*Research Article*

*DOI Number: 10.5958/2320-608X.2020.00013.X*

# Somatosensory Evoked High Frequency Oscillations in a Homogeneous Population of Drug Naive Migraineurs

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## Abstract

Introduction: High band pass filtering of evoked potentials have produced the results of decreased early High frequency oscillations (HFOs) in previous studies of migraine patients. However, in most of these studies, the study population has been heterogeneous. The only study till date which used homogenous drug naive group of patients has actually produced contradictory results to the previous studies showing. Aim: We aimed to clarify the status of HFO amplitudes and latencies in drug-naive newly diagnosed patients. Methods: In the present study, we evaluated the 20 newly diagnosed and drug naive migraine patients using electrophysiological assessments using Somatosensory evoked potentials (SSEPs) and compared their SSEP parameters with those of the healthy age and gender matched normal controls. Median nerve SSEP was obtained by standard protocols. High frequency oscillations were extracted from the broad-band evoked potentials by digitally filtering using high pass filtering at 450Hz-1KHz. Early HFOs were identified when occurred before the N20 peak. Results: No differences were observed in the broad-band SSEPs i.e., N20 amplitudes and latencies. The maximal peak to peak amplitudes in the drug naïve migraineurs in between the attacks for the early HFOs (occurring before the N20 peak) were significantly smaller than the normal controls (p=0.046). The number of negative peaks were also fewer in the migraineurs in a statistically non-significant way. Discussion: This is the first HFO study on a homogenous population of migraineurs which shows decreased early HFOs, thus implicating weaker thalamocortical activity and contradicting the results by Lai et al[1].

***Keywords:*** *SSEP, HFO, drug naïve migraineurs, thalamocortical activity*

## Introduction

Migraine is one of the most common neurological disorders with a prevalences of nearly 8% and 12-15% in males and females respectively[2]. It is a disabling condition characterized by excruciating headaches which vary widely in duration and intensity and almost universally the condition causes severe interference with daily life activities of the patient. The headaches are characterised by throbbing in nature and unilateral in location along with the additional features of nausea, sensitivity to light, sound, and exacerbation with body and head movements. The International Classification of Headache Disorders (ICHD) has provided the operational clinical criteria for migraine diagnosis which includes the migraine with and without aura. Inspite of its high prevalence and being studied scientifically for several decades now, the etiopathogenesis of migraine remains poorly understood. Recently the theoretical standpoint for the etiopathogenesis of headaches has shifted from the vascular hypersensitivity theory to the cortical hyperactivity theory proposing that it is the abnormal cortical excitability leading to enhanced pain perception.

Electrophysiological methods have proved to be vital for assessments in such conditions because they have allowed in vivo measurements of the migraineur's cortical responses to various sensory stimuli. Especially, the SSEPs have been studied for exploring the neurophysiological abnormalities in migraine. Some very important electrophysiological findings have been noted in migraineurs in-between the attacks. The most well established electrophysiological abnormality

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in migraine has been the lack of adequate habituation response of somatosensory cortex to stimuli meaning that the migraine patients fail to show a decremental response to repeated stimuli[3]. This finding led the researchers in this field to search and speculate for the possible neurophysiological mechanisms underlying the failure of this habituation response. It has been hypothesized that pre-activation excitability of cortex could be the etiology of this lack of habituation[4]. However, the mechanisms underlying this pre-activation excitability remain a matter of speculation. Among the hypotheses, altered activity of thalamo-cortical connections leading to cortical inhibition has been proposed [3,5] which subsequently result in the lack of habituation response. This abnormal information processing has been proposed to be responsible for the hypersensitivity of cortex leading to enhanced perception of pain.

In order to develop a clearer comprehension and clarity of the mechanisms underlying the deficit seen in habituation in migraine, more sophisticated analysis of evoked potentials (especially the somatosensory evoked potentials) have been applied. Analysing the HFOs in evoked potentials is one such sophisticated method. HFOs are the low amplitude (around 100 nVs) high frequency (>600 Hz) waves embedded within the broad-band fluctuations obtained in the usual fluctuations of the SSEPs. These can be elicited by using digital high-pass filtering (>400 Hz) during the recording or offline analysis of various evoked potentials. HFOs in SSEPs are classified into two types according to their theoretical sources of origin. Whereas the early HFOs (those occurring before the peak of N20) are thought to reflect spike activity in the activation from thalamo-cortical cholinergic fibres, the late HFOs (following the peak of N 20) originate theoretically due to the cortical inhibitory GABAergic interneuron[6]. A study of SSEP HFOs in migraine therefore theoretically explores the thalamo-cortical activation as well as the intrinsic inhibition of the parietal cortex simultaneously. In recent years, few studies have been conducted for evaluating the early and late HFOs in migraine. Mostly, HFOs in migraineurs have been studied on the SSEPs. Earliest study with this methodology was conducted by [7] who found that HFOs in SSEPs were decreased generally in migraine patients in between the attacks. Subsequently this finding was reproduced by few other studies [3,9]. However, the conclusion from these studies is far from universally accepted. Whereas a majority of such studies show a decreased HFOs (maximal amplitude and area under curve) in migraineurs as compared to healthy controls [3,9] some studies actually show the opposite findings with increased HFO amplitudes between migraine as compared to controls[1]. The study [1] raises some important issues because it was the only study that we could find which was conducted on untreated migraine patients. Therefore it raises the speculation that untreated migraine patients could be having a hyperexcitable rather than a hypoexcitable cortex between the attacks. Therefore, the treatment naive condition of such patients could be the reason that the HFO findings were different from other patient samples who are undergoing treatment or whose clinical pictures are improving [3,9]. This raises the question whether the earlier findings of low HFO amplitudes between the attacks could be because of inhomogeneity in the sample population. Especially, the effects of chornicity of migraine or treatment related improvements could have influenced other findings. It has been observed that the changes in the clinical status in the course of migraine is associated with changes in HFOs with the amplitudes decreasing with worsening of symptoms and increasing with improvement in the symptoms[8]. In another recent study the maximal peak to peak amplitudes in Chronic migraine patients were similar to the normal subjects whereas the maximal amplitudes in interictal periods of migraine were significantly smaller than normal subjects[9]. Therefore, the variations in findings in these previous studies could have been due to inhomogenous population of samples with regards to chronicity and clinical status. We aimed to control these variables by selecting a sample of young and newly diagnosed patients suffering from migraine who were treatment naive. We conducted broad band SSEPs as well as high band filtering to obtain early (presynaptic) HFOs in a homogenous population.

## Methodology

**Sample:** In present study, we evaluated 20 patients newly diagnosed as migraine and compared them with healthy age and gender matched normal controls. The patients were recruited from the out patients department of the neurology department. All the patients were newly diagnosed with migraine. The diagnosis was made as per the guidelines provided by the International classification of headache disorders 3rd edition[12]. Subjects were excluded if they fulfilled the criteria of chronic migraine according to the ICHD criteria or any other neurological condition. The electrophysiological examination was conducted on the next day of diagnosis before beginning

with the medications. Therefore during the examination, the patients were drug-naive. It was also assured that the patients did not receive any specific anti migraine medications in past. Even when they had been taking non-specific analgesics, it was not on a regular basis to avoid the inclusion of medication overuse headache. All the subjects had given written informed consent and the study was approved by the institutional ethical committee.

**Somatosensory evoked potentials:**

Stimulus delivery: Electrical stimuli in the form of constant current duration of 0.2 ms width square wave pulses were applied to the right wrist for stimulation of the right median nerve. The stimulus were delivered at a regular interval with a stimulation frequency of 4.2 Hz. The anode was placed in strategic way at the wrist such that it overlapped the median nerve. The location was just at the proximal palmar crease. The cathode was placed at a location of 3 cm proximal to the anode. The stimulus intensity was calculated using the motor threshold and was set slightly above the same. The placement of recording electrodes was done at C3' and Fz as per the guidelines of the International 10-20 System. The reference electrode was placed on the forehead. Impedances of the electrodes were kept below the levels of 10 kΩ. A trial of 500 stimuli was applied and the consequent responses were used for averaging SEP. Subjects were asked to sit in a relaxed posture on a comfortable chair. The room was adequately and the subject was asked to keep their eyes opened with their attention fixed on the wrist movement. Fifty milliseconds duration of the post-stimulus period were sampled at a frequency of 5000 Hz.

*Broad band and High frequency oscillation analysis:* The usual broad-band SEP responses were obtained by using a band-pass filter of the range from 0.5-2000 Hz. The HFOs were separated and isolated from the underlying N20 primary cortical responses, by offline analysis. HFOs were extracted from the broad band recording by altering the band frequency settings at 450 Hz and 1 KHz which made evident the small amplitude waves existing between this frequency range (Fig.1). The HFOs were marked only for the oscillations which were at least double the amplitude of the background noise[1]. Two separate bursts of HFOs could be identified in most of the SSEP response traces: the first burst, also known as the early burst was the one occuring before the onset of N20 peak which usually began with the initiation of the ascending limb of N20 or just before it. In literature, this has been referred to as the early or pre-synaptic HFOs (Coppola et al 2005). In general, the frequency of oscillations was observed to be higher in the first HFO burst as compared to the second burst. For marking these HFOs, we included the wavelets occurring before the peak of N20 as the early HFOs and those occurring after the peak of N20 as the late HFOs. We chose to a 5ms gap before and after the onset of this 5 ms because sometimes the onset and offsets of HFOs are controversial as they may originate before the ascending limb/onset of N20. Therefore, to maintain uniformity, we chose to have a fixed time interval.

In HFOs, we measured the latency of the negative oscillatory maximum, the number of negative peaks and the maximum peak-to peak amplitudes. The latency was automatically marked by the software on the X-axis and the negative peaks were manually counted. All measurements were performed separately on the two HFO bursts-early and late. Standardised measures of latencies and peak to peak amplitudes were used to calculate the parameters of Latencies of the negative oscillatory maxima and maximum peak-to-peak amplitudes for the early HFO-components defined as those peaking before the peak of N20 waveform. Latencies and amplitudes of the late HFO subcomponents were computed in the same way as for the early HFO burst peaking after the N20 maximum[6]

Statistical analysis: For statistical analysis, SPSS 16$^{th}$ version was used. The data was expressed as means and standard deviations. Independent samples t test was applied to find the difference between broad-band as well as the HFOs variables between the cases and the controls. For categorical variables, chi-square test was applied.

## Results

The results have been expressed in Tables 1,2 and 3. Table No.1 shows the comparison of the sociodemographic variables between the cases and controls. All the subjects of cases and control groups were right handed. There were no statistical differences between the two groups on the parameters of age and gender and height. Controlling these four variables (Handedness, age, gender and height) was important as these are known to influence the SSEP waveform parameters[10].The comparison of N20 wave form amplitudes and latencies obtained from broad

band filtering of SSEP have been presented in Table No.2. The results show that there were no statistical differences between the amplitudes and the latencies between the groups. Table No.3 show the comparison of HFOs parameters between the groups. We found statistically significant difference only in the maximum peak to peak amplitudes of early HFOs such that the amplitude was lesser in the migraine patients (0.07± 0.049 μV) as compared to the normal controls (0.12 ± 0.10 μV). The number of negative peaks were also lesser in the migraine patients (2.73 ± 0.71) as compared to the normal controls (3.07 ± 0.76).

**Table No.1: Sociodemographic Variables of Cases and Controls**

| | **Cases** | | **Controls** | | |
|---|---|---|---|---|---|
| | **Mean/N** | **SD/%** | **Mean /N** | **SD/%** | **p-value** |
| Age (Years) | 24.25 | 5.92 | 25.05 | 5.57 | 0.66 |
| Gender (Males) | 7 | 17.9 | 9 | 23.1 | 0.32 |
| (Females) | 13 | 33.3 | 10 | 25.6 | |
| Height (cms) | 164.89 | 4.15 | 166.78 | 4.97 | 0.34 |
| Handedness (Right) | 20 | 100% | 20 | 100% | 1 |
| (Left) | 0 | | 0 | | |
| Education status | | | | | 0.11 |
| Undergraduate | 0 | 0 | 0 | 0 | |
| Graduate | 14 | 35.9 | 8 | 20.5 | |
| Postgraduate | 6 | 15.4 | 11 | 28.2 | |
| Employment status | | | | | 0.27 |
| Student | 14 | 35.9 | 14 | 71.8 | |
| Unemployed | 4 | 10.3 | 1 | 12.8 | |
| Employed | 2 | 5.1 | 4 | 15.4 | |

No significant differences were observed among the cases and controls over the variables of age, gender, educational status and employment status

**Table No.2: Broad Band Pass Filtering of SSEP Showing N20 Amplitudes and Latencies**

| | **CASES** | | **CONTROLS** | | |
|---|---|---|---|---|---|
| | **MEAN** | **SD** | **MEAN** | **SD** | **p-value** |
| N20 AMPLITUDE (μV) | -1.65 | 1.39 | -2.27 | 1.89 | 0.49 |
| N20 LATENCY (ms) | 18.64 | 1.30 | 18.51 | 1.14 | 0.81 |

No significant differences were observed in the broad band variables of N20 in both the amplitude and latency

**Table No.3: Electrophysiological parameters of high frequency oscillations of SSEP**

| | CASES | | CONTROLS | | |
|---|---|---|---|---|---|
| | **MEAN** | **SD** | **MEAN** | **SD** | **p-value** |
| LATENCY OF MAXIMUM NEGATIVE PEAK (ms) | 16.20 | 1.54 | 16.08 | 1.92 | 0.82 |
| NUMBER OF NEGATIVE PEAKS | 2.73 | .71 | 3.07 | .76 | 0.14 |
| MAXIMUM PEAK TO PEAK AMPLITUDE (μV) | .07 | .049 | .12 | .10 | 0.046 |

No significant differences were observed in the latency of maximum negative peak. A trend difference was observed in the number of negative peaks with lesser number of peaks in migraine patients as compared to healthy controls. The maximum peak to peak amplitude was significantly reduced in cases as compared to controls (p=0.046)

## Discussion

In this small study, we aimed to evaluate the HFOs in newly diagnosed drug-naïve migraine patients. But more importantly, this study was aimed to investigate if the HFO related findings in earlier studies were affected by the inhomogenity of their sample populations. In order to make our study sample homogeneous, we eliminated the variations in chronicity, age and drug treatment status across the patient group. Ours is the first study conducted with this level of controlling of patient parameters. The mean age of our patients group was 25 years showing that they were in the early stages of migraine. This was important in our study to eliminate the element of chronicity for which we also excluded the subjects fulfilling the ICHD criteria for chronic migraine. Such an age-specific assessment was necessary because it has been observed that the clinical features of migraine change with age[11]. Other sociodemographic conditions like gender were also controlled so that there were no significant differences between the two groups (Table No.1). Our study findings are important to clarify the exact status of HFOs in newly diagnosed drug naive patients. Whereas most of the studies have reported decreased HFO amplitudes in the interictal period of migraine [3,9], the patients included in these studies have been heterogenous in terms of chronicity and clinical condition. On the other hand the only study which recruited homogenous drug naive patients with lack of chronicity showed contradictory results by eliciting high HFO amplitudes in between the attacks[1]. This raises the speculation that if the drug naivety and lack of chronicity the patient's group were the reasons for this contradictory finding[1]. Therefore we aimed to clarify these findings. In our study we controlled these factors by only recruiting newly diagnosed patients before being started on any anti-migraine medications. The importance of recruiting young patients has been discussed above.

However, inspite of our sample being similar to that of Lai et al (2011), our results are in sharp contrast to theirs and are in line with previous study results by Coppolla et al (2005;2013). We found that HFO amplitudes in migraineurs were smaller than the healthy controls. Additionally we also found lesser number of negative peaks in early HFOs in our migraine patients (Although not statistically significant, p=0.15) again strengthening the idea that the early HFOs are weakened in migraine patients in between the attacks. Our results therefore echo the idea that in between the attacks, activity in the thalamocortical excitatory cholinergic afferents are decreased, thus indicating subcortical hypoexcitability [3,9]. On the basis of our results we therefore conclude that in drug naive and non-chronic migraine patients, the thalamocortical projection activity is less leading to a state of hypoexcitability of cortex. However, we recommend that before any

electrophysiological assessment, it is important to keep the migraine patient group as homogeneous and as well defined as possible because the demographic related or treatment related variables can very well affect the clinical condition of migraine thereby causing errors in the assessment findings.

## Conclusion

Our study clarifies the prevailing confusion regarding status of SSEP HFO amplitudes in newly diagnosed drug naive patients by showing that even in homogenous drug naïve patients, the early HFO amplitudes are smaller. Thus we conclude that in drug naïve young patients suffering from migraine, the HFO negative peaks are smaller and lesser in number which is indicative of hypexcitability of cortex. In future studies, homogeneity of the population should be ensured to avoid any interference on the results arising from the disease related or treatment related confounding variables.

**Conflict of Interest:** 'The author(s) declare(s) that there is no conflict of interest'

**Source of Funding:** Self

**Ethical Clearance:** Obtained from the Institutional Ethical committee.

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