Background: Behçet’s disease is a chronic, multisystemic disease of unknown etiology in which eye involvement is the most common cause of morbidity. In this study, we investigated the possible relation between serum homocysteine level and ocular involvement in patients with Behçet’s disease.

Methods: One hundred and fifty patients who fulfilled the criteria of the International Study Group for Behçet’s disease (96 females and 54 males) were enrolled. All the patients were evaluated carefully by an experienced ophthalmologist for the diagnosis of ocular involvement. Serum homocysteine, vitamin B12, and folate levels were determined. The patients were categorized according to the presence or absence of uveitis. The data were statistically analyzed by using Student’s t-test and P values less than 0.05 were considered statistically significant.

Results: Fifty-nine patients (39.3%) had eye involvement, which included anterior uveitis, vitritis, macular damage, optic atrophy, panuveitis, posterior uveitis, retinal vasculitis, and retinal hemorrhage. Serum levels of folate and vitamin B12 were comparable in patients with Behçet’s disease. There was no significant correlation between serum homocysteine level in patients with and without eye involvement.

Conclusion: Our findings suggest that homocysteine level does not have significant effect on eye involvement in patients with Behçet’s disease.

Keywords: Behçet’s disease • eye • homocysteine • hyperhomocysteinemia

Introduction

Behçet's disease (BD) is a chronic, relapsing, multisystemic, inflammatory disorder of unknown origin characterized by recurrent oral aphthous, genital ulcers, skin lesions, and eye involvement. Ocular involvement occurs in 50 – 70% of patients, and is characterized by periphlebitis, periarteritis, vascular occlusion, and thrombosis, which may lead to blindness despite intensive treatment. The central feature of the histopathology of BD is an obliteratorative and necrotizing vasculitis that affects both the arteries and veins.

Homocysteine, a sulfur-containing essential amino acid, is derived from methionine. It is formed during the conversion of methionine to homocysteine. Elevations in total plasma homocysteine level may be caused by folate and vitamin B12 deficiencies, which are the cofactors for the enzyme reactions involved in homocysteine metabolism.

Hyperhomocysteinemia is a known risk factor for cerebrovascular, peripheral vascular, and coronary heart diseases. Elevated serum homocysteine levels have been suggested as a risk factor for nonarteritic anterior ischemic neuropathy, and retinal vascular occlusive disease.
There are controversial reports about the role of hyperhomocysteinemia in the eye involvement of BD. Okka and colleagues showed that homocysteine might play a role in ocular involvement of BD. They concluded that chronic inflammation could induce hyperhomocysteinemia, leading to thrombosis in the retinal vascular bed. On the other hand, Calikuglu and coworkers found that homocysteine levels were not elevated in BD. Korkmaz and colleagues found no association between homocysteine level and vascular involvement.

Having considered the impact of eye involvement and the controversy surrounding its etiology in BD, the present study was performed to investigate the possible role of serum homocysteine in the eye involvement in BD.

**Patients and Methods**

The study population consisted of 150 consecutive patients who fulfilled the International Criteria for BD, and referred to the Rheumatology Clinic at Shiraz University of Medical Sciences from September 2006 through March 2007. Patients with diabetes mellitus, hyperlipidemia, end-stage renal failure, psoriasis, inflammatory bowel disease, and those taking methotrexate as well as pregnant women were excluded.

Routine history taking and physical examination were performed. All the patients were evaluated by an experienced ophthalmologist for the presence of uveitis, using the criteria of the International Study Group. Moreover, blood samples were withdrawn from a peripheral vein after an overnight fasting. All the patient were informed about the aims of the study and written consents were obtained from them. The blood samples were centrifuged for 20 minutes at 2,000 rpm. The sera were collected and kept at -70°C until assays. The measurement of homocysteine level was performed using enzyme-linked immunosorbent assay (ELISA) kit (DRG Diagnostics Inc., USA). Moreover, serum vitamin B12 and folate levels were determined by radioimmunoassay. Serum folate levels above 1.5 ng/mL and serum vitamin B12 levels above 160 pg/mL were considered normal.

The patients were then categorized according to the presence or absence of eye involvement.

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral aphthous</td>
<td>150 (100%)</td>
</tr>
<tr>
<td>Genital aphthous</td>
<td>118 (78.8%)</td>
</tr>
<tr>
<td>Positive Pathergy test</td>
<td>111 (74%)</td>
</tr>
<tr>
<td>Skin lesions</td>
<td>73 (48.7%)</td>
</tr>
<tr>
<td>Eye involvement</td>
<td>59 (39.9%)</td>
</tr>
<tr>
<td>Vascular involvement</td>
<td>25 (16.7%)</td>
</tr>
<tr>
<td>Neurologic involvement</td>
<td>7 (4.7%)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>20 (13.3%)</td>
</tr>
</tbody>
</table>

The patients with uveitis, retinal vasculitis, retinal hemorrhage, retinitis, optic atrophy, episcleritis, papilledema, and macular damage were considered having eye involvement and those without these signs were categorized otherwise.

The serum levels of homocysteine were then compared in the two groups. Moreover, in both groups the correlation between serum levels of homocysteine and folate or vitamin B12 was examined.

The data were presented as mean±standard deviation (SD) and analyzed using SPSS software version 13. Student's t-test and correlation tests were used to compare the variables. P values ≤0.05 were considered statistically significant.

**Results**

The patients were consisted of 96 females and 54 males with a mean age of 35.72 years (range: 16 – 60). The mean duration of disease was 6.5 years (range: 1 – 28). The clinical signs and symptoms of the participants are shown in Table 1.

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinal vasculitis</td>
<td>16</td>
</tr>
<tr>
<td>Anterior uveitis</td>
<td>14</td>
</tr>
<tr>
<td>Panuveitis</td>
<td>9</td>
</tr>
<tr>
<td>Optic atrophy</td>
<td>8</td>
</tr>
<tr>
<td>Posterior uveitis</td>
<td>5</td>
</tr>
<tr>
<td>Retinitis</td>
<td>4</td>
</tr>
<tr>
<td>Cataract</td>
<td>4</td>
</tr>
<tr>
<td>Retinal hemorrhage</td>
<td>3</td>
</tr>
<tr>
<td>Episcleritis</td>
<td>1</td>
</tr>
<tr>
<td>Papilledema</td>
<td>1</td>
</tr>
<tr>
<td>Macular damage</td>
<td>1</td>
</tr>
</tbody>
</table>
were taking prednisolone, colchicine, sulfasalazine, azathioprine, cyclosporine, and cyclophosphamide to control the disease. Cataract was present in four patients, all of whom had received steroids.

Serum levels of homocysteine, folate, and vitamin B12 in patients with and without eye involvements are shown in Table 3. The serum levels of homocysteine, folate, and vitamin B12 did not show any statistically significant differences in our patients with or without eye involvement.

**Discussion**

Ocular involvement was the most common organ involvement after mucocutaneous manifestations in our patients (39.9%). In this study, we found that homocysteine level in patients with BD was not elevated.

Although many hypotheses have been suggested as the cause of retinal vasculitis and thrombosis, the exact etiology is still unknown. Some studies showed that elevated homocysteine level might increase the risk of retinal vascular diseases such as retinal artery and retinal vein thrombosis and occlusion.9

Homocysteine generates superoxide and hydrogen peroxide, both of which have been linked to endothelial damage.14 Homocysteine can promote clotting cascade via activation of protein plasma C, activation of coagulation factor V, and inhibition of thrombomodulin.15–16

There are controversial reports regarding hyperhomocysteinemia in BD. Aksu et al. found that hyperhomocysteinemia might be assumed to be an independent risk factor for venous thrombosis in BD.17 In contrast, Calikoglu et al. found that homocysteine levels were not elevated in BD.11

Most of the previous studies were about the role of hyperhomocysteinemia in thrombosis formation in BD. There are only few and controversial reports about the possible role of homocysteine in the eye manifestations of BD. Er et al. found that elevated serum homocysteine might be responsible for the endothelial damage in BD and might be an additional risk factor for the development of retinal vascular occlusive disease, contributing to the poor visual outcome in such patients.18 They studied only 43 patients of whom 27 (62.7%) had chronic intraocular manifestations of BD. Our study was done on 150 patients and only 39.9% had eye involvement. One of the contributing factors in this difference is the different sample size and the difference in presentations of our patients. Okka et al. showed that homocysteine might play a role in ocular involvement but they evaluated only 29 patients.10

In our patients, there were no significant differences between the serum homocysteine levels of those who had eye involvement with those who had not. Korkmaz et al. showed no association between homocysteine levels and vascular involvement in BD patients,12 which is in agreement with our findings.

There are two shortcomings in our study. The first one was the lack of evaluation of disease activity because there is no clinically acceptable scoring system. The second one is that we measured serum homocysteine level only once for each patient because of financial problems. Further studies are needed to collect the samples at least twice in three-month intervals for more accuracy.

In conclusion, our findings suggest that serum homocysteine level has no meaningful correlation with eye involvement in patients who are diagnosed as having BD.

**Acknowledgment**

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