The Egyptian Rheumatologist (2014) **36**, 29–34

Egyptian Society for Joint Diseases and Arthritis

The Egyptian Rheumatologist

www.rheumatology.eg.net
www.sciencedirect.com

ORIGINAL ARTICLE

Serum homocysteine level and eye involvement in Egyptian patients with Behçet's disease

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Received 13 September 2013; accepted 19 September 2013
Available online 29 October 2013

KEYWORDS

Behçet's disease;
Homocysteine;
Eye involvement

Abstract *Aim of the work:* To investigate the possible role of serum homocysteine in the eye involvement in Egyptian patients with Behçet's disease (BD).

Patients and methods: A case–control study was made on 27 patients with BD (17 males and 10 females with a mean age of 32.11 ± 7.16 years) and 19 healthy control subjects. All patients fulfilled the criteria of the International Study Group for BD. The patients were categorized as BD with eye involvement (n = 12), or BD without eye involvement (n = 15). Serum homocysteine and C-reactive protein levels were studied in all patients and controls.

Results: The mean serum homocysteine concentrations were significantly higher in BD patients than in healthy controls (15.56 ± 3.52 and 7.32 ± 1.38 μmol/L, respectively; $P < 0.001$). Also, the mean serum homocysteine concentrations were significantly higher in BD patients with eye involvement compared to those without eye involvement (18.50 ± 3 and 13.2 ± 1.61 μmol/L, respectively; $P < 0.001$). CRP, as a marker of disease activity was significantly higher in BD patients than in controls (14.33 ± 8.28 and 3.21 ± 1.72 mg/L, respectively; $P < 0.001$), however, no significant difference ($P = 0.213$) in CRP levels was found between BD patients with or without eye involvement.

Conclusion: Homocysteine may play a role in BD patients with ocular involvement. Assessment of homocysteine may be important in the investigation and management of patients with BD, especially with ocular disease.

1. Introduction

Behçet's disease (BD) is a systemic disorder associated with characteristic vasculitis that can involve veins and arteries of all sizes [1]. Mucocutaneous, ocular, genital, articular, vascular, central nervous system and gastrointestinal involvements may occur during the course of BD. Thrombophlebitis, deep vein thrombosis, arterial obstruction, and aneurysms are the more frequent vascular damages in BD [2]. Ocular involvement

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Peer review under responsibility of Egyptian Society for Joint Diseases and Arthritis.

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http://dx.doi.org/10.1016/j.ejr.2013.09.002

occurs in 50–70% of patients [3], and is characterized by periphlebitis, periarteritis, vascular occlusion, and thrombosis, which may lead to blindness despite intensive treatment [4]. The central feature of the histopathology of BD is an obliterative and necrotizing vasculitis that affects both the arteries and veins [5].

Homocysteine, derived from methionine, is a sulfur containing essential amino acid. Hyperhomocysteinemia may occur in the course of diabetes mellitus, hyperlipidemia, end stage renal failure, psoriasis and inflammatory bowel disease [6]. It may also occur due to vitamin B12 or folate deficiency [7] or secondary to treatment with some drugs, such as methotrexate (MTX) [8]. It is not only an independent risk factor for atherosclerosis but is also a causative risk factor for vascular disease and thrombosis [9]. As vitamin B6, vitamin B12, and folic acid can decrease homocysteine levels, treatment with these vitamins can be considered to reduce the risk of venous and arterial thrombosis [10].

There are controversial reports about the role of hyperhomocysteinemia in the eye involvement of BD. Multiple studies have shown that elevated homocysteine levels may be associated with ophthalmic vascular disease [11–17]. On the other hand, Calikoglu et al. found that homocysteine levels were not elevated in BD [18]. Korkmaz et al. found no association between homocysteine level and vascular involvement [19].

The present study was performed to investigate the possible role of serum homocysteine in the eye involvement in Egyptian patients with BD.

2. Patients and methods

This case–control study was conducted on BD patients attending the outpatient clinics of Ophthalmology and Rheumatology and Rehabilitation Departments, Sohag University Hospital, in the period between April 2012 and April 2013. Twenty-seven BD patients (17 men and 10 women; mean age 32.11 ± 7.16 years), fulfilling the criteria of the International Study Group for Behçet's Disease [20], and 19 matched healthy controls (11 men and 8 women; mean age 32.05 ± 7.69 years) were enrolled in this study. The exclusion criteria for these patients were: malnutrition or body mass index (BMI) less than 19, diabetes mellitus, hyperlipidemia, end stage renal failure, chronic hepatitis, cardiovascular diseases, thyroid dysfunction, cancers, psoriasis, inflammatory bowel disease and other rheumatic diseases, and those taking methotrexate as well as pregnant and lactating women. Routine history taking and physical examination were performed. All the patients were evaluated by an experienced ophthalmologist for the presence of ocular involvement using the criteria of the International Study Group [20]. All the patients were informed about the aims of the study and written consents were obtained from them. The study was approved by the local ethics committee of Sohag-University Scientific Review Board.

2.1. Determination of homocysteine levels

Venous blood samples were collected from every subject by sterile veni-puncture on the same day of history taking and clinical examination. Separated serum was kept frozen at −70 °C till the time of estimation of serum homocysteine. Serum homocysteine levels were determined by the ARCHITECT Homocysteine assay. It is a one-step immunoassay for the quantitative determination of total L-homocysteine in human serum or plasma using chemiluminescent microparticle immunoassay (CMIA) technology, with flexible assay protocols, referred to as Chemiflex. Bound or dimerised homocysteine (oxidized form) is reduced by dithiothreitol (DTT) to free homocysteine, which is then converted to *S*-adenosyl homocysteine (SAH) by the action of the recombinant enzyme *S*-adenosyl homocysteine hydrolase (rSAHHase) in the presence of excess adenosine. The SAH then competes with acridinium-labeled *S*-adenosyl cysteine for particle-bound monoclonal antibody. Following a wash stage and magnetic separation, pre-trigger and trigger solutions are added to the reaction mixture and the resulting chemiluminescence is measured as relative light units (RLUs). An indirect relationship exists between the amount of homocysteine in the sample and the RLUs detected by the ARCHITECT i System optics. The homocysteine concentrations were expressed as μmol/L.

2.2. Determination of C-reactive protein (CRP) levels

Serum CRP concentrations were determined by immunonephelometry methods on Turbox nephelometer (Orion diagnostica, Finland). The concentrations were expressed as mg/L. Concentrations ⩾6 mg/L were considered positive for CRP.

The patients were then categorized according to the presence or absence of eye involvement. The eye involvement group included those with uveitis, retinal vasculitis, optic atrophy, retinitis, retinal hemorrhage, episcleritis, papilledema, and macular damage.

Statistical analysis: The results were analyzed by IBM-SPSS (version 19). Results were given as means and standard deviation. Mann–Whitney test for continuous variables was used to examine the significance of differences between BD and control groups. The correlations between serum homocysteine levels and age, disease duration and CRP levels were analyzed by Spearman correlation analyses. *P*-values less than 0.05 were considered statistically significant.

3. Results

The cumulative clinical characteristics of BD patients are shown in Table 1.

Twelve patients with BD (44.4%) had eye involvement. The results of ophthalmologic examination are shown in Table 2.

Mean serum homocysteine concentrations in total BD patients (15.56 ± 3.52 μmol/L) were significantly higher ($P < 0.001$) than in the healthy controls (7.32 ± 1.38 μmol/L). Similarly, mean serum CRP levels were significantly higher ($P < 0.001$) in total BD patients (14.33 ± 8.28 mg/L) compared to healthy controls (3.21 ± 1.72 mg/L). Age was not significantly different between total BD patients and healthy controls (Table 3).

Mean serum homocysteine concentrations were significantly higher ($P < 0.001$) in BD patients with eye involvement (18.50 ± 3.00 μmol/L) compared to those without eye involvement (13.20 ± 1.61 μmol/L). Age, disease duration and CRP levels were not significantly different between BD patients with and without eye involvement (Table 4).

Table 1 Clinical characteristics of Behçet's disease patients (n = 27).

Characteristics	Number (%)	Homocysteine level (μmol/L)
Oral ulceration	27 (100)	15.56 ± 3.52
Genital ulceration	22 (81.5)	14.77 ± 3.09
Skin lesions	21 (77.8)	14.86 ± 3.14
Positive pathergy test	13 (48.1)	15.96 ± 3.59
Joint involvement	6 (22.2)	16.33 ± 3.98
Eye involvement	12 (44.4)	18.50 ± 3.00
Vascular involvement	11 (40.7)	17.91 ± 3.86
CNS involvement	3 (11.1)	19.67 ± 2.08

Table 2 Ophthalmologic characteristics of the Behçet's disease patients with eye involvement (N = 12).

Characteristics	Number	Homocysteine level (μmol/L)
Retinal vasculitis	4	19.75 ± 3.59
Anterior uveitis	4	17.25 ± 2.99
Panuveitis	3	19.33 ± 2.52
Optic atrophy	2	16.5 ± 0.71
Posterior uveitis	6	18.17 ± 3.76
Retinitis	1	18.04 ± 0.00
Cataract	2	18 ± 1.41
Retinal hemorrhage	3	19.67 ± 4.73
Episcleritis	1	16.32 ± 0.00
Cystoid macular edema	1	17.11 ± 0.00

Mean serum homocysteine concentrations were also significantly higher ($P < 0.001$) in patients without eye involvement (13.20 ± 1.61 μmol/L) compared to healthy controls (7.32 ± 1.38 μmol/L).

No sex difference in demographic characteristics, homocysteine and CRP levels was found either in total BD patients or BD patients with or without eye involvement (Table 5).

Serum homocysteine levels were not significantly correlated ($P > 0.05$) with age, disease duration or CRP levels in all groups of BD patients (Table 6).

4. Discussion

Behçet's disease (BD) is a chronic, multisystemic disease of unknown etiology in which eye involvement is the most common cause of morbidity [21]. Since there is no available diagnostic laboratory test, the clinical diagnosis of BD is based on several signs. Uveitis is one of the major criteria established by the International Study Group for BD [20]. In this study, eye involvement was detected in 44.4% of BD patients. In other studies, the frequency of ocular involvement ranges between 39% and 75% [22–26], and is characterized by repeated, explosive ocular inflammatory attacks that heal spontaneously. Between attacks there is little or no evidence of inflammation in the eye. The anterior segment disease is usually accompanied by recurrent retinal vaso-occlusive disease, which is sight-threatening with repeated attacks. Complications of the chronic inflammation include retinal and optic atrophy, vitreous hemorrhage, neovascular glaucoma and retinal detachment. Despite therapeutic interven-

Table 3 Comparison of demographic characteristics, homocysteine and C-reactive protein levels between BD patients and healthy controls.

Mean ± SD	Behçet's disease (n = 27)	Healthy controls (n = 19)	P value
Male/female	17/10	11/8	–
Age (years)	32.11 ± 7.16	32.05 ± 7.69	0.90
Disease duration (years)	4.98 ± 2.76	–	–
Homocysteine (μmol/L)	15.56 ± 3.52	7.32 ± 1.38	< 0.001[a]
C-reactive protein (mg/L)	14.33 ± 8.28	3.21 ± 1.72	< 0.001[a]

[a] Highly significant difference.

Table 4 Comparison of demographic characteristics, homocysteine and C-reactive protein levels between Behçet's disease (BD) patients with and without eye involvement.

Characteristic	BD with eye involvement (n = 12)	BD without eye involvement (n = 15)	P value
Male/female	8/4	9/6	–
Age (years)	30.67 ± 8	33.27 ± 6.45	0.19
Disease duration (years)	4.83 ± 2.86	5.13 ± 2.67	0.66
Homocysteine (μmol/L)	18.5 ± 3	13.2 ± 1.61	< 0.001[a]
C-reactive protein (mg/L)	16.58 ± 8.43	12.53 ± 7.98	0.09

[a] Highly significant difference.

Table 5 Comparison of demographic characteristics, homocysteine and C-reactive protein levels between male and female patients with BD in different groups.

Characteristic	Total BD patients (n = 27)		BD with eye involvement (n = 12)		BD without eye involvement (n = 15)	
	Males (17)	Females (10)	Males (8)	Females (4)	Males (9)	Females (6)
Age (years)	34.18 ± 7.69	28.6 ± 4.6	32.5 ± 9.01	27 ± 4.32	35.67 ± 6.48	29.67 ± 4.84
Disease duration (years)	5.35 ± 2.96	4.4 ± 2.22	5.5 ± 3.25	3.5 ± 1.29	5.22 ± 2.86	5 ± 2.61
Homocysteine (μmol/L)	15.53 ± 3.9	15.6 ± 4.35	17.88 ± 2.7	19.75 ± 3.59	13.44 ± 1.51	12.83 ± 1.84
C-reactive protein (mg/L)	16.76 ± 9.09	10.2 ± 4.59	18.25 ± 9.36	13.25 ± 5.8	15.44 ± 9.18	8.17 ± 2.32

There is no significant difference between male and female patients with BD in the different groups.

Table 6 Correlations between serum homocysteine levels and patients' characteristics in different groups.

Characteristic	Total BD patients (n = 27)		BD with eye involvement (n = 12)		BD without eye involvement (n = 15)	
	R	P	R	P	R	P
Age (years)	−0.32	0.10	−0.33	0.30	0.03	0.92
Disease duration (years)	−0.16	0.41	−0.34	0.29	0.01	0.97
C-reactive protein (mg/L)	0.26	0.18	−0.29	0.37	0.17	0.55

There are no significant correlations between serum homocysteine levels and patients' characteristics in the different groups.

tion, about 25% of the patients with ocular lesions eventually become blind [22].

In the current study, higher levels of homocysteine in Egyptian BD patients were found compared to healthy controls. This is in concordance with several reports on Tunisian, Turkish and Iranian patients with BD [21,27–34]. In contrast, other studies found that homocysteine levels in patients with BD were not elevated [18,26].

The etiology of elevated serum homocysteine is multifactorial. Homocysteine is a metabolite of methionine and can be converted back to methionine or to cysteine via remethylation or transsulfuration. The enzyme methylenetetrahydrofolate reductase (MTHFR) is a pivotal enzyme in homocysteine metabolism. The genetically determined thermolabile variant of MTHFR which exerts less enzymatic activity has received considerable attention. However, most reported studies fail to demonstrate correlation between homozygosity for thermolabile MTHFR and retinal vascular disease [11]. These contrasting reports of the relation between TT genotype and total homocysteine (TH) levels may be related to the age of the patients studied. Genetic determinants of TH may be more important in younger patients with premature vascular disease, whereas nutritional factors may be more important in older patients [35]. The most important nutritional factors include the vitamins folate, B6 and B12 and excessive intake of methionine rich proteins [14]. Therapy with folic acid, vitamin B6 and Vitamin B12 has been shown to lower homocysteine levels and may prevent venous occlusive disease in patients with hyperhomocysteinemia [15].

In our BD patients, serum homocysteine levels were significantly higher ($P < 0.001$) in BD patients with eye involvement compared to those without eye involvement and healthy controls. They were also higher ($P < 0.001$) in patients without eye involvement compared to healthy controls. These results are in agreement with other studies [10], and are contradictory with others [19,26,35]. The causes of these different study outcomes are not clear. The different sample sizes, different disease durations or study patients under treatment that might affect outcomes could have contributed. In addition, the question whether hyperhomocysteinemia depends on the inflammation or not remains unanswered [10].

The exact mechanism by which hyperhomocysteinemia causes vascular disease and/or thrombosis is not known. However, there are two widely accepted hypotheses. According to the first, hyperhomocysteinaemia has deleterious effects on endothelial cells, causing endothelial cell damage, smooth muscle cell proliferation and increased oxidative stress [36]. In vitro studies are in favor of this hypothesis. In vitro endothelial cell cultures showed that homocysteine interfered with vasomotor regulatory and endothelial anticoagulant functions of vascular endothelial cells. Vessels from monkeys with moderate hyperhomocysteinaemia exhibited increased platelet mediated vasoconstriction, impaired endothelium dependent vasodilatation and decreased thrombomodulin dependent activation of protein C [37].

According to the second hypothesis, homocysteine mediated vascular disease/thrombosis occurs via interference with coagulation mechanisms. Homocysteine inhibits the expression and activation of thrombomodulin, which is a cofactor for protein C activation [37]. Homocysteine also suppresses the anticoagulant action of antithrombin III [38].

In this study, statistically significant differences in the levels of CRP were found between patients with BD and healthy controls. Similar results were reported by Kartal Durmazlar et al. [10]. However, no significant differences in CRP levels were found between BD patients with and without eye involvement. Several laboratory markers correlate in varying degrees with activity of BD, such as CRP, interleukins 6 and 8, C9, neuropteran and erythrocyte sedimentation rate. Of these, CRP correlates well with signs such as erythema nodosum, acute thrombophlebitis, and acute arthritis [38]. However, the association of CRP with mucocutaneous, ocular, or central nervous system activities is weaker [39].

In the present study, no sex difference in homocysteine levels was shown in our patients with BD. This was the same

as previously seen in Turkish and Iranian patients [30,34]. In contrast, other studies reported significantly higher levels of homocysteine in male patients with BD which might explain the higher incidence of thrombosis in men with BD [11,21,35].

In our study, homocysteine levels were not significantly correlated with age, disease duration and CRP levels either in total BD patients or BD patients with or without eye involvement. In contrast, Cahill et al. reported that increasing age is a known risk factor that elevates homocysteine levels [11].

Our study has two shortcomings. 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, we suggest that chronic inflammation may lead to hyperhomocysteinemia, which, in turn, may contribute to vasculopathic complications of BD including uveitis and retinal vascular disease. Assessment of homocysteine may be important in the investigation and management of patients with BD, especially those with ocular disease.

Conflict of interest

The authors declare no conflicts of interest.

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