Assessment of Cardiovascular Autonomic Functions in Migrainous patients

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ABSTRACT

Background: Migraine is primary episodic headache disorder characterized by various combinations of neurological, gastrointestinal and autonomic changes. The aim of this study was to assess the cardiovascular autonomic function in migraineurs. Methodology: Fourteen migrainous patients were subjected to clinical assessment, EEG and autonomic function tests, including blood pressure response to change of posture to assess sympathetic function and test for heart rate response (RR test) in response to normal breathing, deep breathing, Valsalva maneuver and standing up, to assess parasympathetic function. Results: EEG changes were detected in 50% of patients. Postural hypotension was found in 28.57%. There was no statistically significant difference in RR interval variability with normal breathing compared to control. 42.9% of patients had abnormal heart rate response to deep breathing. 42.9% of patients had abnormal Valsalva ratio and 50% had abnormal 30:15 heart rate ratio on standing up. There was no significant relation between clinical characteristics and autonomic function tests. Results indicate autonomic dysfunction in migraineurs. Conclusion: Autonomic nervous system may have a role in the pathophysiology of migraine. Better understanding of autonomic functions in migraine may help to more effectively diagnose and treat migraine. (Egypt J. Neurol. Psychiat. Neurosurg., 2006, 43(1): 179-186).

INTRODUCTION

Migraine pathogenesis is now believed to involve both neuronal and vascular components¹,². The autonomic nervous system (ANS) is involved in the pathophysiological mechanism of migraine because symptoms are common during acute migraine headaches. Symptoms include nausea, vomiting, or diarrhea, cutaneous vasoconstriction (pallor), vasodilatation (flushing), piloerection and diaphoresis³.

Many authors believe that the nuclei that participate in the pain control system can also induce vascular changes similar to those observed during migraine attacks, most probably through connections with the cranial parasympathetic system¹,⁴,⁵. Several lines support the involvement of the cranial parasympathetic system in migraine. First, migraine associated autonomic symptoms; facial flushing, lacrimation and nasal stuffiness. Secondly, increased cranial venous blood levels of the parasympathetic neurotransmitter vasoactive intestinal polypeptide were found during attacks in patients with symptoms of lacrimation and rhinorrhea⁶. Thirdly, intranasal installation of lidocaine, which can block parasympathetic outflow to the cranium, is an effective treatment for cluster headache and for many migraine attacks⁷. Fourth, Drummond and Lance⁸ have shown augmented forehead vasodilatation in response to irritation of the eye with diluted soapy drop on the symptomatic side in cluster headache patients, the same cranial parasympathetic vasodilator reflex might be impaired in migraine⁹.
Many trials to evaluate autonomic function and sympathovagal balance in migraineurs were performed. Autonomic nervous system studies included tests of sympathetic function as the quantitative sudomotor axon reflex test, beat-to-beat blood pressure responses to the Valsalva maneuver, sustained handgrip, cold pressor test and head-up tilt test. Other tests to assess parasympathetic function as heart rate responses to deep breathing and the Valsalva maneuver.

Other authors studied ECG changes during a migraine attack, proposing that during an attack, autonomic imbalance within the heart and vessels results in ECG abnormalities.

The aim of this study was to assess the cardiovascular autonomic functions in migraineurs between attacks to explain and relate clinical symptoms to possible autonomic dysfunction in migraineurs.

**SUBJECTS AND METHODS**

Fourteen patients were recruited from the outpatient clinic, Kasr El-Aini hospital.

**Identification and selection of migraine cases:**

Migraine cases were diagnosed according to the International Headache Society (IHS) criteria for migraine.

**Exclusion criteria included:**

- Cardiovascular disorders.
- Central and peripheral nervous system disorders, detected clinically or through neuroimaging.
- Use of prophylactic medications for migraine.
- Chronic use of medications for reasons other than migraine, which may interfere with autonomic nervous system balance e.g. anticholinergic medications.
- Patients with possible causes of dysautonomia like diabetes mellitus, or patients with collagen vascular diseases.

The study also included age and gender matched 14 non-migraineur subjects for comparing the means of RR interval variability with normal breathing.

All patients included in the current study were subjected to the following:

1. Full medical history taking and assessment of headache character, frequency and severity according to Blanchard and Andrasik scale.
2. General and neurological examination.
3. Cardiological assessment and ECG to detect cardiac disease or arrhythmias.
4. Laboratory work up: Fasting and post prandial blood sugar, complete blood picture, kidney and liver function tests, erythrocyte sedimentation rate.
5. Computerized Tomography (CT) scan of the brain; which was done to exclude any focal cranial lesions.
6. EEG was done under standard conditions with photic stimulation and hyperventilation.
7. Assessment of cardiovascular autonomic functions:
   All patients were assessed during the headache free period.

**Clinical evaluation:**

- Questionnaire for autonomic symptoms according to Low and Zimmerman.
- Assessment of blood pressure response to change of posture was done according to Mohoek et al.
  A fall of systolic blood pressure of 20 mm Hg or more and/ or diastolic pressure of 10 mm Hg was considered abnormal. This procedure assesses sympathetic function.

**Tests for heart rate responses (RR test):**

RR interval variability in response to normal breathing and deep breathing to assess vagal function, Valsalva's maneuver to assess both sympathetic and vagal functions, mainly vagal, and lastly in response to standing up to assess mainly vagal function, using Keypoint® software version 3.00; the interval program.
Recording:
Two surface disc electrodes were placed over the radial pulse, one in each arm.

Analysis:
An epoch of one minute was analyzed. A plot of RR intervals versus time was displayed on a computer screen.

RR interval variation in response to normal breathing "respiratory sinus arrhythmia" and deep breathing, was calculated according to the following algorithm:

The difference between the shortest RR and the longest RR intervals during 1 minute given in percent of the mean of all maximal and minimal peaks: \[ \frac{[RR_{(max)} - RR_{(min)}] \times 100}{RR_{(mean)}} \].

Normally the heart rate should increase 10 beats or more after deep breathing, values less than 10 beats were considered abnormal\(^\text{16}\).

Valsalva ratio. It was calculated as follows: The ratio of the longest RR interval, 40 seconds after the maneuver, to the shortest RR interval during the maneuver (within 10-40 seconds), a ratio of 1.2 or more is considered normal\(^\text{18}\).

Heart rate response to standing: Using computer analysis, the 30:15 ratio was automatically calculated, by dividing the length of the longest RR interval at beat 30 after standing by the length of the shortest RR interval at beat 15 after standing; ratios less than 1.03 were considered abnormal according to Ewing et al.\(^\text{19}\).

Statistical Methods:
Data analysis was carried out with the Statistical Package for Social Sciences (version 10.0, 1999; SPSS Inc. Chicago, IL, USA).

Descriptive statistics: Mean±SD, number and percentage. Analytic tests using the independent t-test were used for all parametric data. P-value <0.05 was considered significant.

RESULTS

Clinical characteristics:
Fourteen migrainous patients were included in this study. All patients had migraine without aura; diagnosed according to International Headache Society (IHS) criteria for migraine\(^\text{12}\). Their age ranged from 22 to 30 years old, with mean (± SD) of 25.93±2.59 years. They were 11 females (78.6%) and three males (21.4%).

The duration of illness ranged from one to five years, with a mean of 2.86±1.35 years.

The headache severity ranged from three to five according to Blanchard and Andrasik scale\(^\text{13}\). Headache was unilateral in eight patients (three reported that it was on the left side while the other five suffered from the headache on the right side) and bilateral in the other six patients.

The frequency of migraine attacks during the last month, prior to examination, ranged from four to nine attacks per month with a mean of 6.21±1.58.

In the present study the EEG examination revealed that seven patients (50%) had EEG changes; one of them had bilateral EEG changes while the other six had focal EEG changes, which was on the same side of headache in four of them.

Clinical Assessment of Autonomic Function:
* The questionnaire of autonomic symptoms (adopted from Low and Zimmerman\(^\text{14}\)) was applied for all patients included in the present work in a structured interview. In this respect, two patients reported palpitations and chest tightness in close temporal relationship with their attacks of headache, while two other patients reported dizziness and sense of collapse, but no frank syncopal attacks.

* Clinical Evaluation: None of our patients had objective dysrhythmia [both clinically and by ECG]. The frequency of patients who experienced symptoms of postural hypotension, throughout the course of their headache, were only four patients (28.57%), all of them suffered from mild degree of postural hypotension.

Neurophysiological tests:
* RR interval variability with normal breathing:
The mean percent of RR interval variability with normal breathing in patients was
71.93±42.14, whereas in the control group it was 70.72±41.50. Comparison between the mean of patients to that of controls showed no statistically significant difference.

**Deep breathing:**
Regarding the changes in the heart rate after deep breathing, six patients (42.9%) out of the 14 patients showed an abnormal response in the form of an increase in the heart rate of less than 10 beats/ minute or showed a decrease in heart rate (Table 2).

**Valsalva**
Six patients (42.9%) out of the 14 patients showed abnormal Valsalva ratio (< 1.2), as shown in figure (1).

**Standing up (30:15 ratio)**
Seven patients (50%) out of the 14 patients showed abnormal ratio (<1.03) as shown in figure (2).

**Relation between Autonomic tests and Clinical Characteristics:**
* There was a statistically significant difference between patients with postural hypotension and those not suffering from postural hypotension in the mean of RR interval variability after standing up. However, there was no statistically significant difference in the mean percent of heart rate change (RR) on deep breathing or the mean heart rate change with Valsalva maneuver between patients with or without postural hypotension.
* All autonomic tests performed showed no statistically significant difference neither in relation to age of patients, headache severity, the duration of illness, the frequency of attacks or with the EEG changes.

### Table 1. Basic clinical characteristics of included patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Range</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>22-30</td>
<td>25.93 ± 2.59</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>11 (78.6%)</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>3 (21.4%)</td>
</tr>
<tr>
<td>Duration of illness</td>
<td>Range</td>
<td>1-5</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>2.86 ± 1.35</td>
</tr>
<tr>
<td>Headache severity*</td>
<td>Range</td>
<td>3-5</td>
</tr>
<tr>
<td>Headache site</td>
<td>Bilateral</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>5</td>
</tr>
<tr>
<td>Frequency in last month</td>
<td>Range</td>
<td>4-9</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>6.21 ± 1.58</td>
</tr>
</tbody>
</table>

* According to Blanchard and Andrasik scale13.

Age and duration figures are in years.

### Table 2. Frequency of patients with abnormal change in the heart rate after deep breathing.

<table>
<thead>
<tr>
<th>Heart rate change</th>
<th>No. (n.14)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase of &lt; 10 beats/ min</td>
<td>2</td>
<td>14.3</td>
</tr>
<tr>
<td>Decrease</td>
<td>4</td>
<td>28.6</td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
<td>42.9</td>
</tr>
</tbody>
</table>
DISCUSSION

The pathophysiology of migraine is still poorly understood. An imbalance of the autonomic nervous system could explain many of the clinical manifestations of the disorder\textsuperscript{10}. It was proposed that migraine and autonomic nervous system dysfunction may share a common neural substrate\textsuperscript{3}.

Autonomic impairment in migraine was previously investigated by many authors; however, the results showed major debates and they were inconclusive. Whereas, some authors reported sympathetic hypofunction\textsuperscript{20-22}, others emphasized sympathetic hyperfunction\textsuperscript{23,24}.

Our aim in this study was to evaluate the changes in the cardiovascular autonomic functions in migraineurs. In accordance to Kruszewski\textsuperscript{25}, we used the RR interval variations as an indicative of cardiac vagal integrity.

In the present study, fourteen migrainous patients were examined, in between attacks of headache and they were not on prophylactic medications for migraine. Their ages ranged from 22 to 30 years, with a mean of 25.93±2.58 years.
which is consistent with common age of onset of migraine before 40 years. They were 11 females and 3 males, which confirms the expected female preponderance, and in accordance with the findings reported by Schechter et al. 1.

The duration of illness ranged from one to five, with a mean of 2.86±1.35 years.

The frequency of migraine attacks during last month prior to examination ranged from four to nine attacks per month with a mean of 6.21±1.58. The headache intensity ranged from three to five on Blanchard and Andrasik scale.

Seven patients (50%) had EEG changes; one of them had bilateral EEG changes while the other six had focal EEG changes, which was on the same side of headache in four of them. Similar results were reported by Slater who detected bilateral but asymmetric, slow wave abnormalities in 82 of 184 (44.5%) migraine patients. He concluded that migraine causes a disorder of cerebral functioning that produces EEG changes. In addition Smyth and Winter found that 43% of 202 migraineurs had abnormal interictal records, with slowing in either the theta or delta range.

In the present work, the heart rate changes during deep breathing were abnormal in six patients (42.9%). While, the heart rate variability in response to standing was abnormal in seven patients (50%).

The RR variation is a measure of variation in heart rate with inspiration and expiration. The absence of or a reduction in beat to beat variation may indicate an abnormality in either parasympathetic or sympathetic function.

The heart rate variability during Valsalva maneuver revealed abnormal response in six patients (42.9%). This could be explained by a parasympathetic hypofunction in response to the Valsalva maneuver in migraine patients. This was also in agreement with Thomsen et al. who mentioned that the cardiovascular reflexes in response to the Valsalva maneuver suggested a mild parasympathetic hypofunction with preserved sympathetic function in migraineurs. The same observations were demonstrated by Schechter et al. But in their study the difference was not statistically significant.

The normal response to the Valsalva maneuver is an increase in intrathoracic pressure and a direct increase in blood pressure. Blood pressure then decreases as a result of reduced venous return and reduced cardiac output. It later stabilizes, partly because of reflex tachycardia and peripheral vasoconstriction. On release of forced expiration, the intrathoracic pressure falls, venous return and cardiac output increase, and there is a blood pressure overshoot. Compensatory reflex bradycardia occurs because of parasympathetic activation. Failure of the heart rate to increase during positive intrathoracic pressure phase of the Valsalva maneuver suggests parasympathetic dysfunction, whereas tachycardia reflects both sympathetic and parasympathetic function; humans are vagal dominant.

Also, in our study, four patients (28.57%) had postural hypotension. There was a statistically significant difference between patients with postural hypotension and those not suffering from the postural hypotension in the mean of RR interval variability after standing up. However, the relation between heart rate variability with the Valsalva maneuver and postural hypotension was non significant. Moreover, there was no statistically significant difference in the mean of heart rate change (RR) on deep breathing between patients with or without postural hypotension. These results proposed that absence of clinical data of autonomic dysfunction in migraine does not exclude presence of subclinical dysautonomia which could be detected neurophysiologically. That was in agreement with Sanya et al., who reported similar findings in their study of the parasympathetic responses in migraine patients.

In our study the autonomic function tests showed no statistically significant difference in relation to age of patients. In this respect, Schechter et al. demonstrated lower responses in autonomic nervous system function testing in an older age group (40-50 years), than those included in our study. However, this difference was not statistically significant.

In the present study autonomic tests performed showed no statistically significant difference in relation to headache severity. This was consistent with three clinic-based studies. On the contrary, other authors reported that patients with severe migraine had
significantly lower RR variation in response to deep breathing than milder migraine cases, however, the Valsalva ratio was not significantly different in relation to headache severity.

In conclusion, the results obtained suggest that autonomic nervous system dysfunction might either render an individual more susceptible to migraine by reacting to triggers at a lower threshold, or it is a consequence of migraine. An enhanced understanding of the autonomic dysfunction in migraine may help to more effectively diagnose, prevent, or treat migraine.

REFERENCES


الملخص العربي

تقييم الوظائف التلقائية للقلب والأوعية الدموية في مرضى الصداع النصفي

الصداع النصفي هو صداع متكرر وله أعراض متصلة أو متغيرة في الجهاز العصبي وجهاز الهضم والوظائف التلقائية بالجسم. كان الهدف من هذا البحث تقييم الوظائف التلقائية للقلب والأوعية الدموية في مرضى الصداع النصفي. أجري هذا البحث على 14 مريضاً بصداع النصفي، تم إجراء بعض الفحوصات لهم كرسم مخ وقياس التغير في ضغط الدم بعد الوقوف وقياس التغير في معدل النبض أثناء التنفس الطبيعي والعميق وبناء القياس بالطريقة فلزقا وعند الوقوف. وقد تبين وجود تغيرات في رسم المخ في 50% من المرضى ووجود انخفاض في ضغط الدم بعد الوقوف في 28.57% من المرضى.

في حين ظهرت استجابة غريبة متعددة في معدل الرياح في 42.9% من المرضى أثناء التنفس العميق. وفي 42.9% من المرضى أثناء القيام بسرعة فلزقا و 50% من المرضى عند الوقوف. وقد نوقشت نتائج هذا البحث من حيث أن الوظائف التلقائية لها علاقة بالصداع النصفي وأن الفهم الأعمق للوظائف التلقائية يؤدي بالنهاية إلى فهم أعمق لأسباب مرض الصداع النصفي وكيفية علاجه.