quantitative and frequency (%) for categorical data.
*Based on independent *t*-test, **Based on Chi-square test

RESULTS

Clinical and demographic characteristics of migraine with aura patients (cases) and healthy volunteers (controls) are detailed in Table 1. There was no statistically significant difference in the age and gender between cases and the control group. The mean age of the participants in the cases and the control group was 32.58±9.4 years and 33.43±8.5 years, respectively, with no statistically significant difference between the two groups. In the migraine with aura group, the maximum number of patients were in the age group of 21-30 years with a mean duration of disease was 9.13±1.32.

When the amplitude of the fourth block was compared with the first block, in controls, highly significant ($P<0.001$) decrease in the amplitude of the fourth block was recorded in both eyes, whereas, in migraine with aura patients a highly significant ($P<0.001$) increase in the amplitude of the fourth block was noted in both eyes (Table 2). The amplitude of the P100 of the fourth block in the migraine with aura patients compared with the amplitude of the fourth block of the controls, in both eyes, a very highly significantly increase ($P<0.001$) in the amplitude of the P100 was noted in the migraine with aura patients (Table 3). The trend of P100 amplitude has been shown in Figure 1, 2 using the line graph. This graphical representation displays the progressive increase in the amplitude from the first block to the fourth block in the migraine with aura suggestive of potentiation. On other hand, amplitude was decreased from the first block to the fourth block in the control group indicating habituation. In migraine with aura patients, the amplitude of the first block is lower than the amplitude of the first block in the controls. As shown in Table 4, there was no significant difference in the latency of N75 between cases and controls and a highly significant decrease ($P<0.001$) in the latency of P100 and N145 waves was noted in both eyes.

DISCUSSION

This prospective study investigated the changes in the VEPs in migraine with aura patients

Table 2: P100 amplitude (mv) in the control group and cases

Side	Pair	N	Controls		Cases	
			Mean±SD	*P*-value	Mean±SD	*P*-value
Left eye	1st block versus	40	7.98±0.39 vs	<0.0001**	6.07±0.77 vs	<0.0001**
	4th block	40	4.18±0.24		7.78±0.78	
Right eye	1st block versus	40	8.06±0.33 vs	<0.0001**	6.03±0.78 vs	<0.0001**
	4th block	40	4.17±0.27		7.73±0.65	

† Statistics were done using paired t-test. SD: Standard deviation, **highly significant

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

Side	Group	N	Mean±SD	*P*-value
Left eye	Cases	40	7.78±0.78	<0.0001**
4th block	Controls	40	4.18±0.24	
Right eye	Cases	40	7.73±0.65	<0.0001**
4th block	Controls	40	4.17±0.27	

† Statistics were done using independent sample t- test.
SD: Standard deviation. **highly significant

compared to controls. Both the controls and cases were stimulated continuously for 15 min in our study. This 15 min duration was divided into four blocks of 3.8 min each. VEPs results were estimated in terms of latency and amplitude. The amplitude of the wave expresses the number of fibres recruited. Increase in the amplitude means the number of fibres is being recruited, whereas, the decreased value indicates vice versa. Latency indicates the time taken for the impulse to travel from the retina to the occipital striate area. We compared the P100 amplitude of the first block and the fourth block; in the controls, there was a very highly significant (P<0.001) decrease in the amplitude of the fourth block, which may be due to habituation, whereas, there was a very highly significant (P<0.001) increase in the amplitude of the fourth block of in migraine with aura patients (Table 2) expressing potentiation. Comparison of amplitude of the P100 of the fourth block in migraine with aura patients with controls revealed that a very highly significant increase (P<0.001) in the amplitude of the P100 was noted in migraine with aura patients (Table 3). At last, 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 with aura patients indicating that more and more number of fibres 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 fibres recruited were decreasing during the continuous period of stimulation, probably due to habituation (Figure 1, 2). This result was consistent with the studies reported by Vijayalakshmi *et al*.[5], Coppola *et al*.[15], Bednar *et al*.[16] and Afra *et al*.[17], which stated that the amplitude of the P100 wave increased in migraine with aura patients when tested interictally during repetitive pattern-reversal stimulation lasting 2 min, whereas it was decreased in healthy control subjects.

However, our study has contradictory outcomes to those by Oelkers *et al*.10, Omland *et al*.13 and Oelkers- Ax *et al*.18, which stated that there was no difference in the VEPs amplitude between the migraine patients and the normal subjects. Previous studies have hypothesized that the use of different stimulation parameters could explain the discrepancy in these findings. Table 5 enlists stimulation parameter in terms of reversal rate used in current and previously reported studies.

As shown in Table 4, there was no significant difference in the latency of N75 between the cases and the controls. These findings are in favor of those reported by Mariani *et al*.[19] and Tagliati *et al*.[20] In our study, a highly significant decrease (P<0.001) in the latency of P100 and N145 waves was noted in both the eyes. Similar findings

Table 4: Comparison of VEPs latency (ms) in cases and controls

Variable	Group	N	Left eye		Right eye	
			Mean±SD	*P*-value	Mean±SD	*P*-value
N75 (ms)	Cases	40	72.68±1.68	0.006*	72.13±1.91	0.06
	Controls	40	73.75±1.72		73.85±1.46	
P100 (ms)	Cases	40	94.58±2.75	<0.0001**	94.63±2.86	<0.0001**
	Controls	40	102.56±2.02		101.93±2.72	
N145 (ms)	Cases	40	137.85±3.54	<0.0001**	137.60±3.11	<0.0001**
	Controls	40	145.53±2.51		145.55±2.21	

† Statistics were done using independent sample t test. SD: Standard deviation,
VEP: Visual evoked potential. *significant, **highly significant

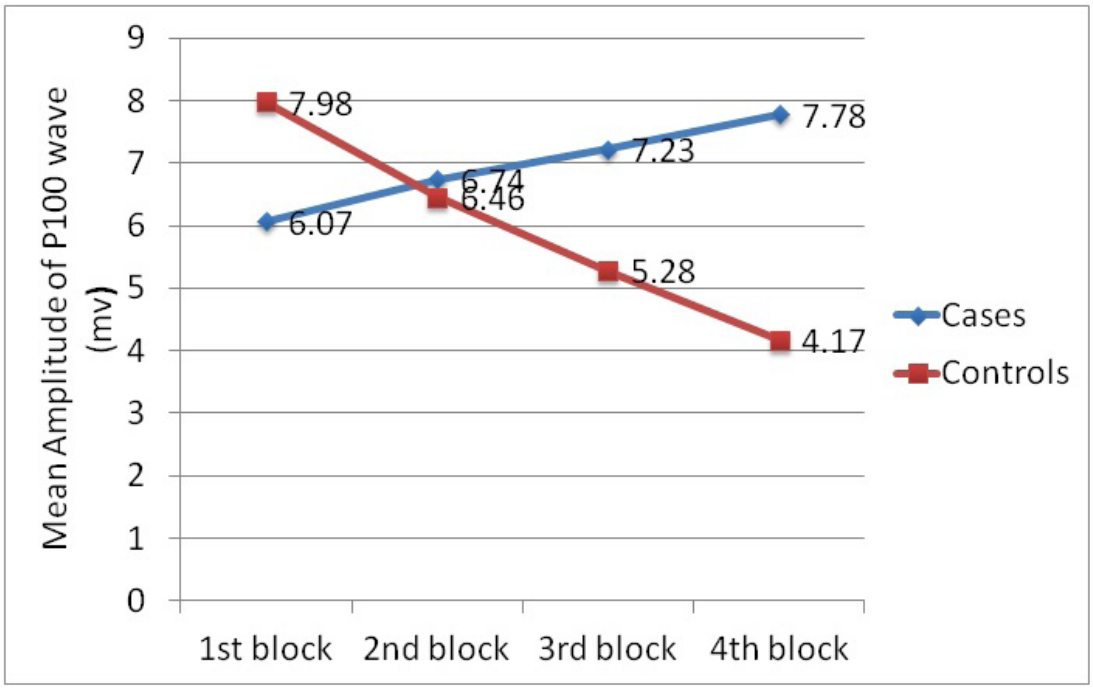

Figure 1. Line diagram showing the trend of P100 amplitude of cases and controls in the left eye

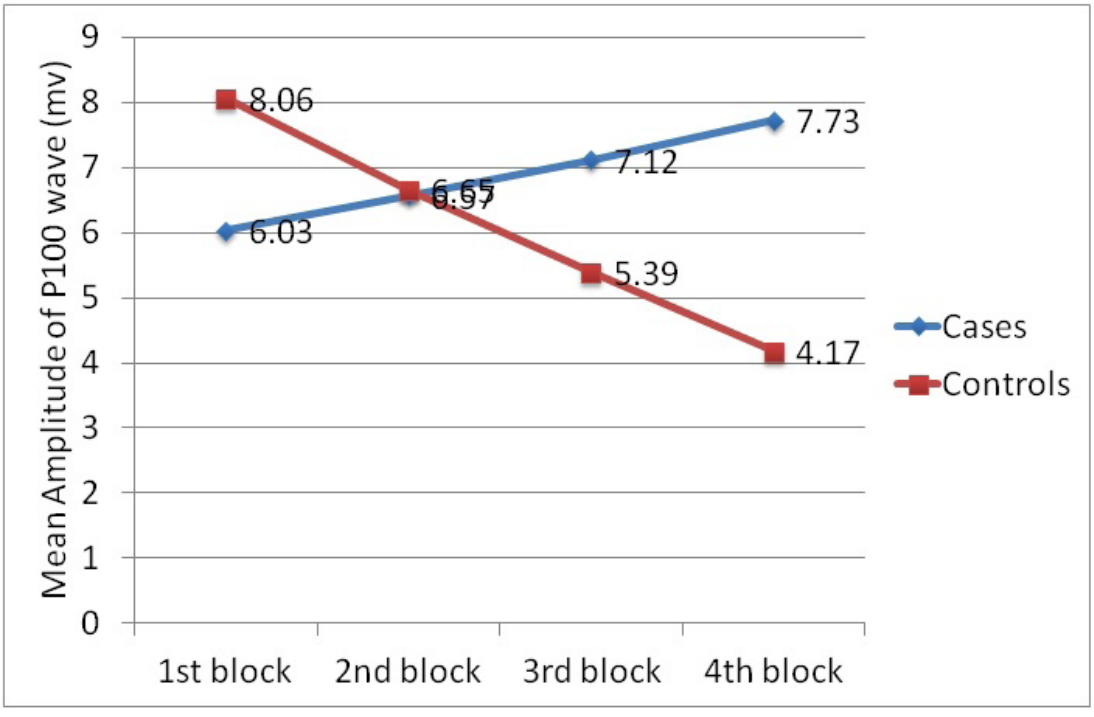

Figure 2. Line graph displaying the trend of P100 amplitude of cases and controls in the right eye

Table 5: Comparison of stimulation parameters among the current study and previously reported studies

Authors, year	Reversal rate (reversals per second)
Oelkers *et al*., 1999[10]	3.7
Omland *et al*., 2016[13]	3.7
Oelkers- Ax *et al*., 2005[18]	3.7
Present study	1-2

proposed by Vijayalakshmi *et al*.[5] This may be due to the increased excitability of the cerebral cortex in migraine patients. So that, habituation "a response decrement as a result of repeated stimulation" in VEPs, which seems to be a physiological phenomenon in the visual cortex, is abnormal in migraine patients as proved by a rise in VEPs amplitude. Habituation in the nervous system is an omnipresent phenomenon with complex, region, and functional-dependent mechanisms. In the cerebral cortex, it is expected to be modulated by excitatory neurons receiving thalamocortical input, intracortical inhibitory interneurons, and subcortical connections of the brainstem including the neurotransmitters such as serotonin, dopamine, noradrenaline, and histamine which usually defend against cortical overstimulation.[21] Serotonin has extensive innervation of sensory cortices and displays tonic pacemaker action and by this way, plays a modulatory role in cortical information and processing. Thus, serotonin plays a pivotal role in migraine pathogenesis, low interictal activity in the serotonergic pathway could be responsible for a low pre-activation level of sensory cortices resulting in both increased detection thresholds and a wider range of suprathreshold activation before reaching saturation or "ceiling" effect.22 This contributes to deficient habituation.

Initially, low amplitudes of P100 recorded in this study may be due to low pre-activation of the visual cortex. Therefore, habituation of the VEPs, which tends to be a physiological phenomenon in the visual cortex, is defective in migraine patients'

Table 6: Comparison of the findings of previous studies with present studies with respect to VEPs changes

Parameters	Coppola *et al*., 2009[15]	Vijayalakshmi *et al*., 2016[5]	Omland *et al*., 2013[12]	Present study
P100 amplitude, mv (1st block)				
Cases	8.27±2.83	5.62±2.66	11.7±5.5	6.07±0.77
Controls	6.97±2.90	6.56±1.32	12.5±5.3	7.98±0.39
P100 amplitude, mv (4th block)				
Cases	8.57±2.81	6.52±2.68	10.3±5.9	7.78±0.78
Controls	6.55±2.74	3.91±1.09	10.4±4.7	4.18±0.24
P100, mv (4th -1st block)				
Cases	0.30	0.90	-	-
Controls	-0.42	-2.6		
N75 latency, ms				
Cases	75.9±4.6	68.04±6.78	-	72.68±1.68
Controls	76.5±6.4	66.43±2.94		73.75±1.72
P100 latency, ms				
Cases	103.4±8.0	93.66±5.97	-	94.58±2.75
Controls	103.5±5.9	95.58±3.46		102.56±2.02
N145 latency, ms				
Cases	142.6±11.4	136.68±11.91	-	137.85±3.54
Controls	144.2±10.4	148.28±10.94		145.53±2.51

in-between attacks. Deficient habitude is not limited to the visual information retrieval alone but also showed the response evoked by cortical sensory, event-related potentials. In agreement with Coppola *et al*.[15], the deficient habituation is completely cortical phenomena, and this is attributed 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) may support hypoactivity at the cortical level triggering deficient habituation resulting in thalamocortical dysrhythmia syndrome. Lactate accumulation in sensory cortices during sustained activation might be another reason for an interictal habituation deficit. The abnormal cortical information processing in migraine during repetitive photic stimulation may have harmful outcomes on the metabolic homeostasis of the brain parenchyma. As habituation guards the cerebral cortex against sensory overload, repeated photic stimulation triggers transient, the abundance of glycolysis followed by a significant rise in lactate levels.[23,24] This verdict is supported by Sappey-Marinier *et al*.[25] and using spectroscopy metabolic shifts were observed in various studies.[21,22,26] Recently, nuclear magnetic resonance (NMR) spectroscopy study performed interictally in migraine with aura patients revealed elevated lactate levels in the occipital cortex.[27]

In literature, many reported studies have only focused on the estimation of average (or global) VEPs amplitude but sill lack of information regarding how amplitude changes during the stimulation. Our study also measured global VEPs amplitude of P100 and findings were in favor of increased VEPs amplitude in migraine patients.

VEPs changes in migraine may be attributed to the chronicity of migraine.28 In the present study, we could not correlate the duration of the disease with VEP changes, though, the mean duration of the disease is 9.13±1.32 years.

In literature, few similar studies have been reported and, comparison of VEP findings between these studies is the most attractive part of the discussion to get a definite judgment regarding VEPs changes in migraine has been favoring or not. Table 6 presents a comparison of the findings of previous studies with present studies with respect to VEPs changes.

The present study has major drawbacks. First, it is a hospital-based study. Secondly, the sample size was too small and only hence may not be representative of the population. Thirdly, migraine subtypes, types of auras could not be separately investigated with respect to VEPs changes. At last, in female, the effect of the menstrual cycle with respect to VEPs could not be determined.

In 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. To sum up, interictal VEP changes occur in the form of potentiation in migraine patients. Further, randomized, multicentered study with blinding is recommended to confirm our findings.

DISCLOSURE

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Conflict of interest: None

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