GEORGIAN MEDICAL NEWS

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9. სტატიის გაზარდებს ძვირფასობაში აქციონალური ექსპერიმენტი, განვითარებული ფუნქციონალურ და უფრო მოთხოვნა; 2) განვითარებული ფუნქციონალური სტატია, რომლის მთავარი მიზანი ჰომგვარი სახელწოდება, მოგვით拉动ი ჰომგვარში სამუშაო ჭრილობა.

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IMPLEMENTING NEW TECHNIQUE TO EVALUATE COGNITIVE FUNCTION IN PATIENTS WITH MIGRAINE DURING THE ATTACK

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Abstract.

Background: Ten to 12 percent of the adult population globally suffers from migraine, which is the second most frequent type of primary headache, according to the American Academy of Neurology. Even though pain and attack-related impairment scored first, cognitive symptoms were the second most common. Objectives: The current study intended to measure the latency of P300 wave during and after an acute attack of migraine among a group of patients known to have migraine in order to introduce an objective method to measure the cognitive function of migraineurs during migraine attack.

Patients and Method: This is a potential cohort study conducted at the neurological outpatient’s clinics of Basra hospitals to the period from January until August 2021. The total number of subjects included in the study were forty-eight (48), thirty (30) patients and eighteen (18) age and gender matched control subjects. Patients were examined and selected by senior neurologist and diagnosed as having common migraine, then referred to the neurophysiology clinic to perform cognitive function tests, for each patient two tests were done; first one during the acute migraine attack and second one after one month far ahead from the end of the migraine attack. In addition, one cognitive function test was done for the control group.

Results: We discovered a highly important variance of the mean P300 latency of the patients during the acute attack of migraine as compared to the same group of the patients after repeating the exam one month far ahead from the end of the last migraine attack and one week ahead of being medication free. Also, we found the mean P300 latency of the patients during the acute attack of migraine is significantly higher than the mean P300 latency of the control subjects (P. value <0.00).

Conclusion: We found that all migraineurs in our study are having higher P300 latency values than control group during moderate migraine attack and this difference was significant which indicates that during moderate migraine attacks there is obvious impairment of cognitive performance abilities of those patients.

Key words. Migraine, cognitive functions, P300 test.

Introduction.

MIGRAINE is the second most common type of primary headache in adults, with a worldwide prevalence of 10 to 12 percent in adults, according to the World Health Organization [1]. Headaches and neurological care center’s witness a high number of persons suffering from migraine, which is a distressing ailment [2].

In addition to physical symptoms, migraine sufferers frequently report difficulties with their mental health, particularly in the areas of attention and memory. A lot of studies have looked into the cognitive problems that migraine sufferers experience [3].

In comparison to the general population, migraine sufferers are more prone to suffer from a decline in cognitive ability. The cognitive impairment experienced by migraine sufferers, particularly in the areas of focus and memory, is a common complaint. Although this is the case, cognitive symptoms are not considered to be a component of migraine's core symptomology. During the premonitory and headache stages of a migraine episode, recurring mental symptoms occur, which may linger until the postdrome stage of the disease [4].

Migraine sufferers may also encounter cognitive difficulties that are unrelated to the occurrence of migraine attacks. Acute assault therapies are not usually effective in alleviating cognitive difficulties. Aside from physical disability, migraine attack-related disability is compounded by cognitive dysfunction, including executive function impairment [5].

In fact, cognitive symptoms were rated second only to pain in terms of intensity and attack-related handicap, making them a significant target for migraine management strategies [2]. Increased levels of attack-related impairment were compounded by lower cognitive function in the aftermath of the attack. As the severity of a migraine headache grows, it is predicted that cognitive decline will occur. This is frequently associated with heightened emotions of melancholy and worry, as well as a lack of restful sleep, among other things [3,6-10].

Summarizing, cognitive function can be characterized as the ability to utilize and integrate core capacities such as perception, language acquisition and expression as well as actions, memory, and thinking. There are several definitions of cognitive function, as well as numerous mental tasks that fall under its purview [11]. It took several years before computer techniques were created that allowed researchers to analyze information processing in the human brain at a physiological level. Detecting event related potentials (ERP), a small phasic brain potential associated with information processing and connections in the brain, can be done non-invasively using a non-invasive technique [12,13].

The most prominent and reproducible waves gained from these potentials called P300 latency wave.

In our study, we have focused to measure the latency of the P300 wave during and after an acute attack of migraine among a group of patients known to have migraine to introduce objective evidence to measure the cognitive function of migraineurs during their acute attacks in order to test their subjective impairment of cognition that are reported repeatedly by those patients.

In addition, we might implement the use of P300 test as a routine test to those patients that are having migraine and state to have cognitive impairment and follow their response to treatment weeks or months later.
Methodology.

This is a prospective cohort study conducted at the neurological outpatient’s clinics of Basra hospitals to the period from January until August 2021.

Patients who presented with a headache attack were examined by a senior neurologist who diagnosed them with common migraine and determined that they were experiencing a migraine attack based on the diagnostic criteria of the International Classification of Headache Disorders [14], which are as follows:

A. A minimum of five attacks that meet the requirements B-D
B. Headache bouts that last between 4 and 72 hours (untreated or unsuccessfully treated)
C. At least two of the four traits listed below are present in the Headache:
   1. unilateral
   2. pulsating nature
   3. the intensity of moderate to severe pain
   4. aggravation caused by or resulting in avoidance of regular physical activity (e.g., walking or climbing stairs)
D. During headache at least one of the following exist:
   1. nausea and/or vomiting
   2. photophobia and phonophobia

We included 30 patients in our study, 12 males and 18 females, all of them had been selected according to the following inclusion criteria:

1. Has a common migraine.
2. Migraine duration between 1-5 years.
3. Age between 30 and 50 years.
4. Graduated from a collage.
5. No clinical evidence of tension component.
6. No other chronic diseases like hypertension or diabetes.
7. No present or past history of epilepsy.
8. Not on chronic drug use of any type including prophylactic anti-migraine drugs.
9. Not on analgesic drugs for the last 6 hours.
10. Normal brain MRI at time of study.

After patients' consent obtained to participate in the research, they were referred to the neurophysiological clinic to perform cognitive function test (P300). First, they fill a questionnaire including name, age, sex, address, email or telephone number, duration of illness and present and past medical and surgical history, then cognitive function test done. Patients were instructed to complete a computerized cognitive test while they were symptomatic.

Patients performed first P300 test during acute attack of migraine without using analgesia for at least six hours, and usually those patients come during migraine attack before using analgesic drugs or they already used some analgesic drugs during previous days but without benefit. We chose those patients with moderate severity attack, and we avoided those with mild attacks or those with severe attacks that need immediate treatment. In addition, we stopped the test and excluded patients that could not tolerate headache pain during the test and gave them analgesia.

We assessed the severity of the migraine attack depending on the assessment of the severity of pain according to 0-10 numerical scale, and we chose those patients with pain scale from 4-6 at time of presentation [14]. But because the pain of migraine attack sometimes is rapidly changing so we stopped the test for those patients that developed more pain severity during the test.

To test for migraine risk, we performed the P300 test to 18 healthy volunteers, seven males and eleven females, using the identical inclusion criteria as above, except that they were not migraineurs.

A computerized Nihon Khoden EMG/EP Neuropack X1-JB2300 system was used to evaluate the P300 evoked response for the cognitive function test (P300). In addition, a 120cm cable and a touch proof connector were used to connect an auditory stimulation system (Agcl) to cup surface electrodes (Agl) (ELTPCO).

After properly cleaning the electrodes with rectified spirit, they were placed to the scalp. In accordance with the 10-20 global system of EEG electrode placement, electrodes were inserted in the Fz, Cz, and Pz regions using EP (MT60) adhesive paste paste. Two linked mastoid process electrodes (M1 and M2) offer reference electrodes, while a forehead (FPz) process electrode provides a ground electrode. For aural stimulation, a headphone with a minidin connector (EPCAP mini) was used that had been calibrated (see Figure 1) [15].

![Figure 1](image)

*Figure 1. Shows the mean P300 latency of patients during the acute migraine attack and one month later after being migraine attack free.*

Auditory discrimination tasks based on the "Odd Ball" paradigm were used to collect event-related potentials.

Non-target (frequent 1000Hz tone) and target (frequent 3000Hz tone) tones were transmitted through a headphone binaurally (non-frequent 2000Hz tone). Target tone: 85db, non-target tone: 70db, with a rise/fall duration of 10msec and a plateau period of 40msec for each. A red piece of paper on the wall was used as a reference point for the patient, who was asked to keep her eyes open and fixated on the paper. The silence was deafening, and the light was dim. For our safety, we instructed him to count the number of targets on the board in a discrete manner (infrequent tones). The first positive peak following stimulation was identified as P200, and the highest positive peak following P200 among potentials between 250 and 500 msec was identified as P300. A total of fifty trials were recorded in ten minutes total recording time due to the difficulty in maintaining subject attention for longer periods of time. To avoid subjects becoming distracted, we were able to record 50
trials in the allotted ten minutes of recording time. To ensure that the results are consistent, the test should be repeated at least twice [15]. After completing the P300 test, which took no more than fifteen minutes, the prescriptions for the patient were given to them. After at least a month without headaches, the patients were given another appointment for the P300 test [16-18].

For the second P300 test, the patient must have been free from migraine for at least a month, as well as medication-free for at least a week prior to the test, in order to be eligible to participate.

**Statistical Analysis:** The data analysis was carried out with the help of the SPSS version 22 (manufactured by Norman H. Nie, C. Hadlai Hull and Dale H. Bent at the university of Stanford, USA) computer tool. In each dataset, the descriptive statistics are provided as mean 2 standard deviations for all data. P300 latency was measured using an independent sample t-test to determine if there was a difference in mean P300 latency between patients and control individuals. Statistical significance was defined as a P value lower than 0.05.

**Results.**

The total number of subjects included in the study were forty-eight (48), thirty (30) patients and eighteen (18) age and gender matched control subjects.

Of the total number of patients twelve (40%) were male and eighteen (60%) were female. The mean age of patient group was $(39.13\pm2.532)$ years which show no significant difference when compared to control groups mean age $(38.61\pm 6.5)$ years (table (1)).

Findings of table 2 shows no significant difference seen in P300 latency for males and female’s patients during acute migraine attacks (p. value >0.05).

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean age±SD</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>39.13±2.532</td>
<td>0.768</td>
</tr>
<tr>
<td>Controls</td>
<td>38.61± 6.5</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Mean age of patients and control group.

<table>
<thead>
<tr>
<th>Patients No.</th>
<th>Mean P300 during the attack (msc)</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female 18</td>
<td>346.28±13.70</td>
<td></td>
</tr>
<tr>
<td>Male 12</td>
<td>348.83±14.2</td>
<td></td>
</tr>
<tr>
<td>Total 30</td>
<td></td>
<td>0.625</td>
</tr>
</tbody>
</table>

Table 2. Comparison of mean P300 latency between males and female’s patients during acute migraine attack.

And after one month of being free from last migraine attack the mean P300 latency still shows no significant difference between males and female’s patients and the p. value were >0.05 as illustrated in table 3.

<table>
<thead>
<tr>
<th>Patients No.</th>
<th>Mean P300 during the attack (msc)</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male 12</td>
<td>315.83±7.98</td>
<td></td>
</tr>
<tr>
<td>Female 18</td>
<td>311.67±9.53</td>
<td></td>
</tr>
<tr>
<td>Total 30</td>
<td></td>
<td>0.221</td>
</tr>
</tbody>
</table>

Table 3. Comparison of mean P300 latency between males and females patients after being one month migraine attack free.

Moreover, when we compared means of P300 latency between males and females in control group we found no significant difference obtained and the P.value was > 0.05 as clarified in table (4).

**Table 4. Comparison of mean P300 latency between males and females in the control group.**

<table>
<thead>
<tr>
<th>Control</th>
<th>No.</th>
<th>Mean P300 latency (msc)</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>7</td>
<td>309.86±14.21</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
<td>307.37±11.71</td>
<td>0.113</td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
<td></td>
<td>0.69</td>
</tr>
</tbody>
</table>

The mean P300 latency of migraine patients during acute attack of migraine (= 347.30±13.72) as compared to the same group of patients after repeating the P300 test for them one month far ahead from last migraine attack and one week ahead of being medication free (= 313.33±9.03), the p. value was < 0.01. This finding had been illustrated in figure (1) also.

**Table 5. Changes of mean P300 latency for patients’ group during and one month after being free from last migraine attack.**

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>P300 latency during the attack (msc)</th>
<th>P300 latency after the attack (msc)</th>
<th>P.value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>30</td>
<td>347.30±13.72</td>
<td>313.33±9.03</td>
<td>0.00</td>
</tr>
<tr>
<td>Control</td>
<td>18</td>
<td>308.33±12.39</td>
<td>308.33±12.39</td>
<td>0.113</td>
</tr>
<tr>
<td>P. value</td>
<td></td>
<td>&lt;0.01</td>
<td>0.00</td>
<td></td>
</tr>
</tbody>
</table>

**Discussion.**

In the current study, we have focused on an objective cognitive function test (namely P300 test) during migraine attack as an attempt to use this objective method to measure the cognitive function of patients during their illness. For that reason, we were highly selective in choosing patients group and control group to get more homogenous P300 readings for both patients and control groups and this is obvious from our inclusion criteria.

For example, we chose a specific age group in order to get more homogenous P300 readings by choosing age group in which the brain reaches its maximum biological development,
in addition, we chose migraine duration not too long to minimize the possible long effect of migraine on the P300 results. Also, both patients and control groups graduated from a college to minimize the normal difference of P300 result between people [19], and so on with other points in the inclusion criteria [20].

It is clear that there is no significant difference of P300 values between males and females in both patients group (table 2 and 3) and control group (table 4). Also, there is no significant difference of P300 values between patients; out of migraine attack; and control group (table 6), and this can be attributed to our method of selection of both patients and control groups as we explained above.

During the attack of migraine, we found all patients were having P300 latency values higher than the control group and the difference was significant; as showed in table 6; and this indicate that the attack of migraine obviously affects cognitive function of patient which may affect their performance abilities during migraine attacks.

The second cognitive function test that performed for the patients showed a significant lower P300 latency value as compared with the first P300 test (table 5) and this result gives clear evidence to the impairment of cognitive function (represented by P300 latency) during migraine attack. It also points to the transient effect of migraine attack on cognitive function of our patients in the view that the second P300 test of the patients that performed to them one month after the end of migraine attack shows no significant difference when we compare it with that of the control group (table 6).

Although there are many theories behind the effect of migraine on different brain functions but the relative associated ischemia of brain secondary to vaso-spasm is still the most plausible one and it can fairly explain the results of our study regarding cognitive function test (i.e., P300 latency results) [21].

We could not assess the duration that needed to return to pre migraine attack level of cognitive function, but because in our study we found no significant difference of mean P300 latency values between patient and control group after one month from the attack; as showed in table 6; we might conclude that one month may be the maximum time that needed by migraineurs to regain their usual cognitive performance abilities after a moderate attack of migraine.

Even though we couldn’t find similar studies to compare with them, we revised some other studies that used different ways to evaluate the long-term effect of migraine on cognitive function, some of them they followed migraineurs for many years [20]. In addition, others tried to know which part of cognitive function affected more by migraine [4]. In general, the vast majority of those studies estimated a clear long-term effect of migraine on the cognitive function. In our study, we did not test the long-term effect of migraine on cognitive functions, but we found that P300 return to normal in our patients; in comparism to control group; after one month from being free from the acute attack of migraine and this could be attributed to relatively short duration of migraine illness in our patients (between 1 and 5 years).

Conclusion.

There is a significant reduction of the cognitive functions of migraineurs during moderate migraine attacks and this mean that those patients should have an effective therapy and enough time for rest to regain their normal cognitive functions as rapid as possible, but whether this reduction is critical to the point that it may affect the cognitive performance of the migraineurs in doing certain activities like driving or pass in to an exam during migraine attack might need further evaluation.

REFERENCES