Autonomic Dysfunction in Migraine; What Do We Need to Know?

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ABSTRACT

Background: Migraine is a chronic neurological disorder that has diverse autonomic manifestations. Yet, studies of the autonomic nervous system in migraine yield controversial results. Heart rate variability (HRV) reflects the autonomic cardiovascular control of the heart and recently has got a prognostic importance. Objectives: The aim of this study is to study HRV in patients with migraine. Methods: Nineteen migraineurs and ten age and sex-matched normal subjects had been subjected to the following tests: Heart rate (HR) and systolic blood pressure (SBP) response to standing, heart rate response to respiration and Valsalva maneuver. Then, a 24-hour Holter electrocardiogram (ECG) was recorded. Results: Migraineurs had significantly lower R-R variation during respiration and almost significant lower response to standing. SBP response and Valsa ratio were not different from controls. The standard deviation of the average N-N interval (SDANN) was significantly lower in migraine patients when compared to control subjects (P= 0.02). This reduction of HRV was significantly greater in female gender and in chronic migraine patients when compared to new-onset cases (P=0.02 and 0.01 respectively). The standard deviation of the NN interval (SDNN) and the square root of the mean squared differences of successive NN intervals (RMSSD) were not significantly different from controls. Conclusion: Our results suggests autonomic dysfunction; mainly parasympathetic hypofunction in migraineurs while the lower SDANN values might be related to physical inactivity character of chronic migraineurs as the global SDNN as a marker of poor prognosis was not significantly affected in migraineurs. (Egypt J. Neurol. Psychiat. Neurosurg., 2009, 46(2): 489-496)

Key Words: Migraine, heart rate variability, prognosis

INTRODUCTION

Migraine is one of the most frequent disabling neurological conditions with a major impact on the patients’ quality of life¹. Yet its pathophysiology and prognosis are still not well known. Autonomic nervous system (ANS) is involved in migraine during headache and in headache-free period; however, studies of ANS in migraineurs are inconclusive². Besides, these studies never highlighted its impact on migraineurs. Among the different available noninvasive techniques for assessing the autonomic status, heart rate variability (HRV) has emerged as a simple, noninvasive method to evaluate the sympathovagal balance at the sinoatrial level. In addition, decreased HRV has been shown to be a strong predictor of increased cardiac and/or arrhythmic mortality, particularly in the post-myocardial infarction setting³, and more recently in epilepsy⁴. The aim of this study is to confirm ANS involvement in migraine and its impact on migraineurs by studying their HRV.

SUBJECTS AND METHODS

Nineteen subjects who were diagnosed as having migraine, according to the criteria of the Headache Classification Committee of the International Headache Society, and reported two or more symptoms of autonomic dysfunction were recruited from the outpatient clinic of neurology department, El-Mansoura University. Patients who were on any prophylactic headache treatment or have a systemic disease that might interfere with
HRV (chronic pain disorders, or endocrinological, or cardiovascular or other neurological diseases) were excluded from the first place. Ten healthy volunteers, matched with the patients in their age and sex, served as controls. The evaluation of subject’s medical condition was based on full medical history and completed physical (by author number 2) and neurological examination (by author number 1). All subjects were referred to the cardiology department at El-Mansoura Specialized Medical Center; irrespective of their diagnosis. After initial adaptation phase, all subjects underwent the following tests to assess autonomic function and their HRV by author number 2.

**Heart rate (HR) and systolic blood pressure responses to active standing:**

After 1 minute of lying supine quietly, subjects were asked to stand up and remain standing quietly for 5 minutes. Ewing ratio or 30/15 ratio is calculated from the longest RR interval around the 30th beat after taking the vertical position divided by the shortest RR interval around the 15th beat. Systolic blood pressure was measured using automatic sphygmomanometer at both supine and vertical positions.

**Heart rate response to the Valsalva maneuver:**

Patients were asked to blow into a mouth piece at pressure 40 mmHg for 15 seconds. The Valsalva ratio calculates the quotient between the longest RR interval after the test and the shortest RR interval during the test. The test was repeated three times and the mean ratio of the 3 trials was recorded.

**Respiratory sinus arrhythmia:**

It was measured as the difference between the shortest RR and the longest RR interval during one minute given in percent of the mean of all maximal & minimal peaks.

Normally, HR increase 10 beats or more after deep breathing. Values more than 10 are abnormal.

**Time domain measure of HRV:**

A 24-hour Holter electrocardiogram ECG (machine used is named Schiller, MT-101 serial No.300. 00596), was recorded and time domain measure of HRV were calculated from continuous ECG recordings. Each QRS complex is detected and the so called normal- to –normal (NN) intervals (that is, all intervals between adjacent QRS complexes resulting from sinus node depolarization) or the instantaneous heart rate is determined.

**Statistics:**

All the results of patients and control were analyzed by the unpaired t-test using GraphPad PRISM version 5.01 software. Migraine patients were further divided into new onset and chronic according to the duration of their headache. Those who had their headache less than year were considered new-onset.

### RESULTS

Migraine patients were more likely to be female, with a median age of 31.58 years. Positive family history was reported in 74% of migraineurs. Seven patients reported aura that was visual in two patients, vertiginous in one and the rest were sensory. Chronic daily headache was characterized in seven patients (Table 1).

**ANS measures:**

Respiratory sinus arrhythmia was assessed as a measure for RR variability. Migraineurs showed significantly lower RR variation than controls (P=0.019) (Table 2). Those with chronic migraine had significantly lower values when was compared to new-onset ones (P=0.03) (Table 3). For cardiovascular reactivity, borderline difference between migraineurs and controls was observed during Valsalva maneuver while heart rate response to standing showed a strong trend for a lower response in migraineurs compared to control but it didn’t reach a significant level (P= 0.073) (Table 2). In addition, no significant difference was noted between chronic and new-onset migraineurs (Table 3). Systolic blood pressure measures during standing were not significantly different from those during supine posture.

**Time domain measure of HRV**

The standard deviation of the NN interval (SDNN); as a measure for all cyclic components responsible for variability in the period of recording, the standard deviation of the average NN intervals
(SDANN); which is an estimate of the changes in HR due to cycles longer than 5 minutes, and the square root of the mean squared differences of successive NN intervals (RMSSD); which is an estimate for high-frequency variations in HR, were estimated (Table 4). SDNN was found to be lower in migraineurs than controls but the difference was not significant. SDANN was significantly low in migraineurs compared to controls (P=0.029). Migraineurs with aura had lower SDANN than those without but the difference was not significant (P=0.11). Females and those with chronic migraine had significantly lower SDANN values than males and those with new-onset migraine (P= 0.026 & P=0.01 respectively). RMSSD was, in contrast, lower in controls than migraineurs but the difference was not significant (P= 0.439).

Table 1. Demographic and clinical characteristics of migraineurs.

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>SEX</th>
<th>FH</th>
<th>DURATION</th>
<th>COURSE</th>
<th>AURA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60</td>
<td>M</td>
<td>+</td>
<td>10 years</td>
<td>Daily</td>
<td>sensory</td>
</tr>
<tr>
<td>2</td>
<td>42</td>
<td>F</td>
<td>+</td>
<td>3 years</td>
<td>episodic</td>
<td>Without</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>F</td>
<td>+</td>
<td>5 months</td>
<td>Episodic</td>
<td>Without</td>
</tr>
<tr>
<td>4</td>
<td>37</td>
<td>F</td>
<td>+</td>
<td>10 years</td>
<td>Daily</td>
<td>Without</td>
</tr>
<tr>
<td>5</td>
<td>42</td>
<td>F</td>
<td>-</td>
<td>8 years</td>
<td>Daily</td>
<td>Without</td>
</tr>
<tr>
<td>6</td>
<td>32</td>
<td>M</td>
<td>-</td>
<td>1 week</td>
<td>Episodic</td>
<td>Without</td>
</tr>
<tr>
<td>7</td>
<td>55</td>
<td>F</td>
<td>+</td>
<td>7 years</td>
<td>Episodic</td>
<td>Sensory</td>
</tr>
<tr>
<td>8</td>
<td>22</td>
<td>F</td>
<td>+</td>
<td>20 years</td>
<td>Daily</td>
<td>Without</td>
</tr>
<tr>
<td>9</td>
<td>35</td>
<td>F</td>
<td>+</td>
<td>10 years</td>
<td>episodic</td>
<td>Visual</td>
</tr>
<tr>
<td>10</td>
<td>26</td>
<td>F</td>
<td>-</td>
<td>5 years</td>
<td>episodic</td>
<td>Without</td>
</tr>
<tr>
<td>11</td>
<td>35</td>
<td>F</td>
<td>+</td>
<td>2 years</td>
<td>episodic</td>
<td>Sensory</td>
</tr>
<tr>
<td>12</td>
<td>37</td>
<td>F</td>
<td>+</td>
<td>2 years</td>
<td>Daily</td>
<td>Vertigo</td>
</tr>
<tr>
<td>13</td>
<td>12</td>
<td>F</td>
<td>+</td>
<td>25 years</td>
<td>Daily</td>
<td>Without</td>
</tr>
<tr>
<td>14</td>
<td>20</td>
<td>M</td>
<td>+</td>
<td>4 months</td>
<td>episodic</td>
<td>Visual</td>
</tr>
<tr>
<td>15</td>
<td>29</td>
<td>F</td>
<td>-</td>
<td>9 months</td>
<td>Daily</td>
<td>Without</td>
</tr>
<tr>
<td>16</td>
<td>25</td>
<td>F</td>
<td>+</td>
<td>5 years</td>
<td>episodic</td>
<td>Without</td>
</tr>
<tr>
<td>17</td>
<td>23</td>
<td>M</td>
<td>+</td>
<td>1.5 years</td>
<td>episodic</td>
<td>Without</td>
</tr>
<tr>
<td>18</td>
<td>28</td>
<td>F</td>
<td>-</td>
<td>5 years</td>
<td>episodic</td>
<td>Visual</td>
</tr>
<tr>
<td>19</td>
<td>22</td>
<td>F</td>
<td>+</td>
<td>2 weeks</td>
<td>episodic</td>
<td>Without</td>
</tr>
</tbody>
</table>

M= male, F= female

Table 2. HRV measures in migraineurs and controls.

<table>
<thead>
<tr>
<th></th>
<th>HR response to standing</th>
<th>Valsalva ratio</th>
<th>Respiratory sinus arrhythmia</th>
<th>SBP to standing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>1.172±0.89</td>
<td>1.371±0.16</td>
<td>7.96±0.50</td>
<td>3.750±2.63</td>
</tr>
<tr>
<td>Mean±SEM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>1.041±0.017</td>
<td>1.303±0.06</td>
<td>15.01±2.02</td>
<td>1.053±2.98</td>
</tr>
<tr>
<td>Mean±SEM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>= 0.073</td>
<td>= 0.642</td>
<td>= 0.019</td>
<td>= 0.588</td>
</tr>
</tbody>
</table>

Values are expressed as mean±standard error of the mean
HR = heart rate
SBP = systolic blood pressure
Table 3. HRV responses in chronic and new-onset migraine.

<table>
<thead>
<tr>
<th></th>
<th>HR response to standing</th>
<th>Valsalva ratio</th>
<th>Respiratory sinus arrhythmia</th>
</tr>
</thead>
<tbody>
<tr>
<td>New-onset migraine</td>
<td>1.050±0.07</td>
<td>1.41±0.15</td>
<td>25±5.68</td>
</tr>
<tr>
<td>Mean±SEM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic migraine.</td>
<td>1.03±0.01</td>
<td>1.28±0.06</td>
<td>13.65±1.83</td>
</tr>
<tr>
<td>Mean±SEM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>= 0.82</td>
<td>= 0.44</td>
<td>= 0.03</td>
</tr>
</tbody>
</table>

Table 4. Time domain measures of HRV.

<table>
<thead>
<tr>
<th></th>
<th>RMSSD</th>
<th>SDNN</th>
<th>SDANN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>61.130±17.160</td>
<td>135.500±21.640</td>
<td>103.900±15.610</td>
</tr>
<tr>
<td>Mean±SEM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>81.05±14.710</td>
<td>115.80±8.484</td>
<td>73.26±5.706</td>
</tr>
<tr>
<td>Mean±SEM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P – value</td>
<td>= 0.439</td>
<td>= 0.3097</td>
<td>= 0.0296</td>
</tr>
</tbody>
</table>

RMSSD=the square root of the mean squared differences of successive NN intervals
SDNN=standard deviation of the NN intervals
SDANN=standard deviation of average NN intervals

**DISCUSSION**

In this study, we first assessed the ANS involvement in migraine using simple bedside reliable tests and then we studied the HRV on long-term 24-hour Holter ECG to assess its prognostic value as a way to delineate its importance for migraineurs.

RSA is heart rate variability in synchrony with respiration by which the R-R interval on an ECG is shortened during inspiration and prolonged during expiration. It has been used not only as an index of cardiac vagal function, but also has positive influence on gas exchange at the level of the lung via efficient ventilation/perfusion motility. RSA in migraineurs was significantly decreased when compared to controls. This was seen in previous studies but not in other studies.

The heart rate response to standing evaluates the cardiovascular response elicited by a change from horizontal to a vertical position. The typical heart rate response to standing is largely attenuated by a parasympathetic blockade. In healthy subjects, there is a characteristic and rapid response to standing that is maximal at approximately the 15th beat after standing. This is followed by a relaxation bradycardia that is maximal at approximately the 30th beat after standing. Migraineurs had almost significantly lower values than controls. In previous studies of adult migraineurs, during active standing, Ewing ratio was found reduced, normal or elevated. In this study, we found a significantly lower values in chronic migraineurs when compared to new-onset ones but was significant only with...
RSA. Similar observation was noticed in patients with disabling migraine\(^2\). Finally, Orthostatic hypotension is a physical finding defined by the American Autonomic Society and the American Academy of Neurology as a systolic blood pressure decrease of at least 20 mmHg or a diastolic blood pressure decrease of at least 10 mm Hg within three minutes of standing\(^6\). Our migraineurs were not different from controls. This was in agreement with\(^{2,14,17}\). However, it was decreased in another 5 studies\(^{11,16,28}\).

The previous results suggest parasympathetic hypofunction. Because combined reductions of the heart rate responses to deep breathing and the Valsalva ratio are used as a standard test of cardiovascular function, the impaired RSA with paradoxically normal Valsalva ratio is not against this observation. Rothschild et al.\(^{28}\) assessed the sensitivity of these two measures to parasympathetic ablation, when 12 nondiabetic subjects were tested before and after graded doses (0.3–4.0 mg i.v.) of atropine. R-R variation was significantly reduced at 0.7 mg, whereas Valsalva ratio was not significantly smaller until the 2.0-mg dose of atropine. While R-R variation continued to become progressively smaller during the 0.85-, 1.0-, and 2.0-mg doses. This was also noticed in our chronic migraineurs when compared to new-onset. Further more, Steinkopff\(^{29}\) found that impaired respiratory sinus arrhythmia with paradoxically normal Valsalva ratio indicates combined cardiovascular and peripheral adrenergic failure. This might further explain the subjective postural hypotension in contrast to the objective absence of measurable systolic decrease in response to standing.

Because the role of RSA in long-term ECG monitoring as an autonomic marker is limited, we chose time domain analysis to clarify HRV prognostic value in migraineurs.

Time domain analysis measures the changes in heart rate over time or the intervals between successive normal cardiac cycles. SDNN is a global index of HRV and only its decrease is a strong predictor of increased all-cause cardiac and/or arrhythmogenic mortality\(^{3,30}\). In our study, though our migraineurs had lower SDNN values, it was not significantly different from controls, negating its bad prognostic index and at the same time, not excluding autonomic involvement. RMSSD corresponds to short-term HRV changes and are not dependent on day/night variations reflecting alterations in autonomic tone that are predominantly vagally mediated\(^1\). RMSSD was not found to be significantly different from controls. SDANN that reflects long-term variations was significantly low in migraineurs. It correlates with lower frequency HRV that constitutes 95% of total power\(^{11}\). Although, its physiological correlates were still unknown\(^3\), its clinical prognostic importance is getting more interest. Recently, Fantoni et al.\(^{28}\) provides strong data that SDANN is an important clinical tool, not only as an autonomic marker but also as an important prognostic factor. The researchers have convincingly shown that 1) successful cardiac resynchronization therapy (CRT) improved SDANN and 2) that an early improvement in SDANN predicted a favorable long-term outcome. The investigators interpret this increase in SDANN as reflecting changes in autonomic tone, specifically modifications of the sympathetic nervous system and parasympathetic nervous system interactions in the heart. In contrast, several observations\(^{18,22,23,24,25}\) argued that SDANN is heavily influenced by physical activity. Adamson et al.\(^{35}\) also reported that a decline in physical activity corresponded with a decrease in SDANN prior to a clinical deterioration. Our results in migraine come along with the two points of view. Autonomic insufficiency was documented by short-term studies while physical inactivity, though we didn’t measure in our study, is common finding in migraineurs. Migraine patients have lower scores for role functioning, social functioning, and their energy score is also remarkably low\(^{17}\). In a Swedish study in 2004\(^{48}\), 65% of migraineurs reported some degree of absence from either school or work during the previous year. This absenteeism was reported also in England\(^{39}\) and in France\(^{46}\). Most of our studied migraineurs were chronic and 7 showed chronic daily headache.

Our study is the first one to our knowledge to highlight the importance of ANS involvement in migraine by partly ruling out the global decrease in HRV (SDNN) that carries a bad prognosis. In addition, physical exercise can be recommended for migraineurs to counteract their reduced SDANN that is potentially reversible. Our results also not only confirm ANS dysfunction in the pathophysiology of migraine but also it could be a subject of
progression over time. Longitudinal studies of HRV in migraineurs are recommended and the effect of measures that improve it like physical exercise could be a subject of future research.

REFERENCES

الملخص العربي

الإضطرابات الوظيفية للجهاز العصبي الذاتي في مرض الشقيقة.
ماذا نحتاج أن نعرف عنه؟

يعتبر مرض الشقيقة من الأمراض العصبية المزمنة ولها أعراض متعددة في الجهاز العصبي الذاتي. على الرغم من ذلك، فدراسات مختلفة عنا الجهاز العصبي الذاتي لمرض الشقيقة مازالت متناوبة النتائج ولم يتم دراسة أميتها.

هدف هذه الدراسة إلى بحث الجهاز العصبي الذاتي وتأثيره على تغيرات معدل نبض القلب لدى مرضى الشقيقة. أدرك

في هذا البحث تسع عشرية عرضياً يعانون من مرض الشقيقة وتم مقارنتهم كمجموعة اختيارية بعشرة أشخاص أصحاء لا

يعانون من أمراض ومصابون في السن والجنس وذلك بعد أجراء الاختبارات التالية لهم:

1. استجابة معدل نبض القلب واضغط الدم الانقباضي للوقوف.
2. استجابة معدل نبض القلب للتنفس.
3. استجابة معدل نبض القلب لطريقة (فلشافا).
4. رسم قلب متواصل أربعة وعشرون ساعة (هولتر).

أظهرت الدراسة أن المرضى الذين يعانون من مرض الشقيقة يعانون من انخفاضاً ذا دلالة إحصائية بتغيرات معدل
نبيض القلب أثناء التنفس وكذلك أظهروا في أغلب الحالات استجابة منخفضة ذات دلالة إحصائية للوقوف. أما استجابة ضغط
الدم الانقباضي ونسبة (فلشافا) كانت غير مختلفة عن المجموعة الضابطة.

فما أظهرت دراسات تغير معدل نبض القلب باستخدام رسم القلب المطول أن معدل الانحراف في متوسط فترة الـ: نون كانت منخفضة في مرض الشقيقة انخفاضاً ذا دلالة إحصائية عن المجموعة الضابطة.

يظهر هذا الانخفاض في تغيرات نبض القلب كانت أعلى إحصائياً في السيدات وفي مرض الشقيقة المزمن عند مقارنتهم
بالحالات المرضية الحديثة مرض الشقيقة.

في حين أن معدل الانحراف في فترة الـ: نون والجزر التربيعية في فرق مربع فترات الـ: نون المتتالية لم تكن
أظهرت تغيرات ذات دلالة إحصائية عند مقارنتهم بالمجموعة الضابطة.

تقتربنا مما هو في ظلية الجهاز العصبي الذي يمارس في مدى مرض الشيقة. كما أن الانخفاض في تغيرات
معدلات نبض القلب يشير إلى نقص النشاط البدني لؤلؤة المرضى أكثر من كمؤشر للمصير السليم (والذي لم يظهر له أي
تأثير ذو دلالة إحصائية) في مرض الشيقة.