Migraine With and Without Aura: Clinical and Electrophysiological Changes

M.F. EL-Shater¹, Y. Abo El-Naga², A. Gaber², A. Hazzo², A. Nassif²
Departments of Neurology, Tanta University¹, Neurology, Ain Shams University²

ABSTRACT

Background: Electrophysiological changes in between migraine attacks may open the door for better understanding of pathogenic mechanisms which underlie migraine. Objectives: Our purpose was to evaluate Visual Evoked Potential (VEP) parameters in migraine with and without aura compared with healthy control subjects and to discuss the benefits and limitations of electroencephalography (EEG) in evaluating patients with migraine.

Methods: 30 migraine patients (11 patients with aura and 19 patients without aura) and 28 controls, age and sex matched were prospectively enrolled in this study. Pattern Reversal–Visual Evoked Potential (PR-VEP) and EEG were performed in all patients and controls and abnormalities were correlated with observed clinical evaluation.

Results: Migraine patients with aura showed significant delay in P100 latency, and significant EEG changes compared with patients without aura and controls. Patients without aura showed non-significant difference compared with controls as regards to P100 latency and EEG changes. Moreover, electrophysiological data were correlated with severity of the attacks, disease duration and frequency of migraine attacks. However, there was no significant difference in P100 amplitude between the patients and controls.

Conclusion: The results of this study demonstrate subtle neuronal damage within the visual system of migraine patients, particularly those with aura which may be due to recurrent cerebral hypo-perfusion and point to cortical hyper-excitability between attacks.

INTRODUCTION

Migraine is worldwide, common neurovascular disabling disorder affecting 10-20% of the population. Indeed, it has a great bad impact on mental, physical, functional, and socioeconomic aspects of patients' life. WHO ranks migraine as a leading cause of health disability which compromise quality of life.

In recent years, research work shifted towards the study of abnormalities occurring between attacks. Indeed, it is now felt that interictal period electrophysiological and clinical findings may hold the key to better understanding of migraine pathogenesis. Visual stimuli can precipitate migraine attacks and most migraine auras are visual, suggesting specific involvement of the visual system in the pathophysiology of migraine. Visual Evoked Potential (VEP) is regarded as a useful, reliable, and non-invasive technique for evaluation of visual pathway.

Numerous studies have reported EEG abnormalities in migraine patients in the headache-free periods and the literature data seem to suggest that there is no specific EEG picture that is characteristic of migraine.

The report of the Quality Standards Subcommittee of the American Academy of Neurology states the following: “The EEG is not useful in the routine evaluation of patients with headache. This does not exclude the use of EEG to evaluate headache patients with associated symptoms suggesting a seizure disorder, such as atypical migrainous aura or episodic loss of consciousness. Assuming head-imaging capabilities are readily available, EEG is not recommended to exclude a structural cause for headache.”

Also it is frequently most useful to measure the individual impact from headache based on overall disability caused by the headache attacks. Brief, simple, patient-completed disability assessments have been desirable not only for research purposes, but also for clinical situations. Migraine Disability Assessment Scale (MIDAS) is one of the best instruments for this purpose.

The aim of this study is to evaluate VEP parameters in migraine with and without aura.
compared with healthy control subjects and to discuss the benefits and limitations of electroencephalography (EEG) in evaluating patients with migraine.

### PATIENTS AND METHODS

The patient group comprised 30 migraine patients (19 females and 11 males; mean age: 29.96). The control group consisted of 28 healthy volunteers (18 females and 10 males; mean age: 29.23 years). The age and sex of the control group did not differ significantly from that of the patient group. The patient group was divided into two subgroups: migraine patients with aura (MA) (7 females and 4 males) and migraine patients without aura (MO) (12 females and 7 males). Each patient received a diagnosis according to the revised criteria of the International Headache Society (ICHD-II).

Nineteen patients presented migraine headache without aura (ICHD-II code 1.1, mean disease duration: 6.1 years, mean attack frequency: 8/month); eleven patients presented migraine headache with typical visual aura (ICHD-II code 1.2.1, mean disease duration: 8.3 years, mean attack frequency: 4/month). All the patients were examined between attacks, at an interval of at least 72 hours from their last migraine attack; no patient was receiving prophylactic medication or using any drugs liable to affect the excitability of the central nervous system. All patients had a visual acuity normal or corrected normal, and none of them had any visual disorder. Migraine frequency varied between one or more attacks per week to one attack per year.

All participants were assessed using clinical neurological examination including fundoscopy, measurement of visual acuity, external ocular movements and Migraine Disability Assessment Scale (MIDAS). MIDAS is one of the best instruments for assessment of disability in migraine patients as it is brief, simple, patient-completed disability assessment scale. It is a five-item questionnaire that focuses on lost time in domains of work, school, household work, family, social, and leisure activities. This scale ranks headache sufferers into groups according to their degree of disability from headaches and has been validated for use in migraineurs. The reader can expect to see headache disability reported in this fashion and may find it useful for clinical practice situations.

Also VEPs and EEG were measured for all participants between the attacks. The correlation between the VEP and EEG was done. The study was performed at the Neurophysiology clinic, Saudi German Hospital, Madina, KSA. All the subjects gave their informed consent and the objectives of the test were explained to all subjects prior to the test session.

### Techniques

All participants were encouraged throughout the tests to maintain their interest and concentration. VEPs were performed by checker board pattern reversal displayed on a TV monitor subtending 15° × 12° at a viewing distance of 100 cm. The stimulus reversal rate was 2 per second and individual squares in the checker board pattern subtended a visual angle of 60°. The subjects were monitored while stimulation was done monocular. Standard disk EEG electrodes were placed at the OZ position of the 10-20 international system (active electrode), the reference electrode was placed at FZ position, and ground electrode on the patient’s hand. Electrode impedance was less than 5 kOhms and stimulation was done in whole field. Two hundred individual trials were averaged and a repeated trial to verify reproducibility of the results was performed. The P100 latency and amplitude were measured.

Digital EEG (DEEG) was acquired for all participants using XLTEK 32 channel apparatus (XLTEK, NwDb Version 3.3.0 Build 171, Ontario, Canada, L6H5S1). Electrodes were placed using the standard positions of the 10-20 system. The recording procedure was standardized. Provocation by hyperventilation for 3 minutes and photic stimulation using 5-30 Hz light flash were used. Each participant had undergone DEEG recording for a minimum of one hour. After recording, the DEEG was reviewed using anteroposterior and transverse bipolar and referential montages.

Statistical analysis was performed using software (SPSS version 10) and significance was defined as P<0.05.

### RESULTS

The main clinical and electrophysiological results are presented in Table (1). A comparison of the mentioned groups revealed a significant difference between P100 latency of MA with the other two groups (P<0.05). However, no significant different was observed with respect to amplitude of P100 wave. P100 latency was 15.3% longer in migraine patients with aura than controls (P<0.05).
but the difference between patients without aura and controls in regard to P100 latency was 2.8% that was not statistically significant (P>0.05). There was no difference with respect to gender, in the P100 latency and amplitude. Also no statistically significant difference was observed between the right and left eye in each group.

We looked for correlations of P100 latency, and EEG activity with different variables: disease duration, frequency of attacks and duration of each attack in all patients and duration of the aura in patients with MA. P100 latency of all patients correlated weakly with the duration of each attack of migraine (r = 0.19, p>0.05). There was significant positive correlation between P100 and MIDAS grads in all patients (r=0.83, p<0.05) (Spearman rank correlation coefficient). More over there was also significant positive correlation between P100 latency and disease duration (r = 0.40, p<0.05) and between P100 latency and frequency of attacks (r = 0.46, p<0.05) (Figs. 1 and 2).

Also patients with MA who have prolonged aura, longer than 1 hour14, (7 patients = 63.63%) have significantly prolonged P100 latency in comparison to MA patients who have aura less than one hour (4 patients = 36.36%) (P<0.05).

The EEG was found to be abnormal in 8 (26.67%) of the migraine patients. The alterations observed were; i) increased frequency and reduced amplitude of background electrical brain activity in three patients, ii) paroxysmal spikes in the occipital region in three patients, iii) paroxysmal spikes located in the central region bilaterally + diffuse sharp waves in one patient, iv) slow paroxysmal activity in one patient. The majority of EEG changes (6 patients = 75%) were observed in migraine patients with aura.

Patients with altered EEG showed significant prolonged P100 latency in comparison with patients with normal EEG (p<0.05).

Altered EEG activity did not show a significant correlation with disease duration (r = 0.037); attack duration (r = 0.037); intensity (r = 0.037) and attacks frequency (r = 0.02).

Table 1. Clinical and electrophysiological findings in the studied groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control Group N = 28</th>
<th>Migraine without aura (MO) N = 19</th>
<th>Migraine with aura (MA) N = 11</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>P100 latency (mean mSec ± SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rt. Eye</td>
<td>98.05±1.72</td>
<td>99.64±3.10</td>
<td>111.94±4.82*#</td>
<td>* Significant compared to MO</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td># Significant compared to Control</td>
</tr>
<tr>
<td>Lt. eye</td>
<td>97.47±1.61</td>
<td>101.84±4.40</td>
<td>113.51±4.49*#</td>
<td>* Significant compared to MO</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td># Significant compared to Control</td>
</tr>
<tr>
<td>Rt. and Lt.</td>
<td>97.76±1.67</td>
<td>100.47±3.75</td>
<td>112.73±4.66*#</td>
<td>* Significant compared to MO</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td># Significant compared to Control</td>
</tr>
<tr>
<td>P100 amplitude (Mean Uv ± SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rt. Eye</td>
<td>7.37±2.79</td>
<td>7.38±2.32</td>
<td>7.42±2.34</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Lt. eye</td>
<td>6.98±1.93</td>
<td>7.11±2.36</td>
<td>7.17±2.35</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>EEG changes</td>
<td>0</td>
<td>2 (10.53%)</td>
<td>6 (54.55%)*#</td>
<td>* Significant compared to MO</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td># Significant compared to Control</td>
</tr>
<tr>
<td>Duration of illness, mean yrs ± SD</td>
<td>7.95±8.67</td>
<td>10±7.04</td>
<td>&gt; 0.05</td>
<td></td>
</tr>
<tr>
<td>Frequency of attacks, Mean n / month ± SD</td>
<td>4.11±3.53</td>
<td>8±2.97*</td>
<td>&lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>Duration of each attack, mean hours ± SD</td>
<td>23.05±21.38</td>
<td>24.0±16.98</td>
<td>&gt; 0.05</td>
<td></td>
</tr>
<tr>
<td>MIDAS Grade I</td>
<td>4 (21.1%)</td>
<td>1 (9.1%)</td>
<td></td>
<td>Mann-Whitney test</td>
</tr>
<tr>
<td>Grade II</td>
<td>5 (26.3%)</td>
<td>3 (27.3)</td>
<td></td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>Grade III</td>
<td>7 (36.8%)</td>
<td>4 (36.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade IV</td>
<td>3 (15.8%)</td>
<td>3 (9.1%)</td>
<td></td>
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</tr>
</tbody>
</table>

577
Fig. (1): Correlations of mean P100 latency with different clinical variables in all migraine patients.

Fig. (2): Correlation of mean P100 latency with frequency of the attacks in all migraine patients.
DISCUSSION

The most striking electrophysiological finding reported here, was longer P100 latency in migraine cases especially those with an aura. This is similar to the findings reported by Kennard et al., who used checker board stimulation and found a prolonged P100 latency in migraine patients. Most previous studies of any size have confirmed prolongation of P100 latency, but normal latencies have been reported in smaller surveys.

Also high P100 amplitudes were reported by some investigators which we were undetected in our study. The basis for the prolonged latencies in migraine is unclear. Kennard et al., suggested that it may have a structural basis, due to ischemic damage during repeated attacks. Hyperexcitability of the brain in migraine might be the cause of the changes in P100 latency, and EEG activity. Clinically, many patients with migraine are intolerant of noises and bright lights and some find these can even precipitate an attack. However, the neurophysiological correlate of the hyperexcitability could be the shorter latency and the higher amplitude of P100. Therefore, Khalil et al. suggest that the prolonged latencies are constitutional, perhaps due to synaptic delay.

This study showed also a significant positive correlation of prolonged P100 latency with disease duration and frequency of the attacks in all migraine patients and with prolonged aura in MA patients. On the other hand the P100 latency showed non significant correlation with the intensity of migraine attacks and average duration of each attack. Bramanti et al. reported the same results. They reported that pattern VEPs particularly the P100 latency are altered significantly in patients with numerous attacks and longer duration of migraine. They stated that the possibility of ischemic damage during repeated attacks may explain the relation of prolonged P100 latency with duration and frequency of the migraine attacks. Also, Polich et al. and Schoenen et al. concluded that the alternation of P100 latency in migraine patients was found mainly in MA patients and it was correlated significantly with the prolonged aura. The absence of a significant correlation between prolonged P100 latency and the intensity of migraine attacks and average duration of each attack may be due in part to the fact that attack intensity and duration of each attack being conditioned by the use of analgesic drugs, by the patient’s psychological state, and by environmental factors, etc., cannot be considered a clear-cut parameter.

Only 26.67% of migraine patients showed altered EEG and 75% of them were among MA patients. Numerous studies have reported EEG abnormalities in migraine patients in headache-free periods and the literature data seem to suggest that there is no specific EEG pictures that is characteristic of migraine. The correlations we considered in our study were not significant.

On the other hand Wenzel et al., Polich et al. and Dean et al. found a good correlation between alternations of VEP and the EEG. Our results reported the same findings.

Conclusion

There is involvement of the visual pathway in MA rather than MOA, and differentiation between these subtypes of the migraine disease may be performed on the basis of VEP findings manifesting by the prolongation of the P100 latency.

Interictal P100 latency and EEG changes with significant correlations to the attacks severity and frequency, disease duration, and prolonged aura may reflect dysfunction of neuronal excitability and cerebral bioelectrical dyshrythmia, possibly due to defective neurotransmitter signaling. Better understanding of the neuropathological processes that trigger migraine attacks will help in the selection of more adequate prophylactic therapies, particularly glutamate antagonist agents. The present work recommends the study of MRI spectroscopy, BOLD MRI, and motor evoked potential in migraine patients under different prophylactic therapies. The results of this preliminary study need to be confirmed in a large sample of subjects.
Acknowledgement

We are greatly indebted to Dr. Abdulaziz Yassine, Assistant Prof. of Family and Community Medicine, Faculty of Medicine, Tanta University for his unlimited help in statistics.

REFERENCES

التغيرات الإكلينيكية والكهروفيزiology لدى مرضى الصداع التصفي المصحوب والغير مصحوب بالنسبة للمرضى العربي

مراجعه البحث: إن دراسة التغيرات الكهروفيزiology في الفترة ما بين نوبات الصداع التصفي قد تؤدي لفهم أفضل للأسباب المرضية للصداع التصفي.

الأهداف: يهدف البحث لدراسة التغيرات الإكلينيكية والكهروفيزiology في الجهد البصري المستنار وتخطيط المخ الكهربائي وفواتنهما في تقييم مرضى الصداع التصفي.

المرضى وطرق البحث: تم دراسة مرضى الصداع التصفي 28 عينة ضبطية من الأصحاء وذلك بالفحص الإكلينيكي واستخدام مقياس شدة الصداع التصفي ومقابل الجهد البصري المستنار وتخطيط المخ الكهربائي.

النتائج: أظهرت نتائج هذا البحث أن مرضى الصداع التصفي المصحوب بالنسبة للمصابين غير المصحوب بالنسبة للخدمة الإحصائية في الجهد البصري المستنار وتخطيط المخ الكهربائي مقارنة بمرضى الصداع التصفي الغير مصحوب بالنسبة للخدمة الضابطة. كما تبين أن التغيرات الكهروفيزiology لها علاقة إحصائية بشهوة نوبات الصداع التصفي وفترة المرض ومتارك النوبات.

خلاصة البحث: أوضحت نتائج البحث وجود خلل في أعصاب الجهاز البصري لدى مرضى الصداع التصفي المصحوب بالنسبة ويمكن تفسير هذا بسبب التقلص المتكرر للأوعية الدمية وقت توقف دم المخ ما يشير إلى حالة من التهيج الكهربائي للشرارة المعنية مابين نوبات الصداع التصفي.