THE PLASMA LEVEL OF PARATHORMON AND HOMOCYSTEINE IN MIGRAINE PATIENTS; ANOTHER ASPECT ON MIGRAINE-STROKE ASSOCIATION

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ABSTRACT

The pathogenesis of migraine has been well studied and it is associated with oxidative stress, neurogenic inflammation, and endothelial dysfunction. To the best of our knowledge, no studies have focused on the impact of the parathormone (PTH) and homocysteine levels in migraine patients. To determine migraine-stroke association, our study focused on the levels of PTH and homocysteine in the blood of migraine patients.

Fifty five migraine patients in the presence or absence of aura were included. The patients in the migraine group were divided into subgroups: (I) migraine in the attack period (with and without aura) (n = 23), and (II) migraine in the interictal period (with and without aura) (n = 32). As a control, 30 healthy volunteers were also enrolled in the study.

As a result, we found that PTH and homocysteine levels of the migraine patients were increased significantly when compared with healthy volunteers (p = 0.001). The PTH and homocysteine levels of the patients with aura were higher than patients without aura in the migraine group (p < 0.05). There were no statistically significant differences between PTH/homocysteine levels and migraine duration or migraine attack frequency (p > 0.05). There was a positive correlation between PTH and homocysteine levels in the migraine patients (p = 0.001, r = 0.49).

To summarize, we found statistically significant increases in PTH and homocysteine blood levels of migraine patients versus healthy volunteers. These results may help to understand the pathogenesis of migraine ischemia, and potentially identify new prognostic markers for this condition.

Key words: Migraine, pathogenesis, parathyroid hormone, homocysteine.

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Introduction

Migraine is one of the most common headache disorders causing discomfort in approximately 20% of the female, and 8% of the male population(1). The prevalence of migraine in children was found in a study in our country to be 8.84%(2). The characteristic of migraine pain is commonly unilateral, severe, and pulsating headache, and this pain usually comes with nausea, vomiting, and low tolerance for light and sound. In addition, obstructive nasal pathologies are increased in patients with migraine(3). Some migraine patients present with neurological problems temporarily, and this phenomenon is known as migraine aura(4).

According to the neurovascular theory, migraine patients initially develop neuronal activation that end with multiple vascular changes. Cerebrovascular events stimulate vascularization at the pain sensitive regions, and cause vasodilation as well as an increase in the frequency of the trigeminal nerve stimulation, followed by migraine pain(5).

Recently, published studies have shown that a migraine associated with aura results in the increased risk of ischemic stroke and cardiovascular disease. However, the exact mechanisms that
lead to migraine related cardiovascular and cerebrovascular events are not fully understood. Past reports suggest that migraine may be related to vascular endothelial dysfunction, which has been shown to be a predictor of the increased rate of cardiovascular disease and cerebrovascular stroke\(^6,7\). Endothelial dysfunction is a process which is commonly caused by oxidative stress, vascular endothelial activation, and impaired vascular reactivity. One of the known mechanisms that increase susceptibility to the vascular endothelial dysfunction is hyperhomocysteinemia, most likely through its facilitation of oxidative stress. Interestingly, homocysteine has been demonstrated as a biomarker for endothelial dysfunction, and has been studied and highly detected in migraine patients\(^8,9\). For these reasons, increased levels of homocysteine may be an independent risk factor for vascular disease in patients with migraines.

Recent data suggests that low vitamin D and high parathormone (PTH) level may increase the susceptibility of cardiovascular diseases. Furthermore, increased PTH levels are a marker for oxidative/nitrosative stress, inflammation, and vascular endothelial activation. Several studies have shown strong evidence for the relationship between oxidative stress, neurogenic inflammation, and endothelial dysfunction. To our knowledge, there are no studies available that analyze the relationship between migraines and PTH and homocysteine levels\(^10-13\).

In our study, we analyzed blood from migraine patients, and determined that there was a strong positive correlation between PTH and homocysteine levels and patients with migraines.

**Materials and methods**

Data of 8 out of 12 patients were retrieved Fifty-five migraine patients and age-sex matched 30 healthy volunteers (control group) were enrolled in the study. An expert neurologist at the Department of Neurology analyzed patients that presented with migraine symptoms in the outpatient clinic at Dicle University. Migraine diagnosis decision was made according to the International Classification of Headache Disorders-II diagnostic criteria\(^15\). Newly diagnosed migraine patients with no administration of prophylactic migraine medication were enrolled into the study. Fifty five migraine patients in the presence or absence of aura were included.

The patients in the migraine group were divided into subgroups: (I) migraine in the attack period (with and without aura) (n = 23), and (II) migraine in the interictal period (with and without aura) (n = 32). A control group (n = 30) was recruited among healthy volunteers that reported no prior problems of primary or secondary headaches and enrolled in the study. Typical exclusion criteria were as follows: suffered from hypertension, diabetes, coronary artery diseases, thyroid disorders, smoking history, vitamin B12 deficiency, macrocytic anemia finding, Alzheimer disease, and Parkinson disease. In addition, other criteria were excluded: patients who had taken drugs that could possibly alter homocysteine levels; patients who had history of renal, hematological, and oncological diseases; and patients who were on vegetarian diet or treatment for vitamin B12 deficiency.

Blood samples were drawn from migraine patients at the time of the migraine headache or the migraine-free period. Each collected blood sample was immediately centrifuged at 4,000 rpm at 4 ºC for 10 min, and then transferred into an eppendorf tube. Samples were immediately put on ice and stored at -50 ºC until end of the study, which was completed in 3 months. Plasma PTH levels were determined by Electrochemiluminescence Immunoassay (ECLIA) (Cobas e601, Roche Diagnostics, GmbH, Germany) and homocysteine levels were determined by a chemiluminescence method (Immulite 2000® analyzer, Diagnostic Products, Los Angeles, CA, USA).

The local Ethics Committee approved the study, and all patients signed the informed consent. Migraine headache attack frequency was noted as the number of attacks per month. Body mass index (BMI) was calculated based on World Health Organization (WHO) recommendations.

**Statistical analyses**

SPSS for Windows version 11.5 was used for statistical analyses. Descriptive data have been presented as means, standard deviations, and frequency distributions. Categorical and continuous data were compared using chi-square test, and Student’s t-test, respectively. A p-value of less than 0.05 was accepted as statistically significant. The correlation analyses were performed with Pearson’s correlation tests.
Results

Demographic and biochemical variables of the patient and control groups are shown in Table 1. No differences were found for mean age, BMI, and blood pressure between two groups (p > 0.05). Migraine patients had higher levels of PTH and homocysteine when compared with healthy volunteers (p = 0.001, Table 1).

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<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Controls (n = 30)</th>
<th>Migraine (n = 55)</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>34.96 ± 8.72</td>
<td>33.27 ± 7.98</td>
<td>N.S.</td>
</tr>
<tr>
<td>Sex (female/male)</td>
<td>26/4</td>
<td>49/6</td>
<td>N.S.</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>25.62 ± 4.82</td>
<td>23.89 ± 4.02</td>
<td>N.S.</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>115.0 ± 10.7</td>
<td>110.6 ± 17.8</td>
<td>N.S.</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>73.3 ± 8.4</td>
<td>69.4 ± 10.5</td>
<td>N.S.</td>
</tr>
<tr>
<td>Parathormone</td>
<td>23.96 ± 9.01</td>
<td>31.82 ± 23.96</td>
<td>0.001</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>7.31 ± 0.64</td>
<td>8.62 ± 0.99</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table 1: Baseline characteristics homocysteine and parathormone levels of migraine patients and healthy controls.

N.S. statistically not significant (p > 0.05)

PTH and homocysteine levels of the migraine subgroups are shown in Table 2. No statistically significant differences were found between PTH and homocysteine levels during the attack and interictal periods for the migraine group (p > 0.05). PTH and homocysteine levels of the patients with aura were higher than the patients without aura in the migraine group (p < 0.05). There were no statistically significant differences between PTH/homocysteine levels and migraine duration or migraine attack frequency (p > 0.05). There was a positive correlation between PTH and homocysteine levels in the migraine patients (p = 0.001, r = 0.49).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Migraine during attack (n = 23)</th>
<th>Interictal period (n = 32)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parathormone</td>
<td>32.9 ± 6.5</td>
<td>31.3 ± 7.0</td>
<td>N.S.</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>8.62 ± 0.89</td>
<td>8.66 ± 1.06</td>
<td>N.S.</td>
</tr>
<tr>
<td>Parathormone</td>
<td>36.13 ± 6.1</td>
<td>30.9 ± 6.5</td>
<td>0.023</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>9.32 ± 1.07</td>
<td>8.46 ± 0.91</td>
<td>0.011</td>
</tr>
</tbody>
</table>

Table 2: Comparison of homocysteine and parathormone levels of the migraine subgroups.

N.S. statistically not significant (p > 0.05)

Discussion

In our study, we showed for the first time increased levels of PTH and homocysteine in patients suffering from migraine with or without aura. Furthermore, there was positive correlation between PTH and homocysteine levels in patients with migraines compared to controls. These findings suggest that homocysteine and PTH may have a role in the pathogenesis or progression of migraine headaches as well as migraine associated ischemic events.

Homocysteine is a sulphur-containing amino acid that is important in the metabolism of methionine. Increased homocysteine plasma levels are an independent risk factor for thrombosis, atherosclerosis, and various forms of ischemic vascular disease, such as stroke and myocardial infarction(16,17). The relationship between migraine and homocysteine has been well studied. Nevertheless, previous studies have resulted in controversial results(12, 17-20).

Our findings are partially consistent with previous studies. Hering-Hanit et al. demonstrated that homocysteine plasma levels were not increased in migraineurs(18). Higher homocysteine plasma levels were shown in a group of migraine patients, which were only significantly increased in those with migraines associated with aura(19).

A large patient cohort study by Oterino et al. showed that plasma levels of homocysteine were significantly higher in men compared to women of the same study. The authors demonstrated that homocysteine increased as methylenetetrahydrofolate reductase -677T allele number increased. Moreover, patients with aura associated migraines had increased homocysteine plasma levels in comparison with migraine patients without aura. A comparison of the homocysteine levels between healthy volunteers and the patient group did not determine any significant differences(17). Isobe et al. showed that migraine patients with aura had significantly higher levels of the total homocysteine in cerebro-spinal fluid. It is known that total homocysteine levels contribute, not only development of atherosclerotic diseases but also to the cardiovascular and cerebrovascular events(12). Migraine and homocysteine association has been well investigated in several studies, whereas some have shown that migraine with aura is strongly associated with increased homocysteine blood levels.

In our study, we found statistically significant levels of increased homocysteine blood levels in
migraine patients compared to healthy volunteers, which is consistent with the previous literature. Moreover, this increase was statistically significant in the aura associated migraine group. These data suggest that increased blood homocysteine is an important blood marker for the ischemic changes in the brain of migraine patients.

Several studies recently suggested that vitamin D and PTH may be important in the pathogenesis of cardiovascular disease\textsuperscript{(13,20)}. A recently published study showed that high PTH and low vitamin D blood levels have been independently associated with higher rates of cardiovascular disease such as hypertension and myocardial infarction\textsuperscript{(21)}. In addition, hypovitaminosis D has been associated with diabetes and stroke\textsuperscript{(22)}. It has been shown in numerous studies that hyperparathyroidism was strongly associated with increased rate of cardiovascular disease\textsuperscript{(23)}. Another former study revealed an association between impaired bone metabolism, microangiopathy, and chronic pain in hemodialysis patients\textsuperscript{(24)}. The same study showed that increased PTH and calcium levels were associated with chronic pain as well\textsuperscript{(25)}. Moreover, 8 patients with chronic cluster type headaches and vitamin D deficiency reported that their headache frequency decreased with vitamin D treatment. Therefore, the authors speculated an association between vitamin D deficiency and headache pathogenesis\textsuperscript{(26)}.

To date, no definitive association has been shown between migraine and increased PTH blood levels and/or vitamin D deficiency. In our study, we showed that there was an increase in PTH blood levels in migraine patients, and put forth the notion that PTH may be an important and feasible blood marker for migraine patients with brain ischemia and potentially early-onset vascular disease. However, further studies are required to determine the exact role for PTH in migraine headaches.

In our study, migraine patients with aura had higher blood PTH levels in comparison with migraine patients without aura (with a strong correlation between PTH and homocysteine). These findings support the relationship between PTH and ischemic risk factors in migraine patients. However, to determine the impact of the blood PTH and vitamin D level on migraine-stroke-ischemia pathogenesis further studies are required. Several limitations of the study should be considered. One potential limitation is the cross-sectional study design. The other limitation of the present study includes the relatively small patient population enrolled and the small number of events in this group. Further studies are needed to explore the possible link between PTH and homocysteine in patients with migraine headaches.

In conclusion, our study demonstrates that PTH was increased in migraine patients versus healthy volunteers. Moreover, patients with aura associated migraines have higher blood PTH and homocysteine levels compared to migraine patients without aura. These results may help to understand the role of PTH and homocysteine in migraine patients. The analysis of PTH and homocysteine levels would be an easy and non-invasive way to detect ischemia in migraine patients. Advanced studies are necessary and crucial to better show the impact of PTH and homocysteine on the pathogenesis of cardiovascular and cerebrovascular diseases.

References


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