Serum melatonin, prolactin and cortisol assessment in chronic migraine

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ABSTRACT

Chronic migraine (CM), previously called transformed migraine, is a frequent headache disorder that affects 2%-3% of the general population. Many disorders are often associated with CM such as insomnia, depression, and anxiety. Hypothalamic involvement has been postulated in its pathogenesis. This study was designed to assess hypothalamic involvement in CM by measurement of melatonin, prolactin and cortisol secretion. 22 patients fulfilling the diagnostic criteria for CM and 10 age and sex matched healthy volunteers were subjected to measurement of melatonin, prolactin, and cortisol concentrations. Two samples were taken at 7 am and at mid-night. Any comorbid disorder was evaluated. An abnormal pattern of hypothalamic hormonal secretion was found in CM. This included decreased nocturnal prolactin peak, increased cortisol concentrations, decreased nocturnal melatonin concentrations in patients with insomnia. These results support hypothalamic involvement in CM. (Egypt J. Neurol. Psychiat. Neurosurg., 2004, 41(1): 263-271).

INTRODUCTION

Chronic migraine (CM) is a debilitating disorder that affects 2.4% of the general population¹,², and accounts for most consultations in headache clinics (40% to 65%)³. Because CM affects people during their peak productive years, it imposes a significant decrease in their quality of life and considerable economical burden to society⁴. Criteria of chronic migraine⁵,⁶:

A. Patients with CM often have a history of episodic migraine beginning in their teenage years.
B. The headache frequency increases and its severity decreases over at least 3 months.
C. Daily or almost daily (>15 days/month) headache for more than 1 month.
D. Average headache duration of 4 hours/day if untreated.
E. The associated symptoms of nausea, vomiting, photophobia, and phonophobia become less prominent.

Chronic migraine is a complex syndrome with many associated conditions including acute medication overuse⁶, generalized anxiety disorder (70%)⁷, major depression (80%)⁷, and insomnia (71%)⁸. Little is known about the causes and mechanisms of CM. The causes of transformation of episodic migraine to CM remains unknown. Several mechanisms have been alleged to be the cause of the change in frequency and symptoms, including chronic neurogenic inflammation, central sensitization, defective central pain modulation, hypothalamic dysfunction, or a combination of these⁹.
MATERIALS AND METHODS

The study was performed from January to June 2001 at Department of Neurology, Kasr El-Aini Hospitals, 22 patients who met the criteria of Mathew and Silberstein were included in the study (group A: study group). A control group included 10 age and sex matched healthy volunteers (group B). In group A, there were 16 females and 6 males. Their ages ranged from 18 to 44 years (mean 32.4±9.1). The control group (group B) included 7 females and 3 males. Their ages ranged from 20 to 43 years (mean 31±8.9).

All patients with CM were instructed not to take medications during the week before the blood analysis. None had taken any preventive medication for at least 3 months before the study. Women's samples were obtained during the follicular phase of the menstrual cycle. Subjects were admitted to hospital at least one week before the blood analysis.

We excluded from this work patients with previous neurological problems, patients with hypertension, history of smoking, drug abuse, alcoholism, or any relevant medical disease.

All patients were subjected to the following:
1. Thorough clinical evaluation.
2. Depression was assessed by the Montgomery and Asberg (MADRS) rating scale, and anxiety by the Hamilton anxiety scale (HAS). Patients were diagnosed as having insomnia according to the following criteria:
   - Difficulty of sleep onset or maintenance,
   - Insomnia at least three times a week for at least 1 month, and
3. Routine laboratory tests including blood sugar, urea, creatinine, complete blood picture, erythrocyte sedimentation rate, cholesterol, triglycerides, and liver function tests.
4. Brain CT scan.
5. Determination of serum melatonin, prolactin and cortisol by radio-immunoassay. Blood samples were taken at midnight and at 7 o'clock am. The averages of 2 samples in patients and controls for each hormone were analyzed. Also, the peak prolactin level (nocturnal sample) was compared with the corresponding level in controls.

Statistical analysis

The Mann-Whitney rank sum test and student's t test were used for comparison. Analysis of variance (ANOVA) with repeated measures was used to compare patients and controls. Pearson's test was used for the correlation analysis. Values are expressed as means (±SD). The level of significance was taken as p<0.05.

RESULTS

Results of the clinical study:

This study included 22 patients with CM (group A) and 10 healthy controls (group B). In group A, there were 16 female (72.73%) and 6 males (27.27%). Their ages ranged from 18 to 44 years (mean 32.4±9.1). The control group (group B) included 7 (70%) females and 3 (3%) males. Their ages ranged from 20 to 43 years (mean 31±8.9) (Table 1).

The duration of CM ranged from 6 months to 28 years.
Depression was present in 6 patients (27.27%), anxiety in 4 (18.18%), and insomnia was present in 10 patients (45.45%) (Table 2).

The Brain CT scan was normal in all patients.

Results of the laboratory study:
1. Melatonin
   There was no significant difference in nocturnal melatonin levels between patients and controls [41.1±18.2 versus 44.2 ± 16.3 pg/ml] (Table 3 & Fig. 1). Patients who had CM plus insomnia (n=10) had melatonin concentrations [27.80±19.6 pg/ml] that were significantly lower than those in patients with CM without insomnia [45.6±9.4 pg/ml pg/ml] p<0.05 (Table 4, Fig. 2), and that were also significantly lower than those in controls [44.2±16.3 pg/ml] (Table 5 & Fig. 3).

2. Prolactin
   The mean concentration of prolactin in patients with CM was not significantly different from controls [27±12 ng/ml versus 37±18 ng/ml respectively, p=0.06]. There was no significant difference in the mean prolactin peak in patients with CM with or without insomnia (Table 6 & Fig. 4).

3. Cortisol
   Patients had higher cortisol concentrations than controls [10.6±4.2 versus 5.8±1.2 µg/dl]. There were no significant differences between patients with or without insomnia (Table 7, Fig. 5).

Table 1. Comparison between patients and controls as regards number, age, and sex.

<table>
<thead>
<tr>
<th></th>
<th>Patients (group A)</th>
<th>Controls (group B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>22</td>
<td>10</td>
</tr>
<tr>
<td>Age (mean±SD)</td>
<td>32.4 ± 9.1</td>
<td>31 ± 8.9</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>16</td>
<td>7</td>
</tr>
<tr>
<td>male</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 2. Associated conditions.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>6</td>
<td>27.27 %</td>
</tr>
<tr>
<td>Anxiety</td>
<td>4</td>
<td>18.18 %</td>
</tr>
<tr>
<td>Insomnia</td>
<td>10</td>
<td>45.45 %</td>
</tr>
</tbody>
</table>

Table 3. Comparison between melatonin concentrations in patients and controls.

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melatonin concentration (pg/ml)</td>
<td>41.1 ± 18.2</td>
<td>44.2 ± 16.3</td>
<td>0.4</td>
</tr>
</tbody>
</table>
Fig. (1): Melatonin concentrations in patients and controls.

Table 4. Comparison between melatonin concentrations in patients with and without insomnia.

<table>
<thead>
<tr>
<th></th>
<th>Patients with insomnia</th>
<th>Patients without insomnia</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melatonin concentration (pg/ml)</td>
<td>27.80±19.6</td>
<td>45.6±9.4</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Table 5. Comparison between melatonin concentrations in patients with insomnia and controls.

<table>
<thead>
<tr>
<th></th>
<th>Patients with insomnia</th>
<th>Controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melatonin concentration (pg/ml)</td>
<td>27.80±19.6</td>
<td>44.2±16.3</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Table 6. Comparison between prolactin concentrations in patients and controls.

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolactin concentration (ng/ml)</td>
<td>27±12</td>
<td>37±18</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Table 7. Comparison between cortisol concentrations in patients and controls.

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol concentration (µg/dl)</td>
<td>10.6±4.2</td>
<td>5.8±1.2</td>
<td>0.03</td>
</tr>
</tbody>
</table>
Fig. (2): Melatonin concentrations in patients with and without insomnia.

Fig. (3): Melatonin concentrations in patients with insomnia and controls.
Fig. (4): Prolactin concentrations in patients and controls.

Fig. (5): Cortisol concentrations in patients and controls.
DISCUSSION

Melatonin, prolactin, and cortisol concentrations were measured at midnight and at 7 O’clock to investigate the role of the hypothalamus in chronic migraine. The hormones were measured during the night as the highest concentrations are usually at this time. We found lower melatonin concentrations in patients with CM with insomnia compared to patients without insomnia and to normal controls, normal mean prolactin secretion and increased cortisol concentrations in patients compared to controls.

Lower melatonin concentrations have been reported in episodic migraine and cluster headache. In our study melatonin concentrations were significantly lower in patients with CM who had insomnia than in patients without insomnia and in controls [27.80±19.6, 45.6±9.4, 44.2±16.3 pg/ml respectively]. Similar results were reported by Peres et al. and low melatonin concentrations have been reported in patients with insomnia by Hajak et al.

The circadian rhythm of melatonin secretion is regulated by the suprachiasmatic nucleus in the hypothalamus. The low melatonin concentrations found in patients with CM who had insomnia than in patients without insomnia and in controls [27.80±19.6, 45.6±9.4, 44.2±16.3 pg/ml respectively]. Similar results were reported by Peres et al. and low melatonin concentrations have been reported in patients with insomnia by Hajak et al.

The second hormone assessed in this study was prolactin. Normal prolactin levels were found (27±12 ng/ml versus 37±18 ng/ml in normal control). Previous studies have reported normal prolactin values in episodic migraine. However some studies have reported low peak prolactin concentrations in patients with CM.

In our study patients had higher cortisol concentrations than controls [10.6±4.2 versus 5.8±1.2 µg/dl]. This agrees with the results of Peres et al., who found higher concentrations of cortisol, and suggested that the hypophyseal-adrenal axis is activated in patients with CM compared with controls.

Cortisol concentrations are raised in many conditions related to CM, such as depression, anxiety, insomnia, and chronic pain. In this study we found no significant difference in cortisol concentrations in patients with or without insomnia. The number of patients with depression and anxiety in our study was too low to permit statistical analysis.

The results of this study suggest a role for the hypothalamus in the pathogenesis of CM. Further research is required to study the impact of these findings on treatment of migraine.
REFERENCES

الملخص العربي

يعتبر الصداع النصفي المزمن من أكثر أنواع الصداع شيوعا حيث أنه يصيب من 2-3% من البشر.
ويتلازم مع هذا الصداع مجموعة من الأعراض من أشهرها القلق النفسي، الاكتئاب والأرق. وقد افترض بعض الباحثين أن اختلال بعض الهرمونات يسبب الصداع النصفي.

وقد أجري البحث الحالي لدراسة هذا الافتراض، حيث اشتمل البحث على 22 مريضا يعانون من الصداع النصفي المزمن، و10 من الأصحاء كجموعة ضابطة، واجرى لكل منهم التالي:

1. فحص اكلينيكي دقيق للجسم والجهاز العصبي
2. دراسة مقياس ‘هاملتون’ للقلق النفسي ومقياس ‘مونتجمري’ لإسبرج’ للأكتئاب
3. اشعة مقطعية بالكمبيوتر للمخ
4. فحوص معملية.
5. قياس مستوى هرمون الميلاتونين والبرولاكتين والكورتيزول بالدم

وقد أظهرت النتائج ما يلي:

1. إن 27.27% من المرضى يعانون من الاكتئاب، و18.18% من القلق و45.45% من الأرق، التي تعتبر من أهم الأعراض المصاحبة للصداع النصفي المزمن.
2. انخفض مستوى هرمون الميلاتونين في الدم في مجموعة المرضى المصابين بالأرق مقارنة بالمرضى غير المصابين بالأرق ونسبة المجموعة الضابطة.
3. لا يوجد فرق ذو دلالة إحصائية في مستوى هرمون البرولاكتين في مجموعة المرضى مقارنة بالمجموعة الضابطة.
4. ارتفاع مستوى هرمون الكورتيزول بالدم في مجموعة المرضى مقارنة بالمجموعة الضابطة.